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Form Revision Date: August 26, 2013

PTO/AIA/15 (10-17)
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Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	3338.0630006/ELE/C-K
First Named Inventor	John P. COGSWELL
Title	See 1 in Addendum
Priority Mail Express® Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☐ **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. ☐ **Applicant asserts small entity status.** See 37 CFR 1.27
3. ☐ **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. ☒ **Specification** [*Total Pages* 105] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. ☒ **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 24]
6. **Inventor's Oath or Declaration** [*Total Pages* 6] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. ☐ Newly executed (original or copy)
   b. ☒ A copy from a prior application (37 CFR 1.63(d))
7. ☒ **Application Data Sheet** ** See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   ☐ Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. ☒ Computer Readable Form (CRF)
   b. ☐ Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ Paper
   c. ☐ Statements verifying identity of above copies

ADDRESS TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**

ACCOMPANYING APPLICATION PAPERS

10. ☐ **Assignment Papers** (cover sheet & document(s))
    Name of Assignee _____
11. ☐ **37 CFR 3.73(c) Statement** (*when there is an assignee*) ☒ **Power of Attorney**
12. ☐ **English Translation Document** (*if applicable*)
13. ☐ **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    ☐ Copies of citations attached
14. ☒ **Preliminary Amendment**
15. ☐ **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. ☐ **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. ☐ **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. ☒ **Other:** **Authorization under 37 CFR 1.136(a)(3) Certification and Request for Prioritized Examination Under 37 C.F.R. 1.102(e)**

***Note**: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

☒ The address associated with Customer Number: **115018** **OR** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Ji-Eun Kim/	Date	June 12, 2018
Name (Print/Type)	Ji-Eun Kim	Registration No. (Attorney/Agent)	68,504

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Addendum

1. CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: COGSWELL *et al.*	Confirmation No.: To Be Assigned
Applicant: Bristol-Myers Squibb Company	Art Unit: To Be Assigned
Application No.: To Be Assigned	Examiner: To Be Assigned
(*Continuation of Appl. No. 14/950,748; Filed: November 24, 2015*)	Atty. Docket: 3338.0630006/ELE/C-K
Filed: Herewith	

Title: **CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING**

Authorization to Treat a Reply as Incorporating an Extension of Time Under 37 C.F.R. § 1.136(a)(3)

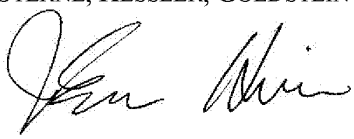
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

The U.S. Patent and Trademark Office is hereby authorized to treat any concurrent or future reply that requires a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. The U.S. Patent and Trademark Office is hereby authorized to charge all required extension of time fees to our Deposit Account No. 19-0036, if such fees are not otherwise provided for in such reply.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Ji-Eun Kim
Attorney for Applicant
Registration No. 68,504

Date: June 12, 2018

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

9449654.1

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	John P. COGSWELL	Nonprovisional Application Number (if known):	To Be Assigned
Title of Invention:	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ **Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ **Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Ji-Eun Kim/	Date June 12, 2018
Name (Print/Typed) Ji-Eun Kim	Practitioner Registration Number 68,504

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3338.0630006/ELE/C-K
	Application Number	
Title of Invention	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	John	P.	COGSWELL	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Yardley	State/Province	PA	Country of Residence	US

Mailing Address of Inventor:

Address 1	Route 206 and Province Line Road		
Address 2			
City	Princeton	State/Province	NJ
Postal Code	08543	Country i	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Stacie	M.	Goldberg	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Potomac	State/Province	MD	Country of Residence	US

Mailing Address of Inventor:

Address 1	9810 Glynshire Way		
Address 2			
City	Potomac	State/Province	MD
Postal Code	20854	Country i	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Ashok	K.	Gupta	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3338.0630006/ELE/C-K
	Application Number	
Title of Invention	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING	

City	Clarksburg	State/Province	MD	Country of Residence	US

Mailing Address of Inventor:

Address 1	22819 Glacier Lily Drive		
Address 2			
City	Clarksburg	State/Province	MD
Postal Code	20871	Country	US

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Maria		Jure-Kunkel	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Plainsboro	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

Address 1	Route 206 and Province Line Road		
Address 2			
City	Princeton	State/Province	NJ
Postal Code	08543	Country	US

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Xi-Tao		Wang	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Wellesley	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	Route 206 and Province Line Road		
Address 2			
City	Princeton	State/Province	NJ
Postal Code	08543	Country	US

Inventor 6 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jon	M.	Wigginton	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Collegeville	State/Province	PA	Country of Residence	US

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3338.0630006/ELE/C-K
	Application Number	
Title of Invention	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING	

Mailing Address of Inventor:			
Address 1	27 Longacre Drive		
Address 2			
City	Collegeville	State/Province	PA
Postal Code	19426	Country i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	115018		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING		
Attorney Docket Number	3338.0630006/ELE/C-K	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	24	Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3338.0630006/ELE/C-K
	Application Number	
Title of Invention	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING	

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	(●) Customer Number	( ) US Patent Practitioner	( ) Limited Recognition (37 CFR 11.9)
Customer Number	115018		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	14950748	2015-11-24

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14950748	Division of	13892671	2013-05-13	9212224	2015-12-15

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13892671	Claims benefit of provisional	61647442	2012-05-15

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13892671	Claims benefit of provisional	61790747	2013-03-15

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3338.0630006/ELE/C-K
	Application Number	
Title of Invention	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING	

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3338.0630006/ELE/C-K
	Application Number	
Title of Invention	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3338.0630006/ELE/C-K
	Application Number	
Title of Invention	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Bristol-Myers Squibb Company		
Mailing Address Information For Applicant:			
Address 1	Rt. 206 & Province Line Road		
Address 2			
City	Princeton	**State/Province**	NJ
Country	US	Postal Code	08543
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3338.0630006/ELE/C-K
	Application Number	
Title of Invention	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	Bristol-Myers Squibb Company

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	Rt. 206 & Province Line Road		
Address 2			
City	Princeton	**State/Province**	NJ
Country i	US	Postal Code	08543
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Ji-Eun Kim/			Date (YYYY-MM-DD)	2018-06-12
First Name	Ji-Eun	Last Name	KIM	Registration Number	68504

Additional Signature may be generated within this form by selecting the Add button.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3338.0630006/ELE/C-K
	Application Number	
Title of Invention	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☑ United States application or PCT international application number 13/892,671 filed on 13 May 2013.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I have reviewed and understand the contents of the above-identified application, including the claims, and I am aware of the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. 1.56.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: John P. Cogswell Date (Optional): 06/10/2013

Signature: John P Cogswell

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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LEGAL NAME OF INVENTOR

Inventor: Xi-Tao Wang Date (Optional): 10 June 2013

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Maria Jure-Kunkel MJK Date (Optional): June 19th, 2013

Signature: MJure-Kunkel

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Jon M. Wigginton Date (Optional): July 17, 2013

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Stacie M. Goldberg Date (Optional): 6/18/13

Signature: Stacie Goldberg

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Ashok K. Gupta Date (Optional): 10 June 2013

Signature: Ashok Gupta

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/AIA/01 form for each additional inventor.

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FIG. 1A

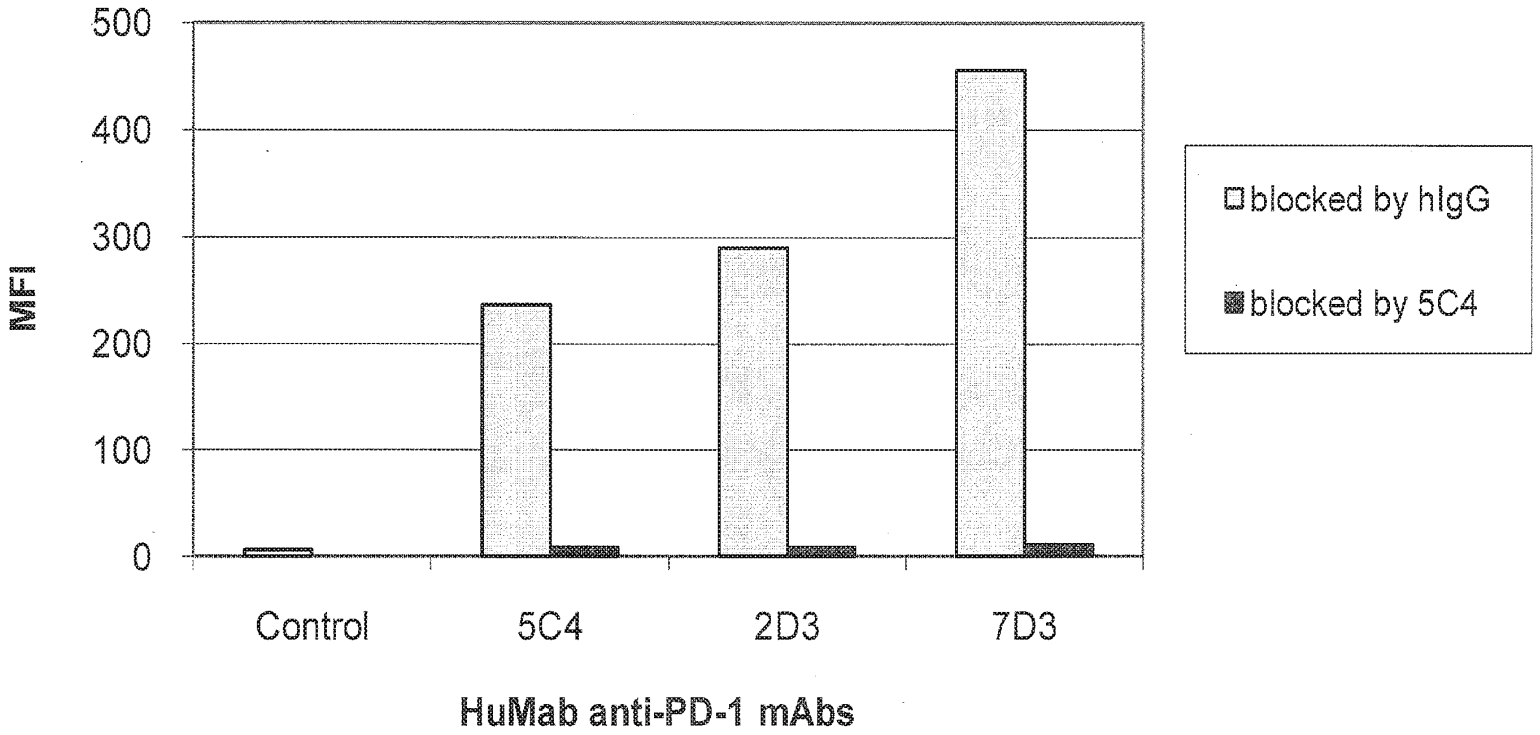

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300
200
100
0
MFI
Control
5C4
2D3
7D3
HuMab anti-PD-1 mAbs
blocked by hIgG
blocked by 5C4

FIG. 1B

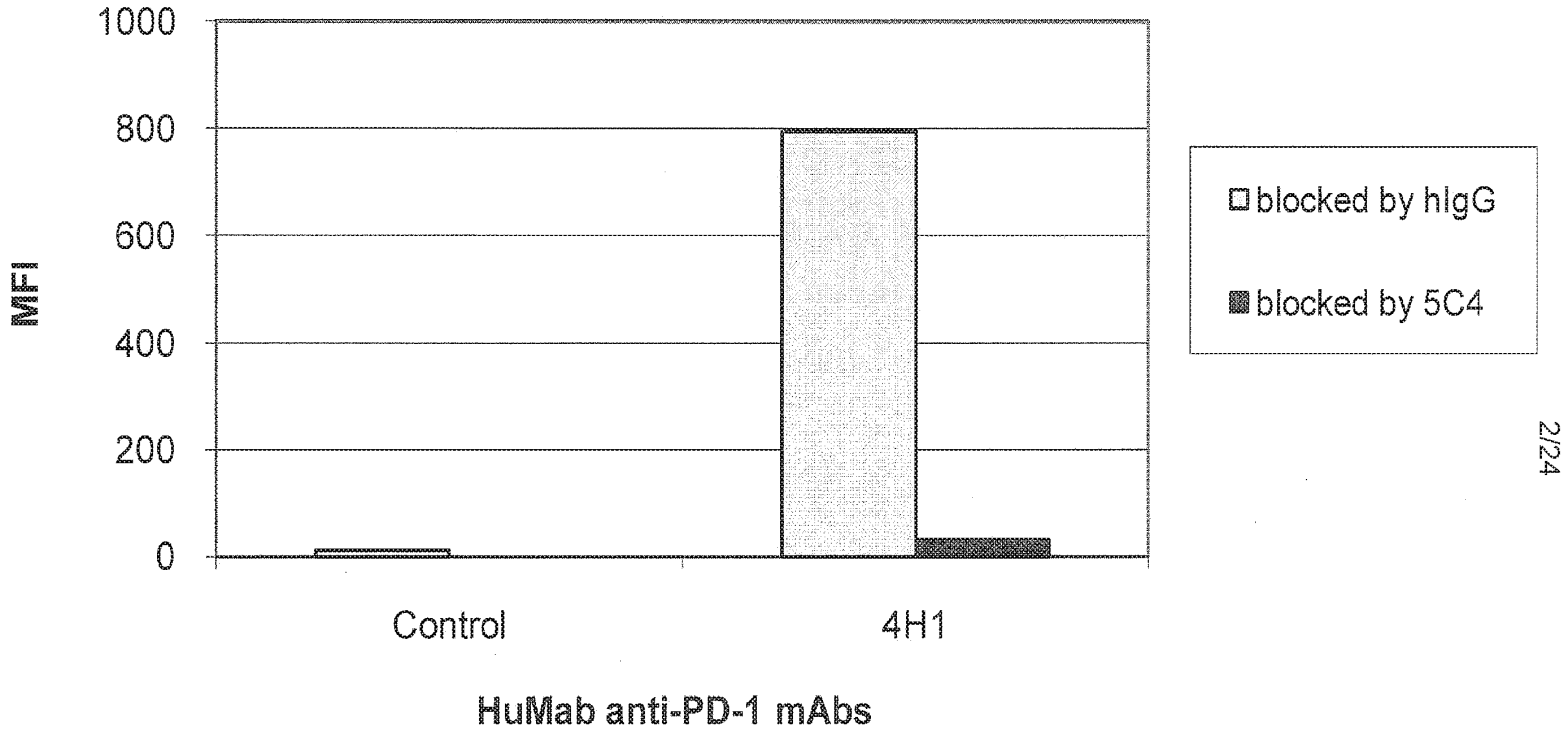

1000
800
600
400
200
0
MFI
Control
4H1
HuMab anti-PD-1 mAbs
blocked by hIgG
blocked by 5C4

FIG. 1C

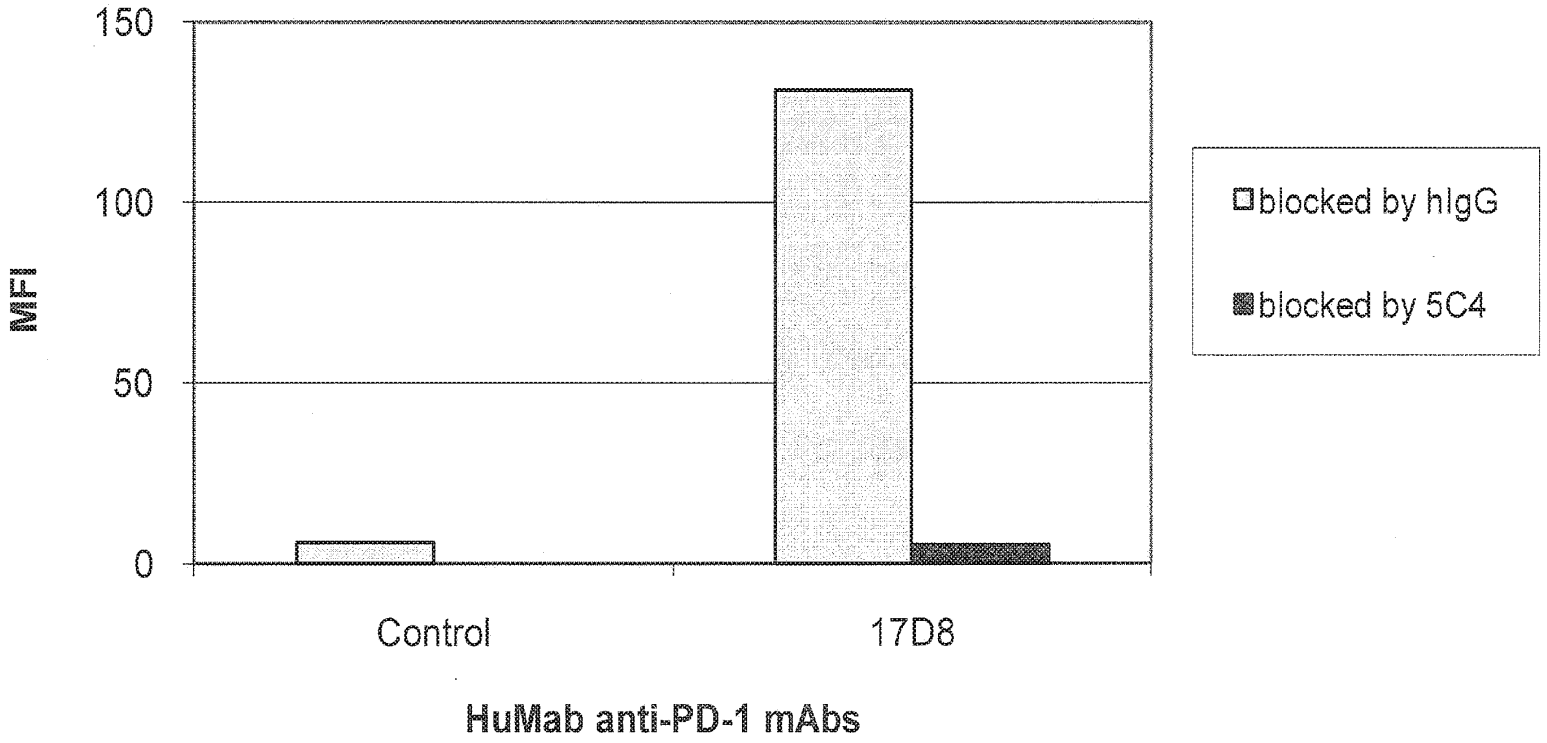
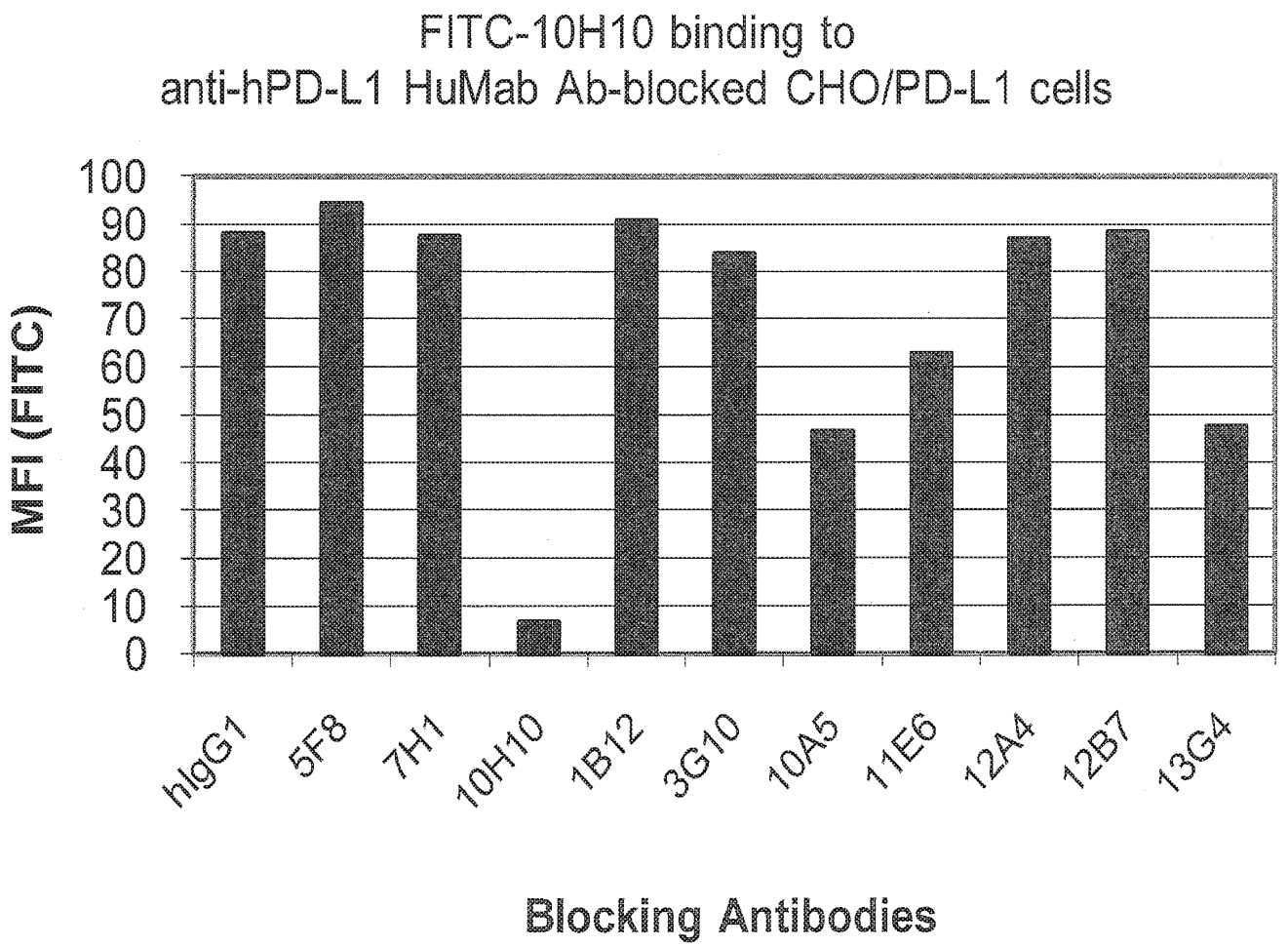

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MFI
Control
17D8
HuMab anti-PD-1 mAbs
blocked by hIgG
blocked by 5C4

FIG. 2A



Atty. Dkt. No.: 3338.0630006

FIG. 2B

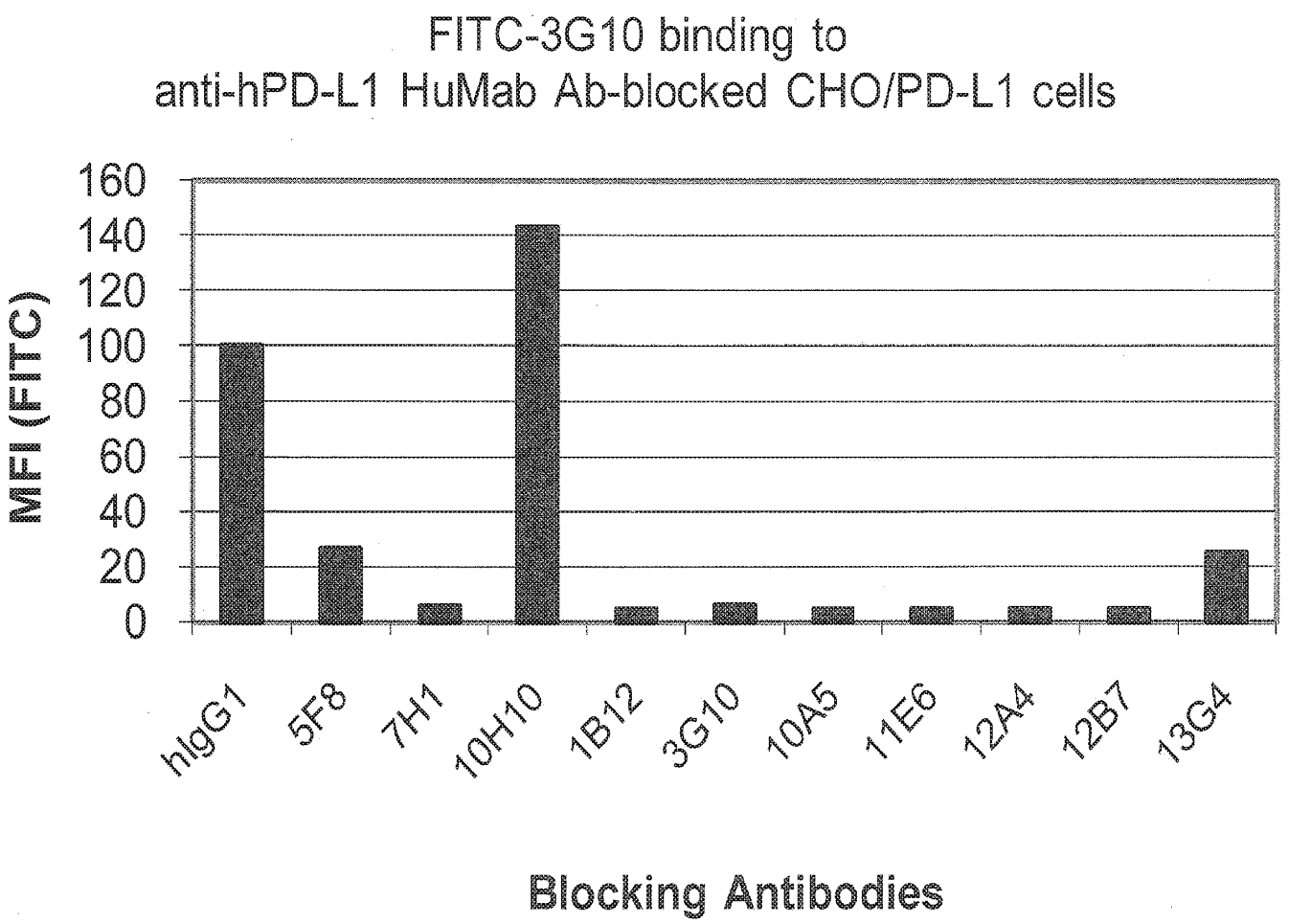
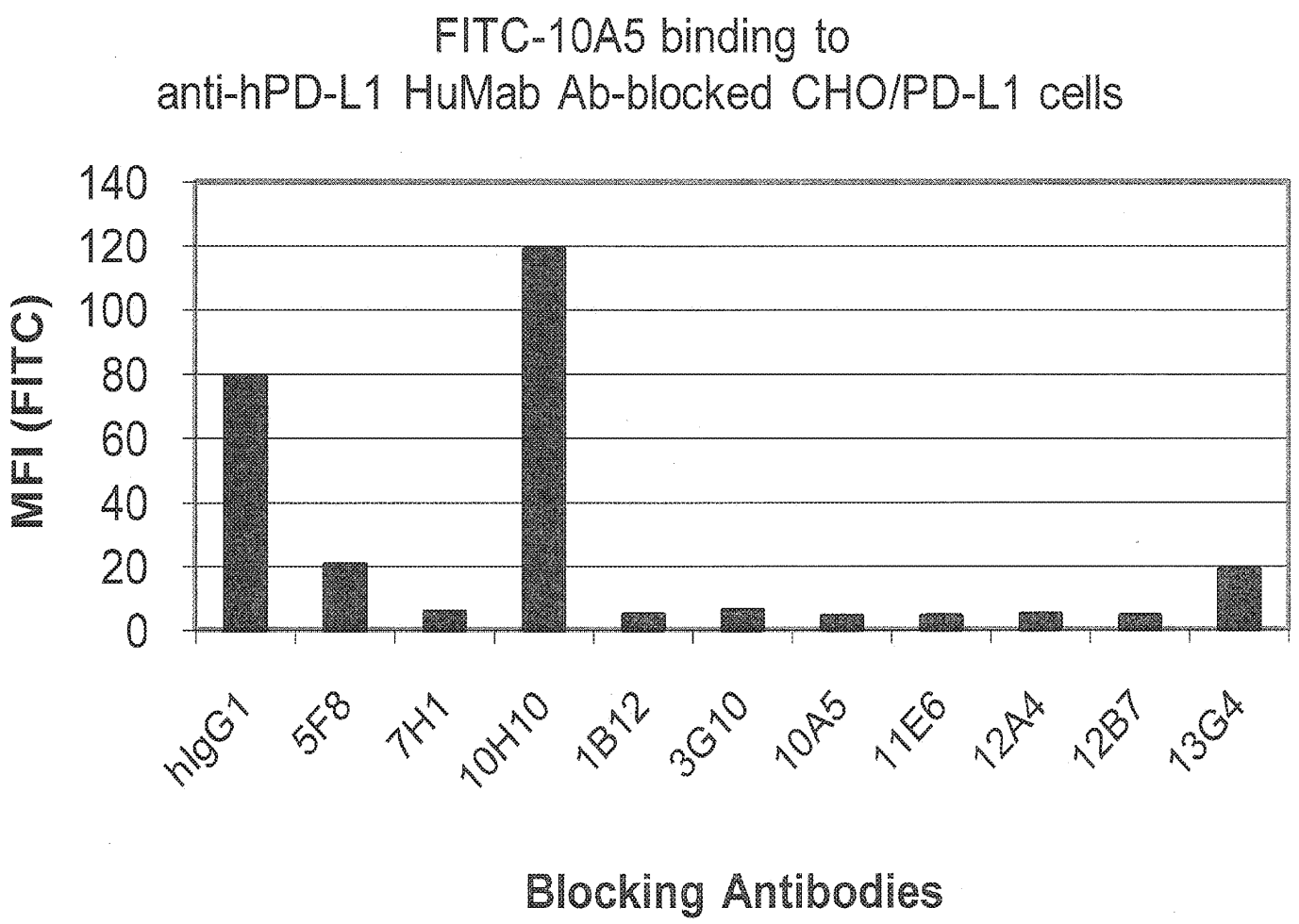

FITC-3G10 binding to
anti-hPD-L1 HuMab Ab-blocked CHO/PD-L1 cells
MFI (FITC)
160
140
120
100
80
60
40
20
0
hIgG1
5F8
7H1
10H10
1B12
3G10
10A5
11E6
12A4
12B7
13G4
Blocking Antibodies

FIG. 2C



Atty. Dkt. No.: 3338.0630006

FIG. 2D

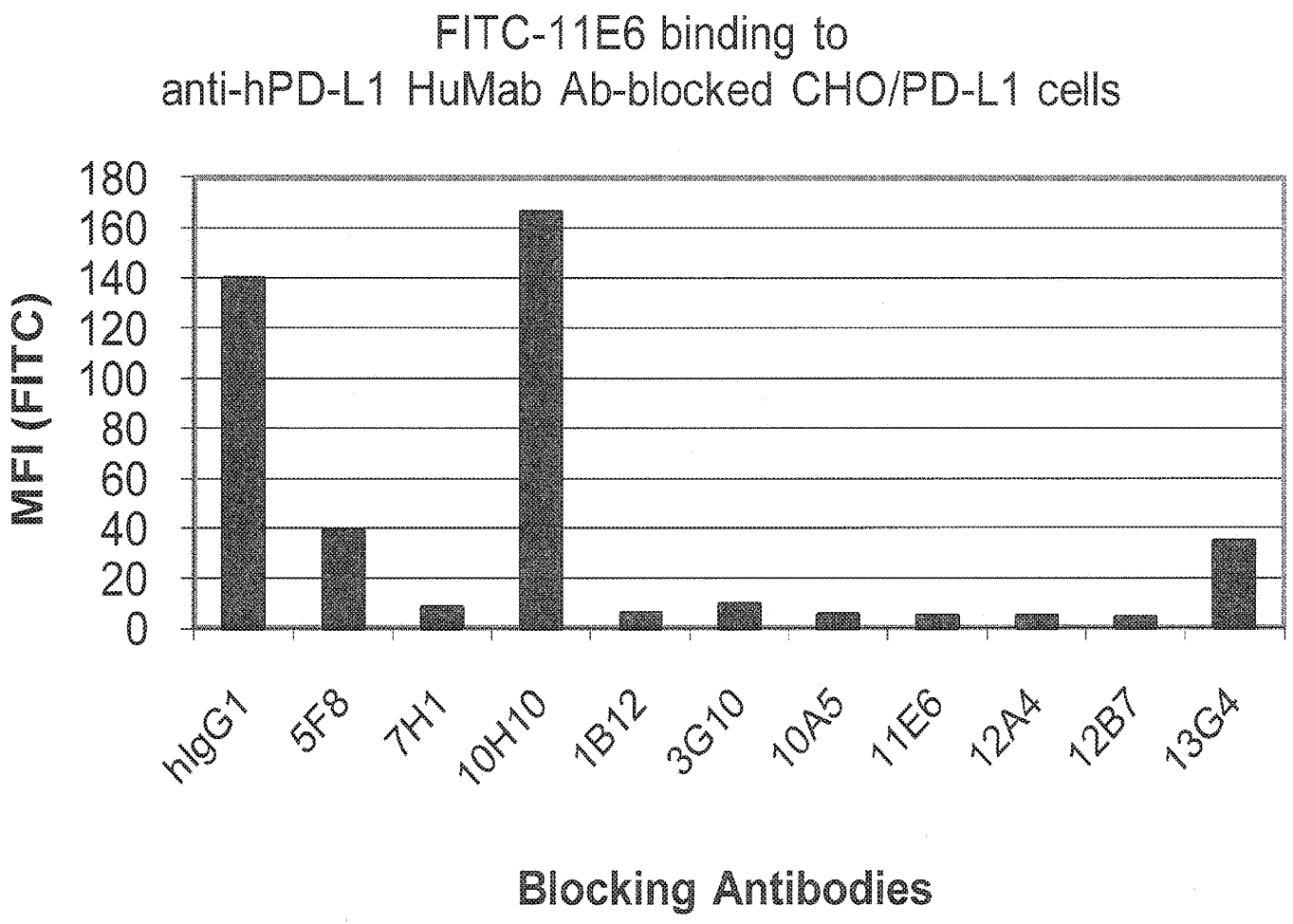
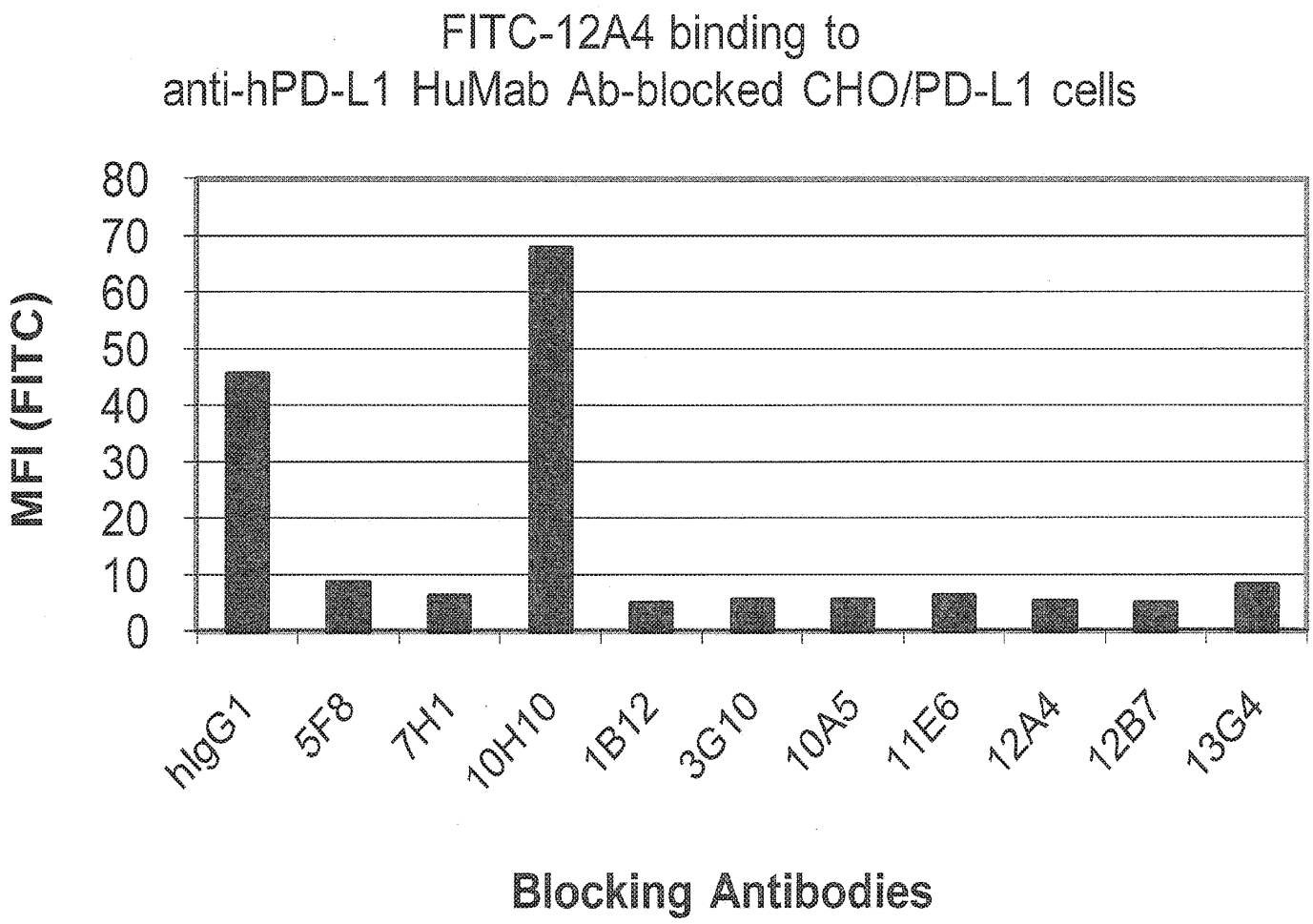
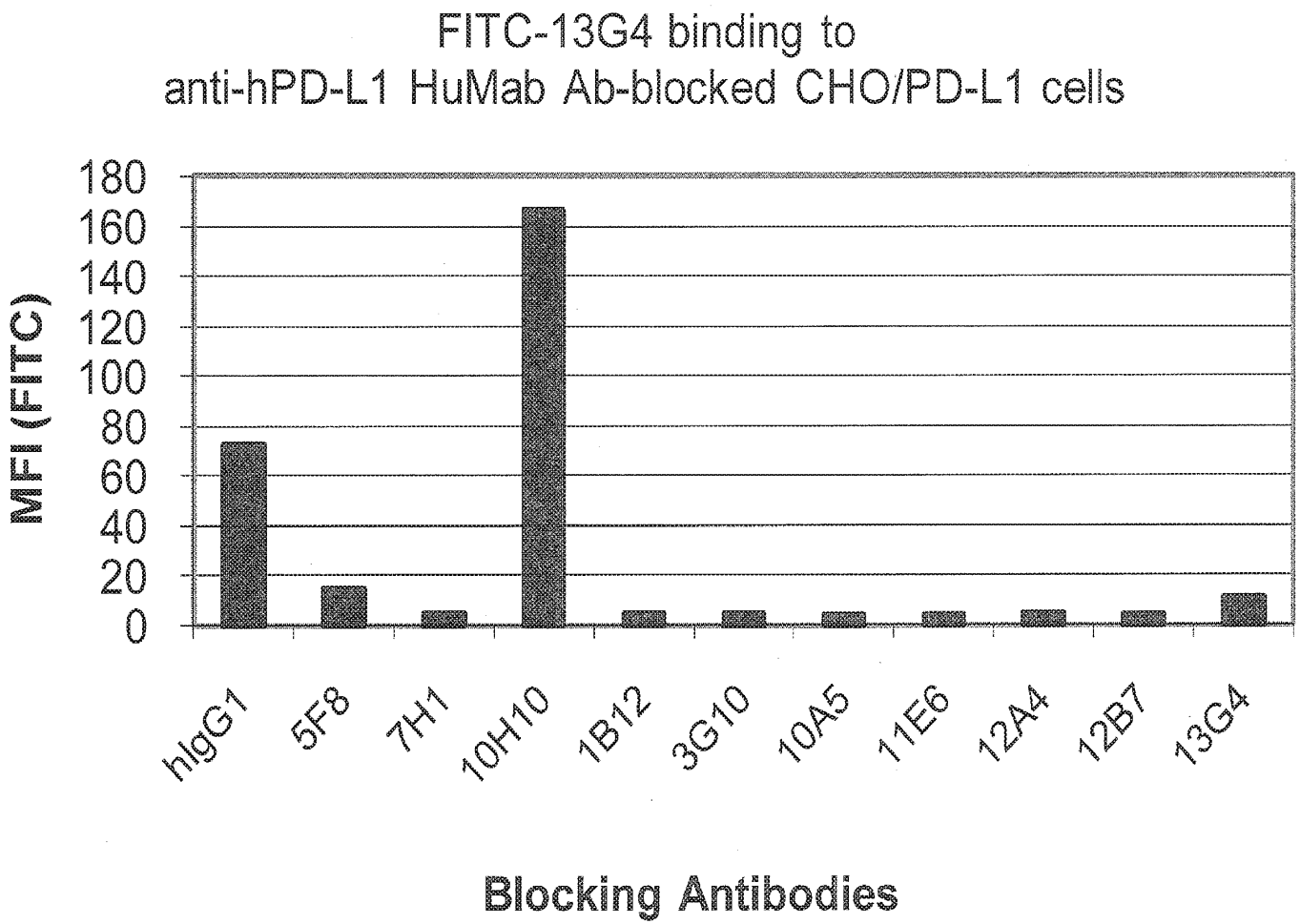

FITC-11E6 binding to
anti-hPD-L1 HuMab Ab-blocked CHO/PD-L1 cells
MFI (FITC)
180
160
140
120
100
80
60
40
20
0
hIgG1
5F8
7H1
10H10
1B12
3G10
10A5
11E6
12A4
12B7
13G4
Blocking Antibodies

FIG. 2E



Atty. Dkt. No.: 3338.0630006

FIG. 2F



Atty. Dkt. No.: 3338.0630006

FIG. 3

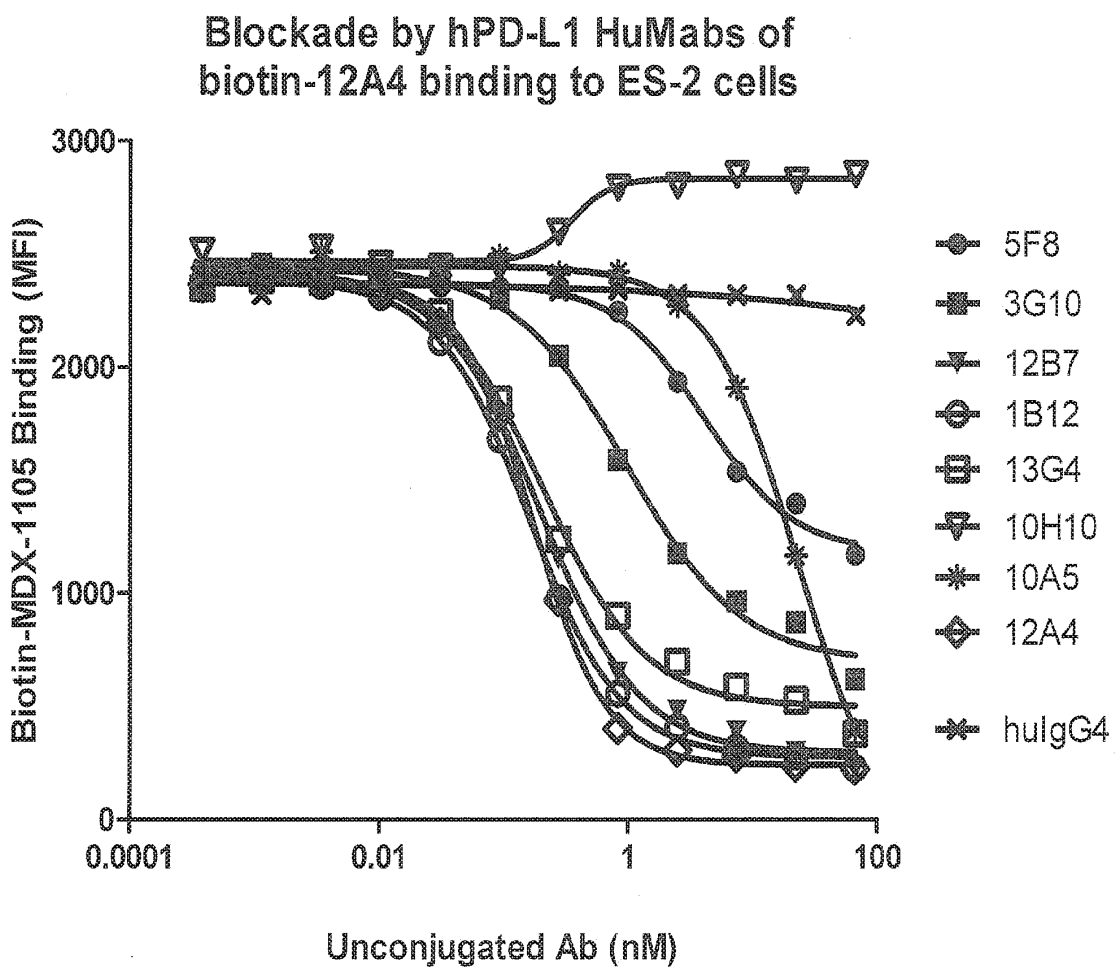
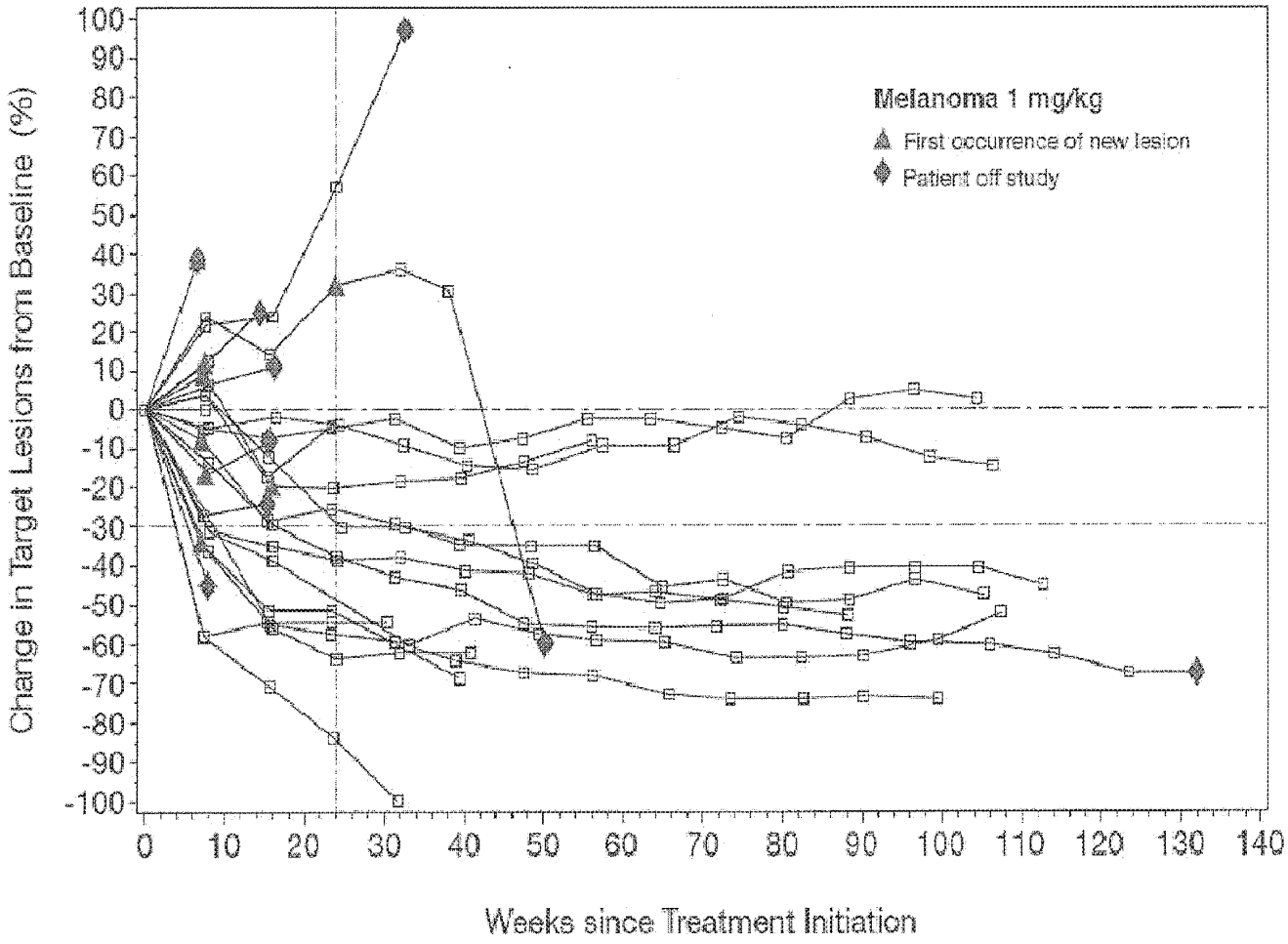

Blockade by hPD-L1 HuMabs of
biotin-12A4 binding to ES-2 cells
Biotin-MDX-1105 Binding (MFI)
3000
2000
1000
0
0.0001
0.01
1
100
Unconjugated Ab (nM)
5F8
3G10
12B7
1B12
13G4
10H10
10A5
12A4
hulgG4

FIG. 4


Melanoma 1 mg/kg
First occurrence of new lesion
Patient off study
Change in Target Lesions from Baseline (%)
Weeks since Treatment Initiation
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140

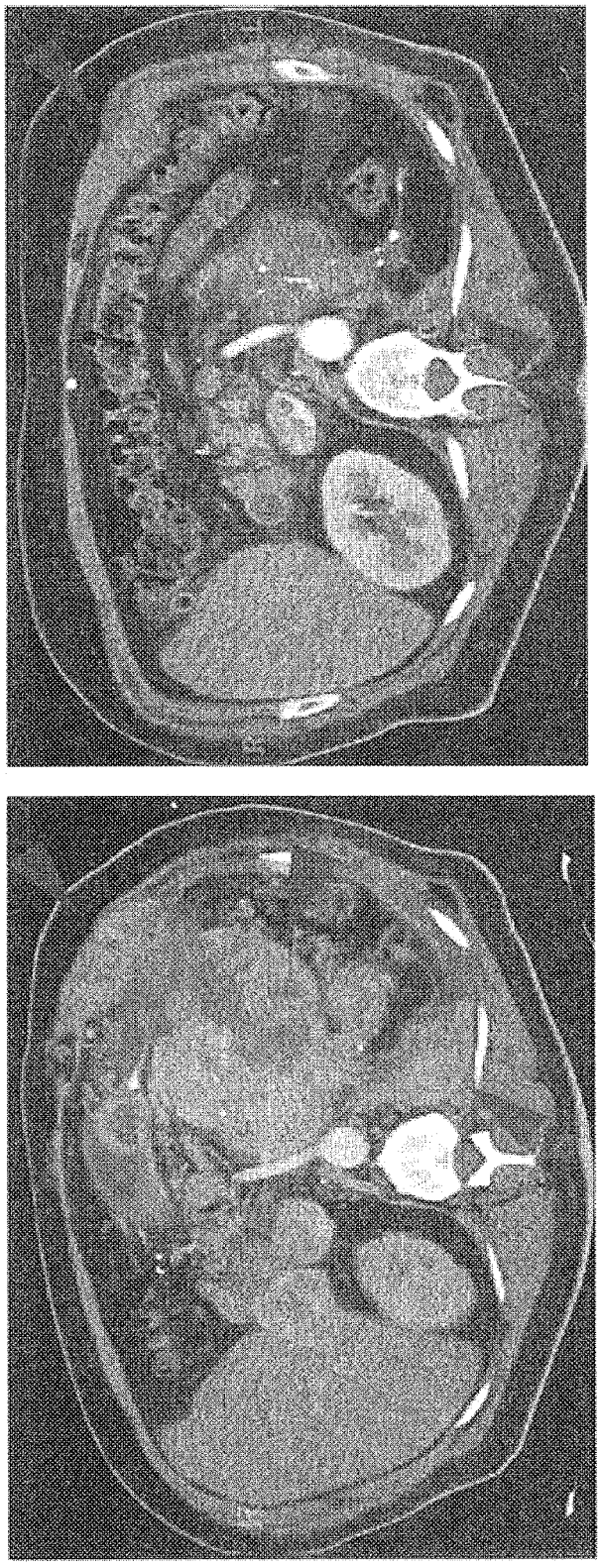
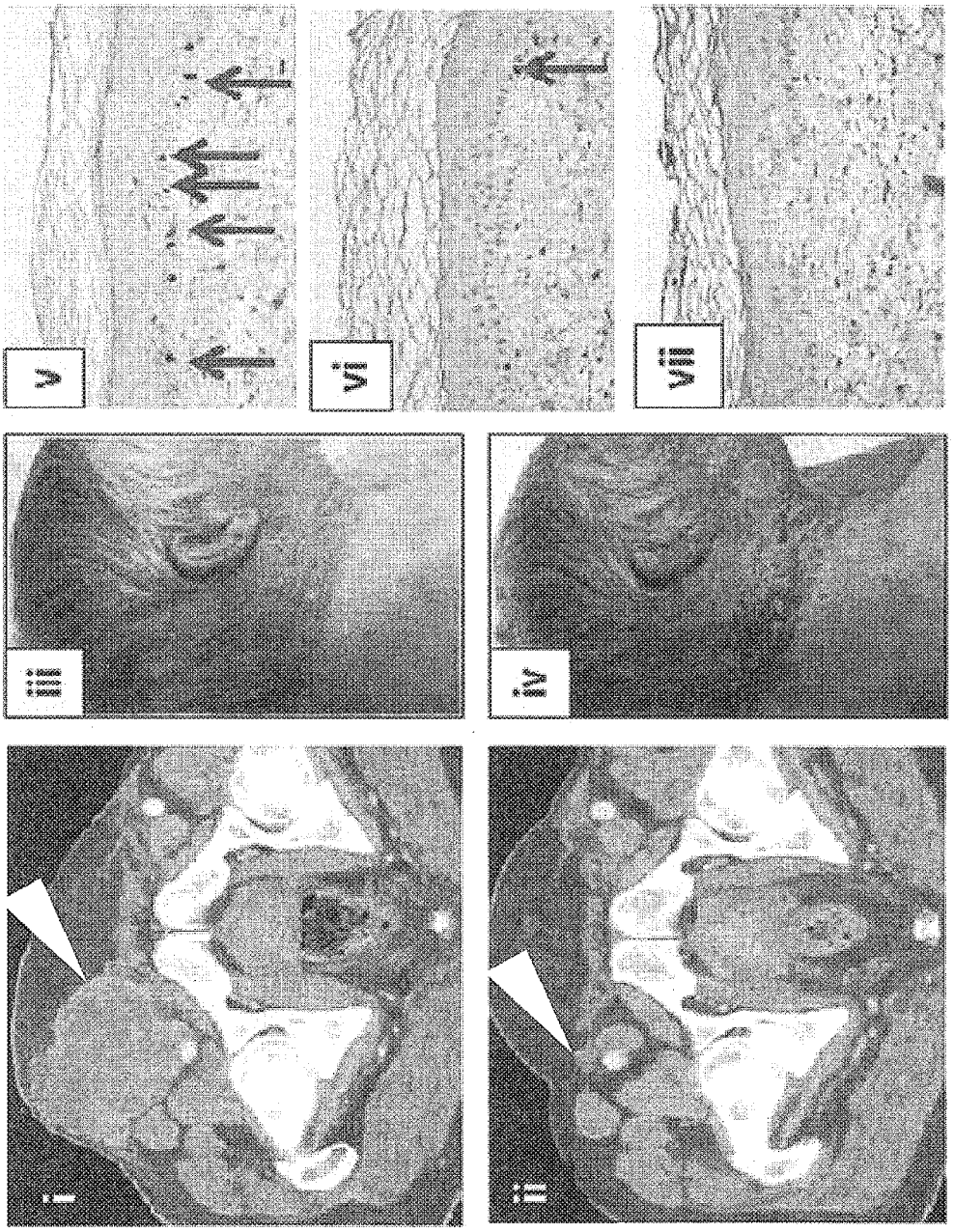


FIG. 5

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FIG. 6



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FIG. 7

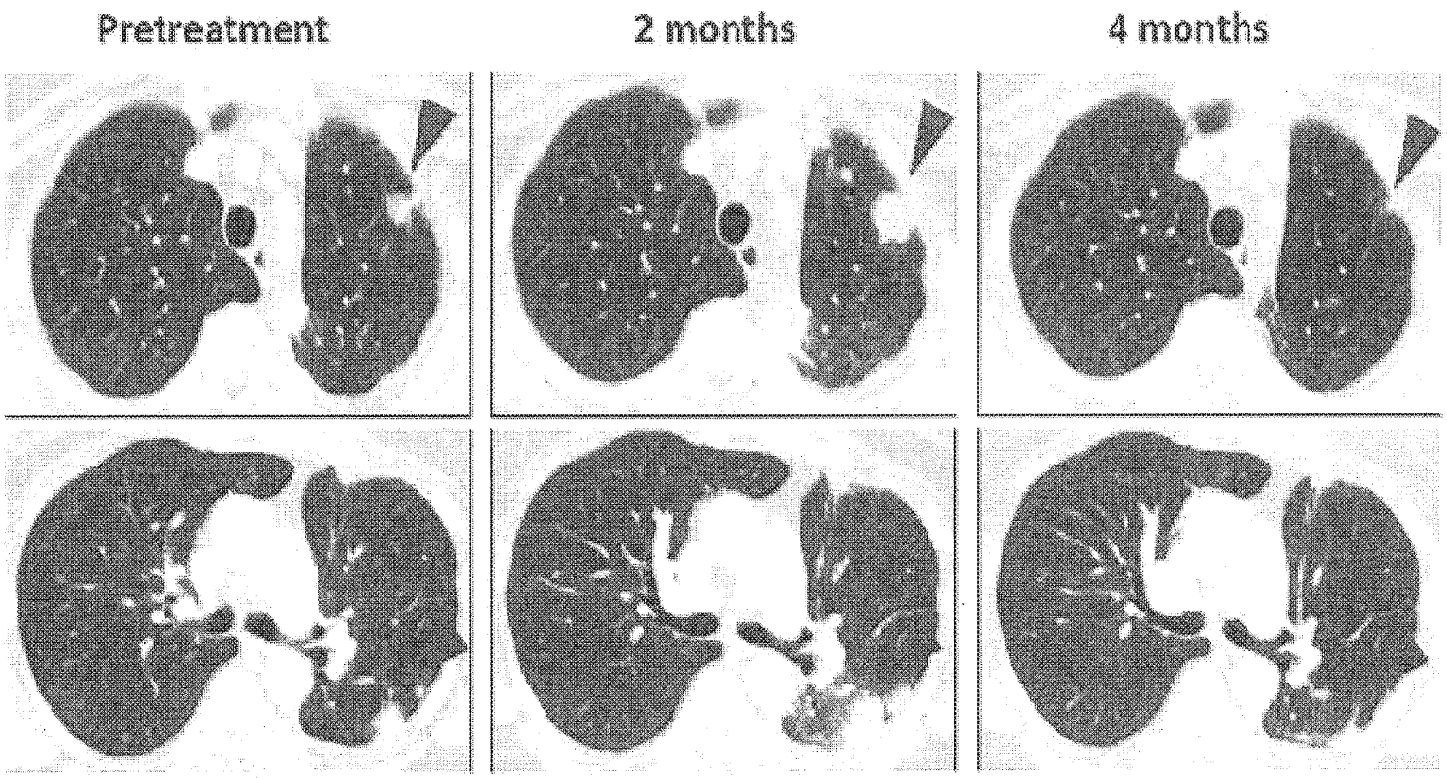
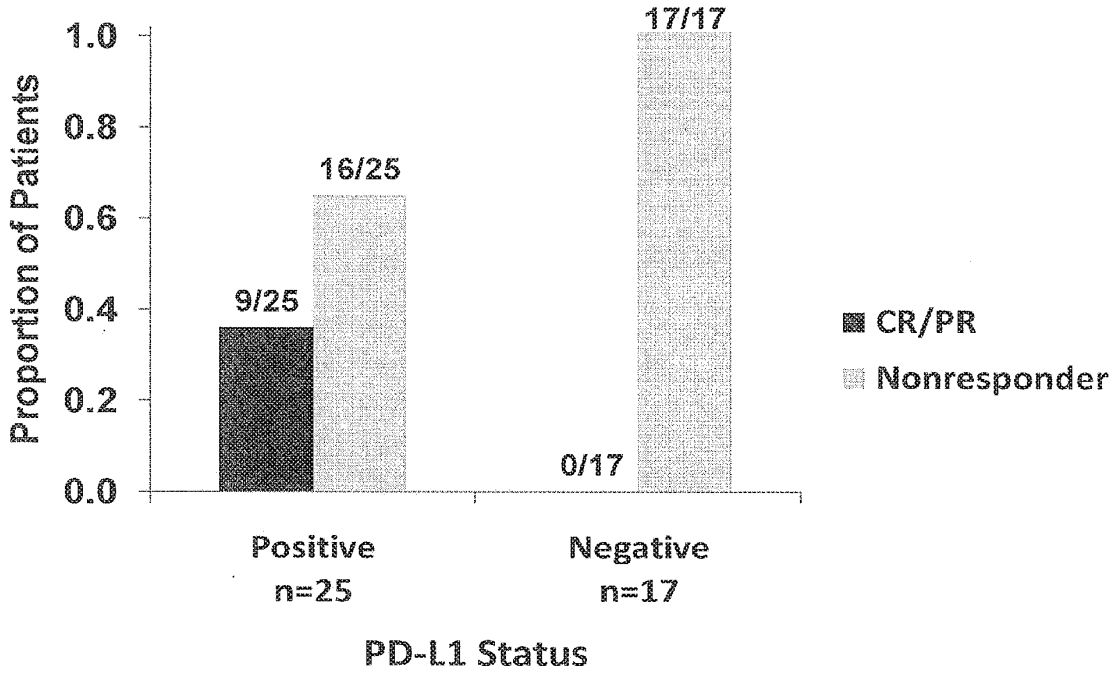


FIG. 8A



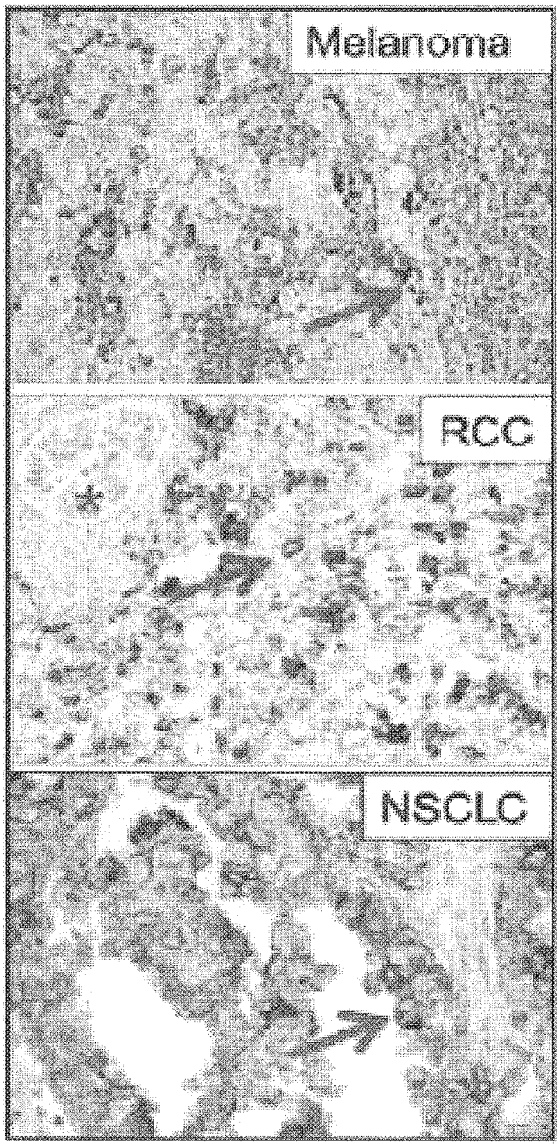
Association Between Pretreatment Tumor PD-L1 Expression and Clinical Response			
Response Status	PD-L1-Positive no. (%)	PD-L1-Negative no. (%)	Total no. (%)
CR/PR	9 (36)	0	9 (21)
Nonresponder	16* (64)	17 (100)	33 (79)
All Patients	25	17	42

Fisher's exact test for association P=0.006.

*Two patients categorized as nonresponders at the time of data analysis are still under evaluation.

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FIG. 8B



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FIG. 9

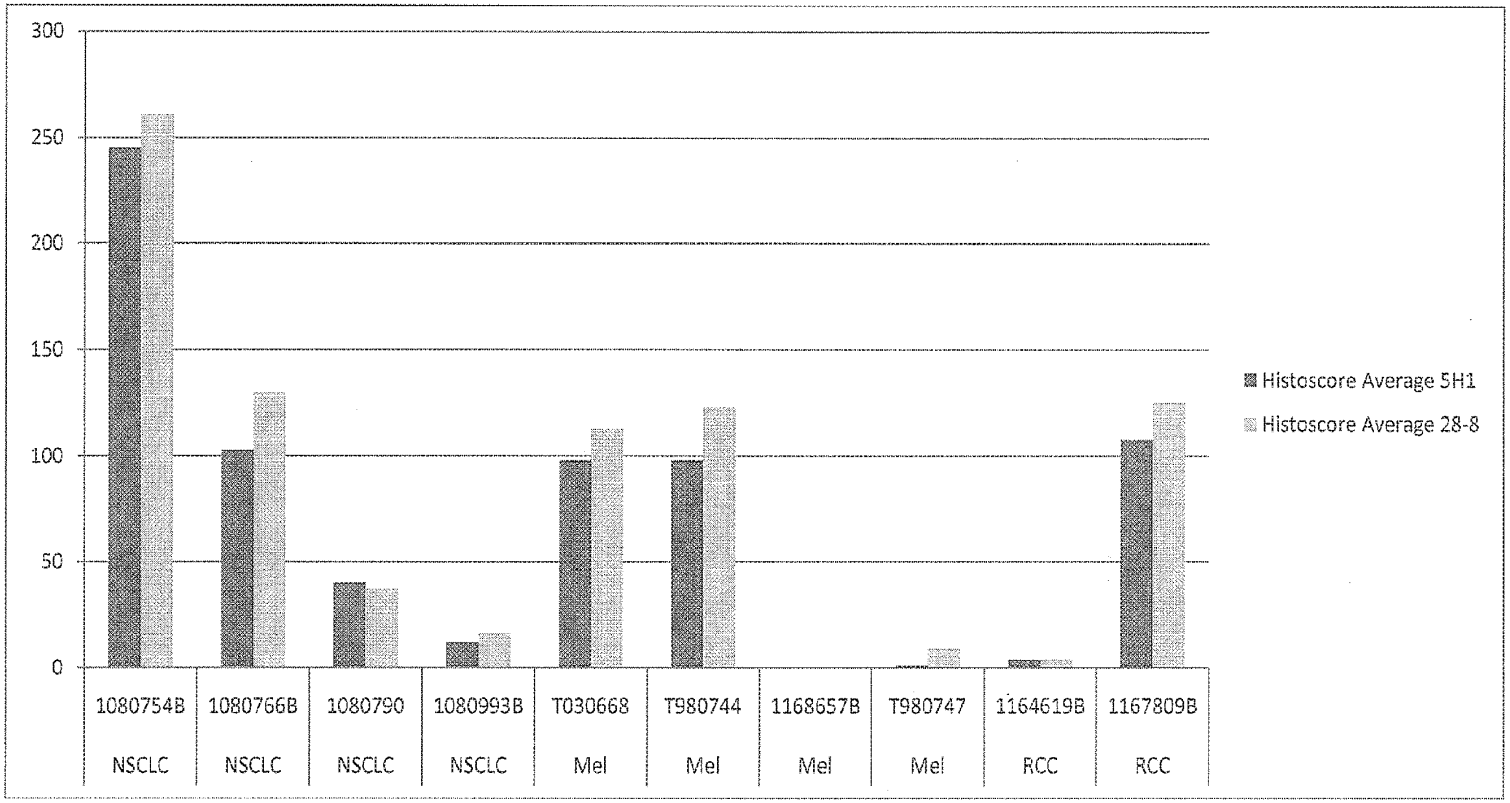

300
250
200
150
100
50
0
Histoscore Average 5H1
Histoscore Average 28-8
1080754B NSCLC
1080766B NSCLC
1080790 NSCLC
1080993B NSCLC
T030668 Mel
T980744 Mel
1168657B Mel
T980747 Mel
1164619B RCC
1167809B RCC

FIG. 10A

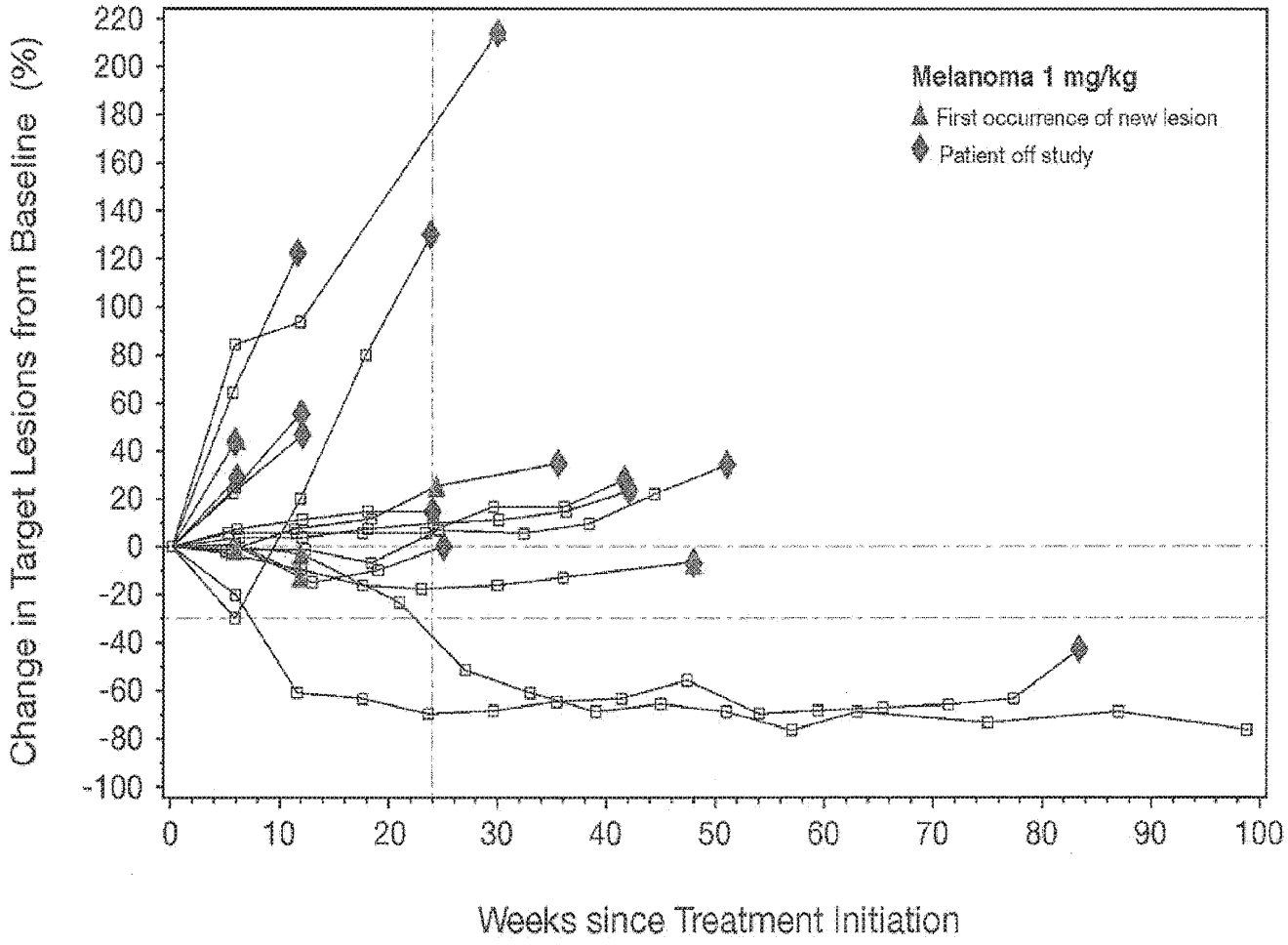

Melanoma 1 mg/kg
First occurrence of new lesion
Patient off study
Change in Target Lesions from Baseline (%)
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
0
10
20
30
40
50
60
70
80
90
100
Weeks since Treatment Initiation

FIG. 10B

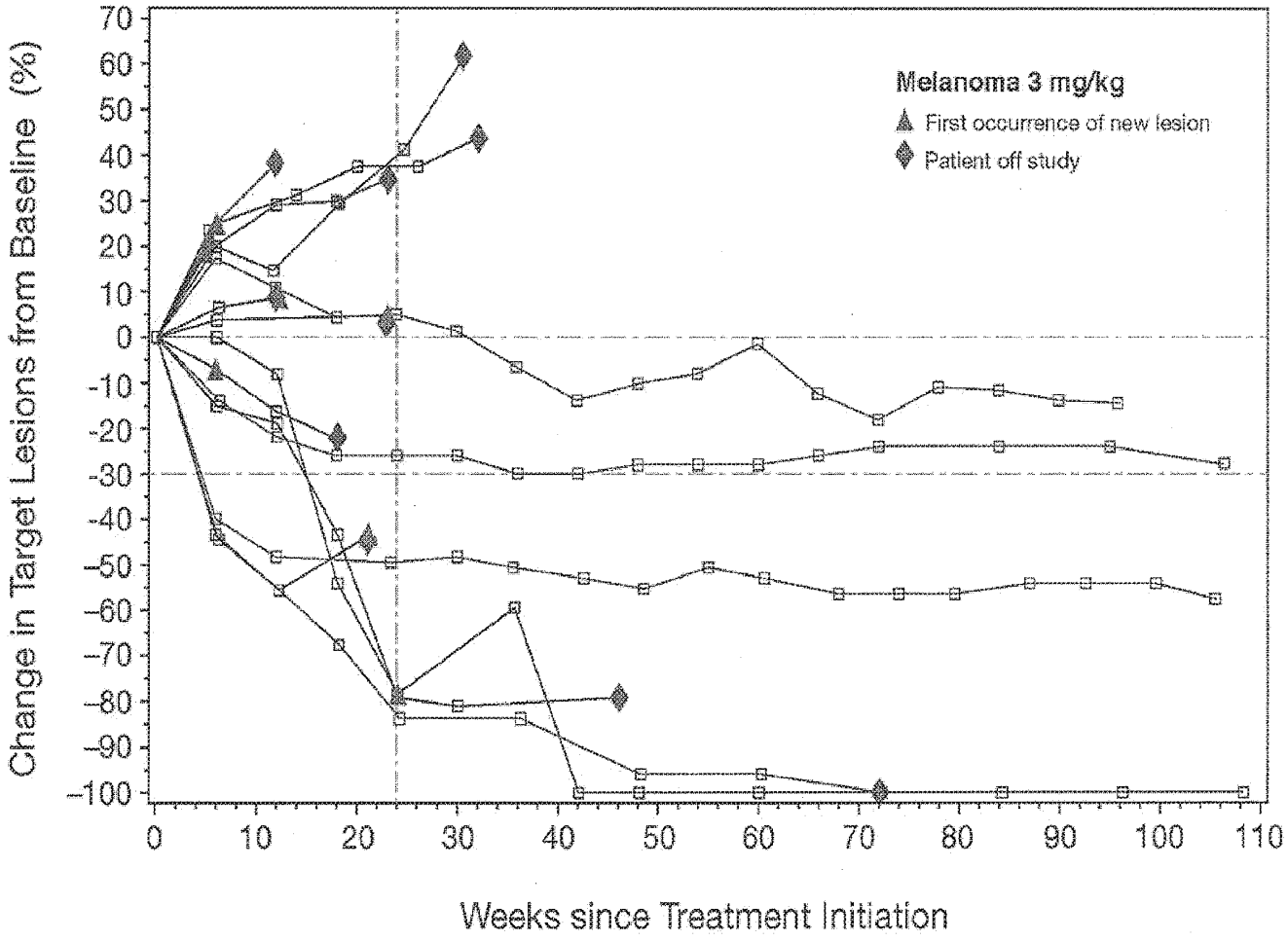

Melanoma 3 mg/kg
First occurrence of new lesion
Patient off study
Change in Target Lesions from Baseline (%)
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
0
10
20
30
40
50
60
70
80
90
100
110
Weeks since Treatment Initiation

FIG. 10C

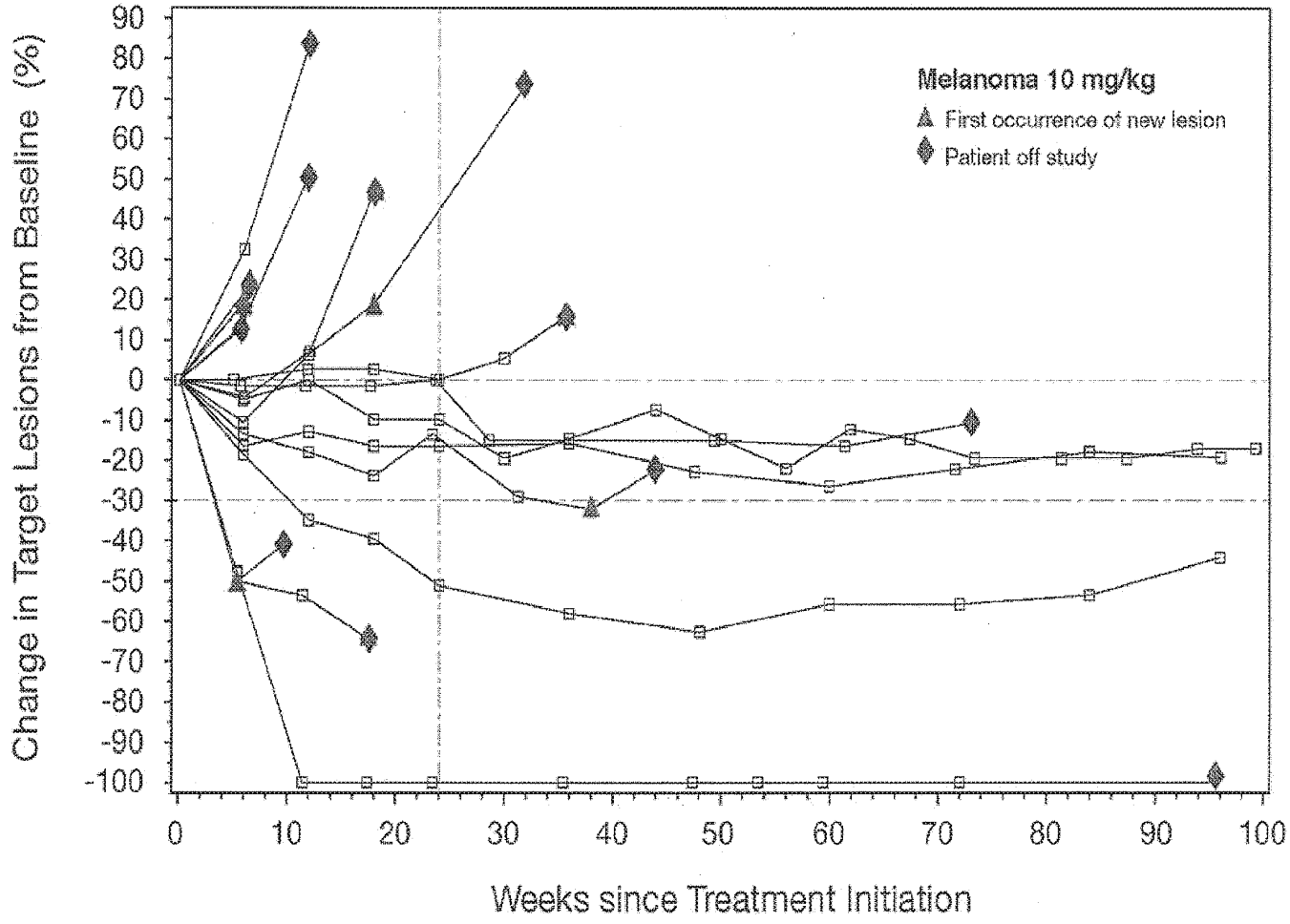

Melanoma 10 mg/kg
First occurrence of new lesion
Patient off study
Change in Target Lesions from Baseline (%)
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
0
10
20
30
40
50
60
70
80
90
100
Weeks since Treatment Initiation

FIG. 10D

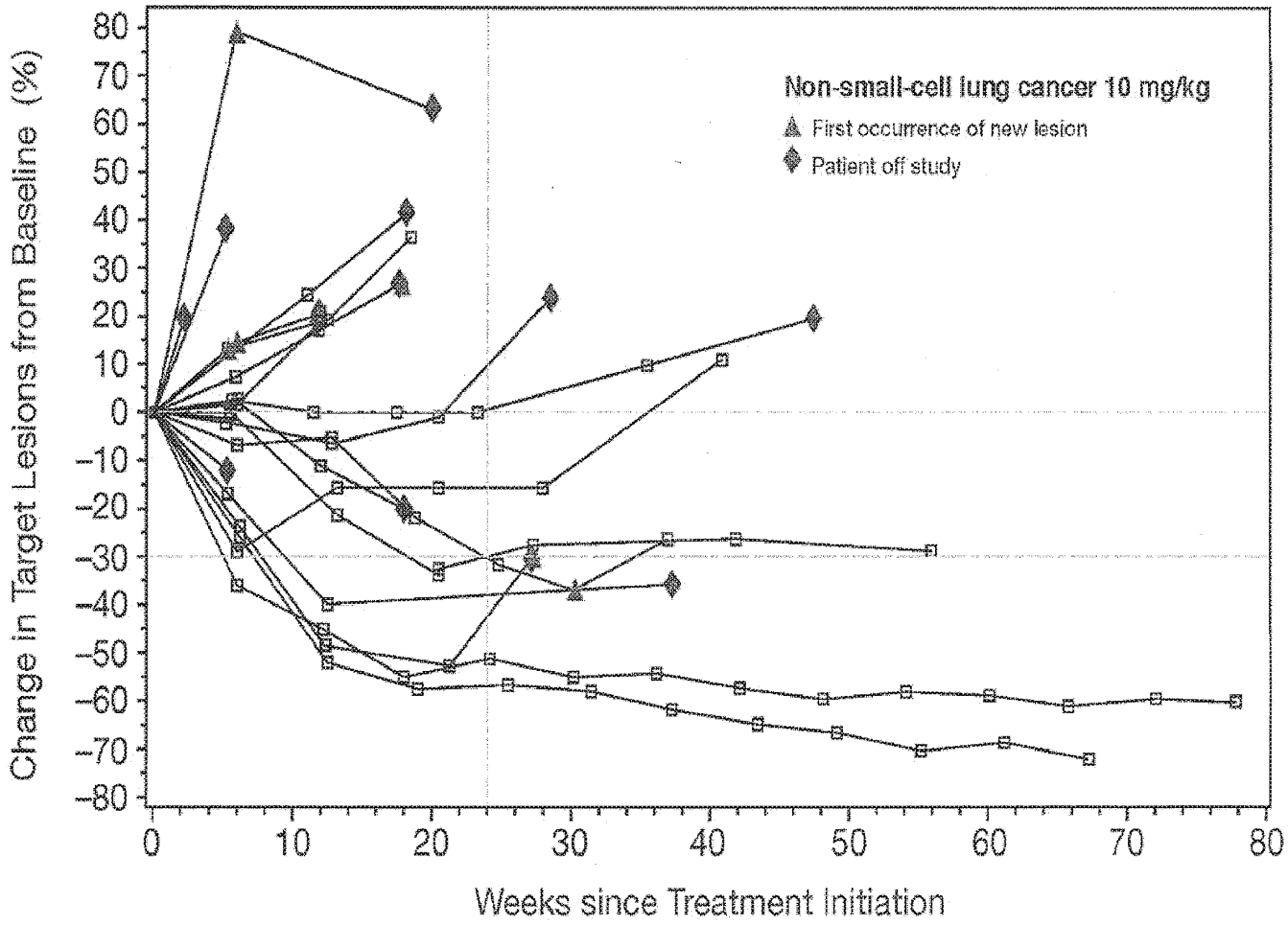
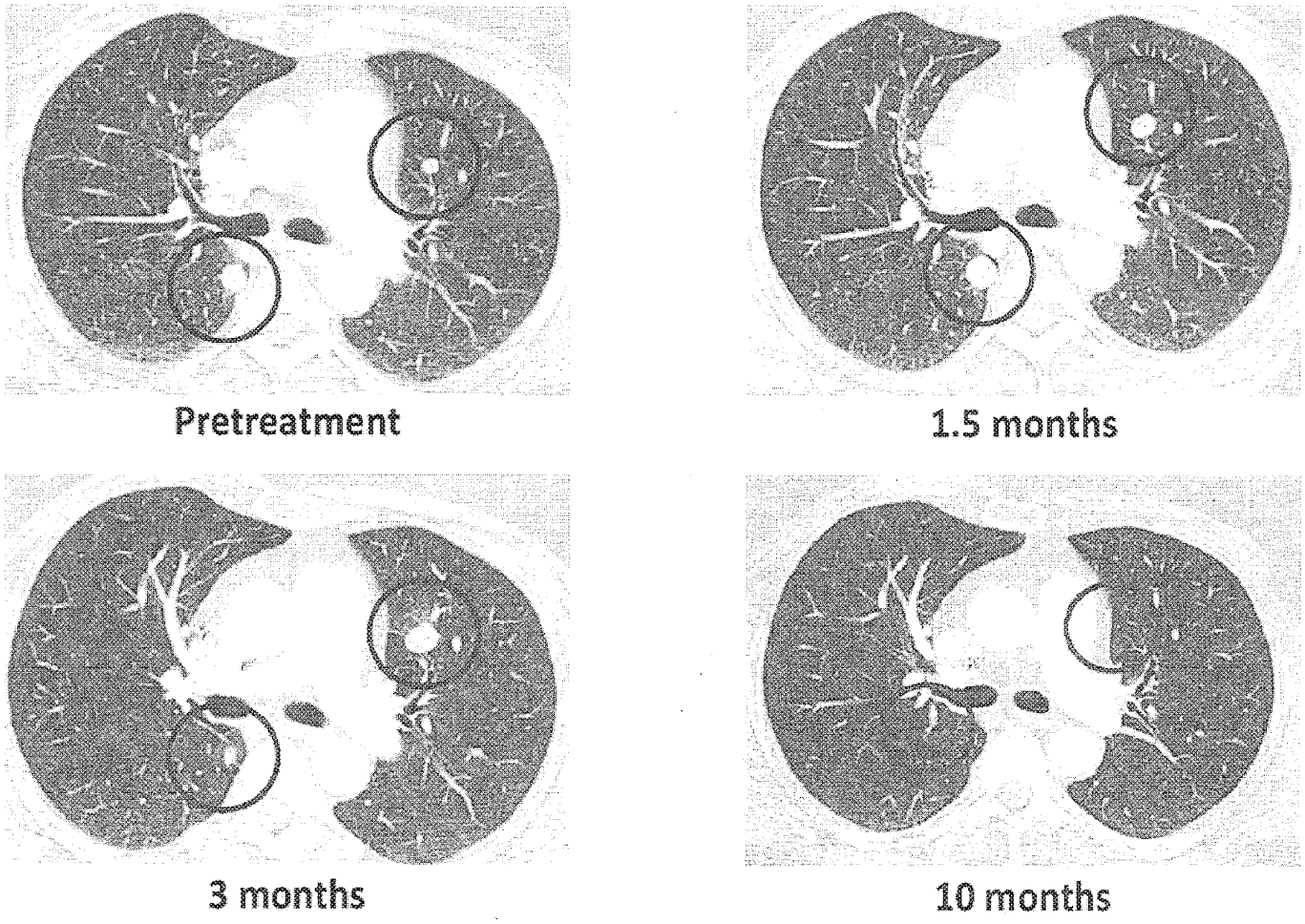

Non-small-cell lung cancer 10 mg/kg
First occurrence of new lesion
Patient off study
Change in Target Lesions from Baseline (%)
80
70
60
50
40
30
20
10
0
−10
−20
−30
−40
−50
−60
−70
−80
0
10
20
30
40
50
60
70
80
Weeks since Treatment Initiation

FIG. 11



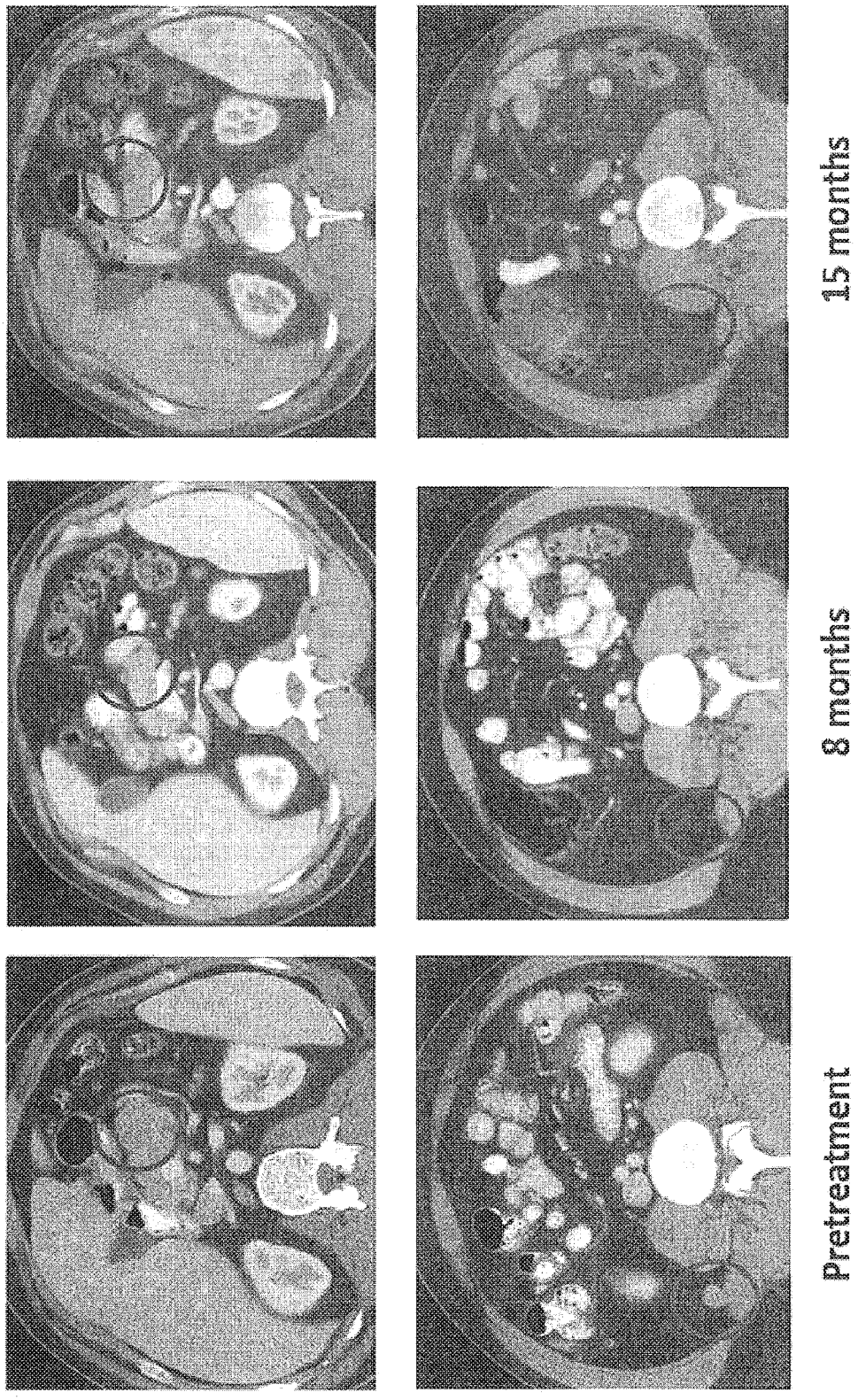
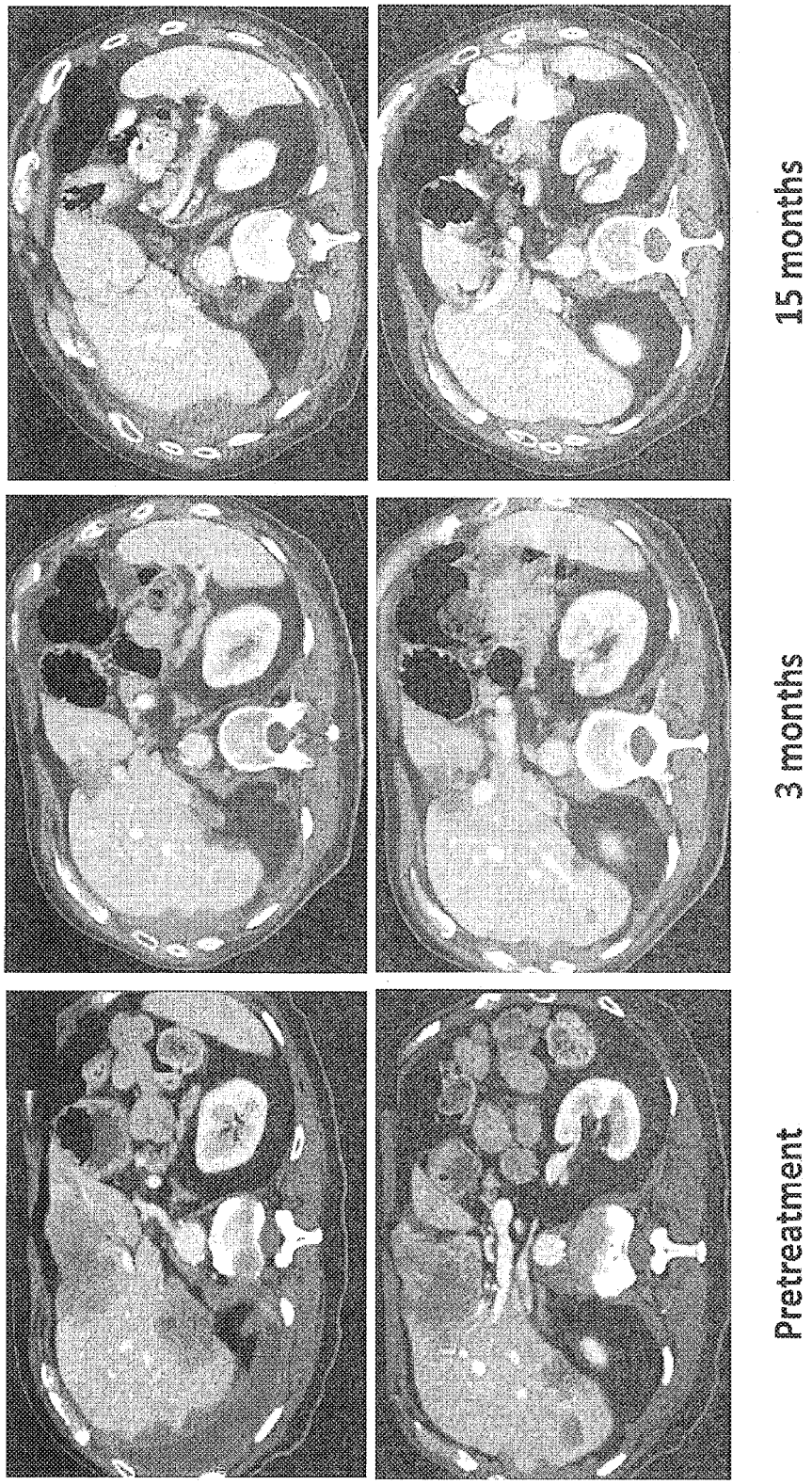


FIG. 12

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FIG. 13



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Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
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NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	To Be Assigned
Filing Date	Herewith
First Named Inventor	John P. COGSWELL
Title	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING
Art Unit	To Be Assigned
Examiner Name	To Be Assigned
Attorney Docket Number	3338.0630006/ELE/C-K

SIGNATURE of Applicant or Patent Practitioner

Signature	/Ji-Eun Kim/	Date (Optional)	June 12, 2018
Name	Ji-Eun Kim	Registration Number	68,504
Title (if Applicant is a juristic entity)	Attorney for Applicant		
Applicant Name (if Applicant is a juristic entity)	Bristol-Myers Squibb Company		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

[X] *Total of one (1) forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: PA..
Document Description: Power of Attorney

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Approved for use through 11/30/2014. OMB 0651-0051
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

[X] I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 115018

OR

[ ] I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

[X] The address associated with the above-mentioned Customer Number

OR

[ ] The address associated with Customer Number: 115018

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

BRISTOL-MYERS SQUIBB COMPANY

[ ] Inventor or Joint Inventor (title not required below)

[ ] Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

[X] Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

[ ] Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	July 31, 2015
Name	Paul D. Golian		
Title	Vice President & Assistant General Counsel, Bristol-Myers Squibb Company		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

[X] Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: COGSWELL *et al.*	Confirmation No.: To Be Assigned
Applicant: Bristol-Myers Squibb Company	Art Unit: To Be Assigned
Application No.: To Be Assigned	Examiner: To Be Assigned
(*Continuation of Appl. No. 14/950,748; Filed: November 24, 2015*)	Atty. Docket: 3338.0630006/ELE/C-K
Filed: Herewith	

Title: **CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING**

Preliminary Amendment Under 37 C.F.R. § 1.115

Mail Stop Amendment

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

In advance of prosecution, Applicant submits the following amendments and remarks.

Amendments to the Specification begin on page 2 of this paper.

Remarks and Arguments begin on page 3 of this paper.

It is not believed that extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any additional fees required to continue prosecution or appeal of this application (including issue fee, fees for net addition of claims or forwarding to appeal) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments to the Specification

Please insert the following into the first line of the specification:

REFERENCE TO EARLIER FILED APPLICATIONS

This application is a continuation of U.S. Application No. 14/950,748, filed November 24, 2015, which is a division of U.S. Application No. 13/892,671, filed May 13, 2013 (issued as U.S. Patent No. 9,212,224 on December 15, 2015), which claims the benefit of U.S. Provisional Application No. 61/647,442, filed May 15, 2012, and U.S. Provisional Application No. 61/790,747, filed March 15, 2013, all of which are incorporated herein by reference in their entireties.

REFERENCE TO SEQUENCE LISTING SUBMITTED
ELECTRONICALLY VIA EFS-WEB

The content of the electronically submitted sequence listing (Name: 3338_0630006_SequenceListing_ST25.txt, Size: 37,922 bytes; and Date of Creation: June 12, 2018) is incorporated herein by reference in its entirety.

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Remarks

The current specification has been amended to add a Reference to Earlier Filed Applications section and a Reference to Sequence Listing Submitted Electronically Via EFS-Web section.

Applicant submits an ASCII text file of the Sequence Listing in lieu of a Computer Readable Form (CRF) of the Sequence Listing. According to Federal Register, vol. 74, no. 153, pages 40163-40165 (Aug. 11, 2009), "[s]equence listings that are submitted online through EFS-Web in the proper text format do not require a separate CRF copy or the associated statement." Therefore, Applicant does not submit a separate CRF copy of the Sequence Listing or a Statement that the paper copy of the Sequence Listing is identical to the CRF copy of the Sequence Listing.

Further, the Sequence Listing text file submitted herewith is identical to the text file originally-submitted in U.S. Application No. 14/950,748, with changes made only to reflect the updated application bibliographic data and the file name.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

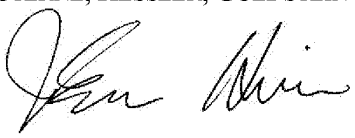
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Conclusion

Prompt and favorable consideration of this Preliminary Amendment is respectfully requested. Applicant believes the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Ji-Eun Kim
Attorney for Applicant
Registration No. 68,504

Date: June 12, 2018

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

9451404_1

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CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING

Throughout this application, various publications are referenced in parentheses by author name and date, or by Patent No. or Patent Publication No. Full citations for these publications may be found at the end of the specification immediately preceding the claims. The disclosures of these publications are hereby incorporated in their entireties by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein. However, the citation of a reference herein should not be construed as an acknowledgement that such reference is prior art to the present invention.

FIELD OF THE INVENTION

This invention relates to methods for immunotherapy of a cancer patient comprising administering to the patient antibodies that disrupt the PD-1/PD-L1 signaling pathway. A biomarker may be used as part of this treatment for identifying suitable patients for immunotherapy and for predicting the efficacy of anti-PD-1 treatment.

BACKGROUND OF THE INVENTION

Human cancers harbor numerous genetic and epigenetic alterations, generating neoantigens potentially recognizable by the immune system (Sjoblom *et al.*, 2006). Although an endogenous immune response to cancer is observed in preclinical models and patients, this response is ineffective, and established cancers are viewed as "self" and tolerated by the immune system. Contributing to this state of tolerance, tumors may exploit several distinct mechanisms to actively suppress the host immune response (Topalian *et al.*, 2011; Mellman *et al.*, 2011). Among these mechanisms, endogenous "immune checkpoints" that normally terminate immune responses to mitigate collateral tissue damage can be co-opted by tumors to evade immune destruction. Intensive efforts to develop specific immune checkpoint pathway inhibitors have begun to provide new immunotherapeutic approaches for treating cancer, including the development of the anti-CTLA-4 antibody (Ab), ipilimumab (YERVOY®), for the treatment of patients with advanced melanoma (Hodi *et al.*, 2010).

Programmed Death-1 (PD-1) is a key immune checkpoint receptor expressed by activated T and B cells and mediates immunosuppression. PD-1 is a member of the CD28 family of receptors, which includes CD28, CTLA-4, ICOS, PD-1, and BTLA. Two cell surface glycoprotein ligands for PD-1 have been identified, Programmed Death Ligand-1 (PD-L1) and Programmed Death Ligand-2 (PD-L2), that are expressed on antigen-

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presenting cells as well as many human cancers and have been shown to downregulate T cell activation and cytokine secretion upon binding to PD-1 (Freeman *et al.*, 2000; Latchman *et al.*, 2001). Unlike CTLA-4, PD-1 primarily functions in peripheral tissues where activated T-cells may encounter the immunosuppressive PD-L1 (B7-H1) and PD-L2 (B7-DC) ligands expressed by tumor and/or stromal cells (Flies *et al.*, 2011; Topalian *et al.*, 2012a). Inhibition of the PD-1/PD-L1 interaction mediates potent antitumor activity in preclinical models (U.S. Patent Nos. 8,008,449 and 7,943,743), and the use of Ab inhibitors of the PD-1/PD-L1 interaction for treating cancer has entered clinical trials (Brahmer *et al.*, 2010; Flies *et al.*, 2011; Topalian *et al.*, 2012b; Brahmer *et al.*, 2012).

The promise of the emerging field of personalized medicine is that advances in pharmacogenomics will increasing be used to tailor therapeutics to defined sub-populations, and ultimately, individual patients in order to enhance efficacy and minimize adverse effects. Recent successes include, for example, the development of imatinib mesylate (GLEEVEC®), a protein tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase, to treat Philadelphia chromosome-positive chronic myelogenous leukemia (CML); crizotinib (XALKORI®) to treat the 5% of patients with late-stage non-small cell lung cancers who express a mutant anaplastic lymphoma kinase (ALK) gene; and vemurafenib (ZELBORAF®), an inhibitor of mutated B-RAF protein (V600E-BRAF) which is expressed in around half of melanoma tumors. However, unlike the clinical development of small molecule agents that target discrete activating mutations found in select cancer populations, a particular challenge in cancer immunotherapy has been the identification of mechanism-based predictive biomarkers to enable patient selection and guide on-treatment management. Advances in validating PD-L1 expression as a biomarker for screening patients for anti-PD-1 immunotherapy are described herein.

SUMMARY OF THE INVENTION

The present disclosure provides a method for immunotherapy of a subject afflicted with cancer, which method comprises administering to the subject a composition comprising a therapeutically effective amount of an agent that reduces or suppresses signaling from an inhibitory immunoregulator. In preferred embodiments, the agent is an Ab. In other preferred embodiments, the inhibitory immunoregulator is a component of the PD-1/PD-L1 signaling pathway. In further preferred embodiments, the Ab disrupts the interaction between PD-1 and PD-L1. In certain embodiments, the Ab is an anti-PD-1 Ab of the invention or an anti-PD-L1 Ab of the invention. In preferred embodiments, the

anti-PD-1 Ab of the invention is nivolumab (BMS-936558) and the anti-PD-L1 Ab of the invention is BMS-936559. In certain embodiments, the subject has been pre-treated for the cancer. In other embodiments, the cancer is an advanced, metastatic and/or refractory cancer. In preferred embodiments, the administration of the antibody or antigen-binding portion to the subject thereof induces a durable clinical response in the subject.

This disclosure also provides a method for immunotherapy of a subject afflicted with cancer, which method comprises: (a) selecting a subject that is a suitable candidate for immunotherapy, the selecting comprising (i) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells, (ii) assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface, and (iii) selecting the subject as a suitable candidate based on an assessment that the proportion of cells in the test tissue sample that express PD-L1 on the cell surface exceeds a predetermined threshold level; and (b) administering a composition comprising a therapeutically effective amount of an anti-PD-1 Ab to the selected subject.

The disclosure further provides a method for treatment of a subject afflicted with cancer, which method comprises: (a) selecting a subject that is not suitable for anti-PD-1 Ab immunotherapy, the selecting comprising (i) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells; (ii) assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface; and (iii) selecting the subject as not suitable for anti-PD-1 Ab immunotherapy based on an assessment that the proportion of cells in the test tissue sample that express PD-L1 on the cell surface is less than a predetermined threshold level; and (b) administering a standard-of-care therapeutic other than an anti-PD-1 Ab to the selected subject.

In addition, the disclosure provides a method for selecting a cancer patient for immunotherapy with an anti-PD-1 Ab, which method comprises: (a) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells; (b) assaying the test tissue sample to determine the proportion of cells therein that express PD-L1 on the cell surface; (c) comparing the proportion of cells that express PD-L1 on the cell surface with a predetermined threshold proportion; and (d) selecting the patient for immunotherapy based on an assessment that PD-L1 is expressed in cells of the test tissue sample.

This disclosure further provides a method for predicting the therapeutic effectiveness of an anti-PD-1 Ab for treating a cancer patient, which method comprises: (a) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells; (b) assaying the test tissue sample to determine the proportion of cells therein that express PD-L1 on the cell surface; (c) comparing the proportion of cells that express PD-L1 on the cell surface with a predetermined threshold value; and (d) predicting the therapeutic effectiveness of the anti-PD-1 Ab, wherein if the proportion of cells that express PD-L1 on the cell surface exceeds the threshold proportion the Ab is predicted to be effective in treating the patient, and wherein if the proportion of cells that express PD-L1 on the cell surface is below the threshold proportion the Ab is predicted to not be effective in treating the patient.

The present disclosure also provides a method for determining an immunotherapeutic regimen comprising an anti-PD-1 Ab for treating a cancer patient, which method comprises: (a) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells; (b) assaying the test tissue sample to determine the proportion of cells therein that express PD-L1 on the cell surface; (c) comparing the proportion of cells that express PD-L1 on the cell surface with a predetermined threshold proportion; and (d) determining an immunotherapeutic regimen comprising an anti-PD-1 Ab based on the determination that the proportion of cells that express PD-L1 on the cell surface exceeds the predetermined threshold proportion.

In certain embodiments of the methods described herein, the test tissue sample is a formalin-fixed and paraffin-embedded (FFPE) sample. In certain other embodiments, assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface is achieved by immunohistochemical (IHC) staining of the FFPE sample. In preferred embodiments, the mAb 28-8 is used in an automated IHC assay to bind to PD-L1 on the surface of cells in the test tissue sample. In preferred embodiments of any of the methods disclosed herein, the cancer is melanoma (MEL), renal cell carcinoma (RCC), squamous non-small cell lung cancer (NSCLC), non-squamous NSCLC, colorectal cancer (CRC), castration-resistant prostate cancer (CRPC), hepatocellular carcinoma (HCC), squamous cell carcinoma of the head and neck, carcinomas of the esophagus, ovary, gastrointestinal tract and breast, or a hematologic malignancy such as multiple myeloma,

B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma/primary mediastinal B-cell lymphoma, and chronic myelogenous leukemia.

This invention additionally provides a mAb or antigen-binding portion thereof that binds specifically to a cell surface-expressed human PD-L1 antigen in a FFPE tissue sample. In preferred embodiments, the mAb or antigen-binding portion thereof does not bind to a cytoplasmic PD-L1 antigen in the FFPE tissue sample. In other preferred embodiments, the monoclonal Ab (mAb) is the rabbit mAb designated 28-8, 28-1, 28-12, 29-8 or 20-12.

Other features and advantages of the instant invention will be apparent from the following detailed description and examples which should not be construed as limiting. The contents of all cited references, including scientific articles, newspaper reports, GENBANK® entries, patents and patent applications cited throughout this application are expressly incorporated herein by reference.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1A-1C. Cross-competition between 5C4 and other HuMab anti-PD-1 mAbs for binding to hPD-1 expressed on CHO cells. A, the 5C4 Fab fragment substantially blocked the binding of mAbs 5C4 itself, as well as the binding of 2D3 and 7D3; B, the 5C4 Fab fragment substantially blocked the binding of mAb 4H1; C, the 5C4 mAb substantially blocked the binding of mAb 17D8.

Figures 2A-2F. Cross-competition of FITC-conjugated human anti-hPD-L1 mAbs for binding to hPD-L1 expressed on CHO cells. A, Binding of labeled 10H10 was partially blocked by 10A5, 11E6 and 13G4 and was significantly blocked by itself; B, Binding of labeled 3G10 was significantly blocked by each of the tested anti-PD-L1 Abs except 10H10; C, Binding of labeled 10A5 was significantly blocked by each of the tested anti-PD-L1 Abs except 10H10; D, Binding of labeled 11E6 was significantly blocked by each of the tested anti-PD-L1 Abs except 10H10; and E, Binding of labeled 12A4 was significantly blocked by each of the tested anti-PD-L1 Abs except 10H10; and F, Binding of labeled 13G4 was significantly blocked by each of the tested anti-PD-L1 Abs except 10H10.

Figure 3. Cross-competitive inhibition of binding of biotinylated mAb 12A4 to ES-2 cells by human anti-hPD-L1 mAbs. Fluorescence of bound biotin-12A4 is plotted against the concentration of unlabeled hPD-L1 HuMabs.

Figure 4. Spider plot showing activity of anti-PD-1 mAb in patients with treatment-refractory melanoma (MEL). A representative plot of changes in tumor burden over time demonstrates the time course of change in the sum of the longest diameters of target lesions, compared with baseline, in 27 MEL patients treated with 5C4 at a dose of 1.0 mg/kg. In the majority of patients who achieved an objective response (OR), responses were durable and evident by the end of cycle 3 (6 months) of treatment (vertical dashed line). Tumor regressions followed conventional as well as "immune-related" patterns of response, such as prolonged reduction in tumor burden in the presence of new lesions.

Figure 5. Activity of anti-PD-1 mAb in patient with metastatic RCC. Partial regression of metastatic RCC in a 57-year-old patient treated with 5C4 at 1 mg/kg is illustrated. This patient had previously undergone radical surgery and had developed progressive disease after receiving sunitinib, temsirolimus, sorafenib, and pazopanib. Arrows show regression of recurrent tumor in the operative field.

Figure 6. Activity of anti-PD-1 mAb in patient with metastatic MEL. A complete response of metastatic MEL is illustrated in a 62-year-old patient treated with 5C4 at 3 mg/kg, associated with vitiligo. (i) Pretreatment CT scan, inguinal lymph node metastasis (arrow); (ii) after 13 months of treatment. Numerous metastases in the subcutaneous tissue and retroperitoneum also regressed completely (not shown). Vitiligo developed after 6 months of treatment; photos taken at 9 months under visible light (iii) and ultraviolet light (iv). Skin biopsies with immunohistochemistry for microphthalmia-associated transcription factor (MITF) show melanocytes (arrows) at the epidermal-dermal junction in normal skin (v), and scarce (vi) or absent (vii) melanocytes in skin partially or fully affected by vitiligo.

Figure 7. Activity of anti-PD-1 mAb in patient with metastatic NSCLC. A partial response is illustrated in a patient with metastatic NSCLC (nonsquamous histology) treated with 5C4 at 10 mg/kg. Arrows show initial progression in pulmonary lesions followed by regression ("immune-related" pattern of response).

Figures 8Aand 8B. Correlation between tumor PD-L1 expression and anti-PD-1 clinical response. Pretreatment tumor cell surface expression of PD-L1, as determined by IHC on formalin-fixed paraffin-embedded specimens, correlates with OR to PD-1 blockade. Forty-two subjects with advanced cancers including melanoma, non-small cell lung cancer, colorectal cancer, renal cell cancer, and castration-resistant prostate cancer (n=18, 10, 7, 5, and 2, respectively) were studied. A, There was a significant correlation

of tumor cell surface PD-L1 expression with objective clinical response. No patients with PD-L1 negative tumors experienced an OR. B, Examples of IHC analysis with the anti-PD-L1 mAb 5H1 are shown in a melanoma lymph node metastasis (top), a renal cell cancer nephrectomy specimen (middle), and a lung adenocarcinoma brain metastasis (bottom). All 400X original magnification. Arrows indicate one of many tumor cells in each specimen with surface membrane staining for PD-L1. Asterisk indicates a normal glomerulus in the nephrectomy specimen, which is negative for PD-L1 staining.

Figure 9. Graphical comparison of the binding of mAbs 28-8 and 5H1 to PD-L1 antigen in tumor tissues by histoscore analysis. The rabbit mAb 28-8 showed higher histoscores in 7 out of 10 samples tested.

Figures 10A-10D. Spider plot showing activity of anti-PD-L1 mAb in patients with treatment-refractory MEL and NSCLC. Representative plots demonstrate the time course of target lesion tumor burden over time in patients with MEL treated with BMS-936559 at doses of 1 (A), 3 (B), 10 mg/kg (C) and in patients with NSCLC treated at 10 mg/kg (D). In the majority of patients who achieved ORs, responses were durable and were evident by the end of cycle 2 (3 months) of treatment, irrespective of dose or tumor type. Tumor regressions followed conventional as well as "immune-related" patterns of response.

Figure 11. Complete response in a patient with melanoma treated with BMS-936559 at 3 mg/kg. Circles indicate an initial increase in the size of pulmonary nodules at 6 weeks and 3 months followed by complete regression at 10 months ("immune-related" pattern of response).

Figure 12. Complete response in a patient with melanoma treated with BMS-936559 at 1 mg/kg. This patient developed an isolated brain metastasis 3 months after initiation of treatment that was successfully treated with stereotactic radiosurgery. A partial response in abdominal disease (circled) was noted at 8 months, with no evidence of disease at 15 months.

Figure 13. Partial response in a patient with NSCLC (non-squamous histology) treated with BMS-936559 at 10 mg/kg. Note the response in disease in right lung pleura and liver.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods for immunotherapy of a subject afflicted with diseases such as cancer or an infectious disease, which methods comprise

administering to the subject a composition comprising a therapeutically effective amount of a compound or agent that potentiates an endogenous immune response, either stimulating the activation of the endogenous response or inhibiting the suppression of the endogenous response. More specifically, the disclosure provides methods for potentiating an endogenous immune response in a subject afflicted with cancer so as to thereby treat the patient, which method comprises administering to the subject a therapeutically effective amount of an Ab or an antigen-binding portion thereof that inhibits signaling from an inhibitory immunoregulator. In certain embodiments, the inhibitory immunoregulator is a component of the PD-1/PD-L1 signaling pathway. Accordingly, certain embodiments of the invention provide methods for immunotherapy of a subject afflicted with cancer, which methods comprise administering to the subject a therapeutically effective amount of an Ab or an antigen-binding portion thereof that disrupts the interaction between the PD-1 receptor and its ligand, PD-L1. In certain preferred embodiments, the Ab or antigen-binding portion thereof binds specifically to PD-1. In other preferred embodiments, the Ab or antigen-binding portion thereof binds specifically to PD-L1. In certain other embodiments, the subject is selected as suitable for immunotherapy in a method comprising measuring the surface expression of PD-L1 in a test tissue sample obtained from a patient with cancer of the tissue, for example, determining the proportion of cells in the test tissue sample that express PD-L1 on the cell surface, and selecting the patient for immunotherapy based on an assessment that PD-L1 is expressed on the surface of cells in the test tissue sample.

Terms

In order that the present disclosure may be more readily understood, certain terms are first defined. As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application.

"Administering" refers to the physical introduction of a composition comprising a therapeutic agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Preferred routes of administration for Abs of the invention include intravenous, intramuscular, subcutaneous, intraperitoneal, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation,

intravenous, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as *in vivo* electroporation. Alternatively, an Ab of the invention can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

An "adverse event" (AE) as used herein is any unfavorable and generally unintended or undesirable sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a medical treatment. For example, an adverse event may be associated with activation of the immune system or expansion of immune system cells (*e.g.*, T cells) in response to a treatment. A medical treatment may have one or more associated AEs and each AE may have the same or different level of severity. Reference to methods capable of "altering adverse events" means a treatment regime that decreases the incidence and/or severity of one or more AEs associated with the use of a different treatment regime.

An "antibody" (Ab) shall include, without limitation, a glycoprotein immunoglobulin which binds specifically to an antigen and comprises at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds, or an antigen-binding portion thereof. Each H chain comprises a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. The heavy chain constant region comprises three constant domains, C_{H1}, C_{H2} and C_{H3}. Each light chain comprises a light chain variable region (abbreviated herein as V_L) and a light chain constant region. The light chain constant region is comprises one constant domain, C_L. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L comprises three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the Abs may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system.

Antibodies typically bind specifically to their cognate antigen with high affinity, reflected by a dissociation constant (K_D) of 10^{-5} to 10^{-11} M^{-1} or less. Any K_D greater than about 10^{-4} M^{-1} is generally considered to indicate nonspecific binding. As used herein, an Ab that "binds specifically" to an antigen refers to an Ab that binds to the antigen and substantially identical antigens with high affinity, which means having a K_D of 10^{-7} M or less, preferably 10^{-8} M or less, even more preferably 5 x 10^{-9} M or less, and most preferably between 10^{-8} M and 10^{-10} M or less, but does not bind with high affinity to unrelated antigens. An antigen is "substantially identical" to a given antigen if it exhibits a high degree of sequence identity to the given antigen, for example, if it exhibits at least 80%, at least 90%, preferably at least 95%, more preferably at least 97%, or even more preferably at least 99% sequence identity to the sequence of the given antigen. By way of example, an Ab that binds specifically to human PD-1 may also have cross-reactivity with PD-1 antigens from certain primate species but may not cross-react with PD-1 antigens from certain rodent species or with an antigen other than PD-1, *e.g.*, a human PD-L1 antigen.

An immunoglobulin may derive from any of the commonly known isotypes, including but not limited to IgA, secretory IgA, IgG and IgM. IgG subclasses are also well known to those in the art and include but are not limited to human IgG1, IgG2, IgG3 and IgG4. "Isotype" refers to the Ab class or subclass (*e.g.*, IgM or IgG1) that is encoded by the heavy chain constant region genes. The term "antibody" includes, by way of example, both naturally occurring and non-naturally occurring Abs; monoclonal and polyclonal Abs; chimeric and humanized Abs; human or nonhuman Abs; wholly synthetic Abs; and single chain Abs. A nonhuman Ab may be humanized by recombinant methods to reduce its immunogenicity in man. Where not expressly stated, and unless the context indicates otherwise, the term "antibody" also includes an antigen-binding fragment or an antigen-binding portion of any of the aforementioned immunoglobulins, and includes a monovalent and a divalent fragment or portion, and a single chain Ab.

An "isolated antibody" refers to an Ab that is substantially free of other Abs having different antigenic specificities (*e.g.*, an isolated Ab that binds specifically to PD-1 is substantially free of Abs that bind specifically to antigens other than PD-1). An isolated Ab that binds specifically to PD-1 may, however, have cross-reactivity to other antigens, such as PD-1 molecules from different species. Moreover, an isolated Ab may be substantially free of other cellular material and/or chemicals. By comparison, an "isolated" nucleic acid refers to a nucleic acid composition of matter that is markedly

different, *i.e.*, has a distinctive chemical identity, nature and utility, from nucleic acids as they exist in nature. For example, an isolated DNA, unlike native DNA, is a free-standing portion of a native DNA and not an integral part of a larger structural complex, the chromosome, found in nature. Further, an isolated DNA, unlike native genomic DNA, can typically be used in applications or methods for which native genomic DNA is unsuited, *e.g.*, as a PCR primer or a hybridization probe for, among other things, measuring gene expression and detecting biomarker genes or mutations for diagnosing disease or assessing the efficacy of a therapeutic. An isolated nucleic acid may be purified so as to be substantially free of other cellular components or other contaminants, *e.g.*, other cellular nucleic acids or proteins, using standard techniques well known in the art. Examples of isolated nucleic acids include fragments of genomic DNA, PCR-amplified DNA, cDNA and RNA.

The term "monoclonal antibody" ("mAb") refers to a preparation of Ab molecules of single molecular composition, *i.e.*, Ab molecules whose primary sequences are essentially identical, and which exhibits a single binding specificity and affinity for a particular epitope. A mAb is an example of an isolated Ab. MAbs may be produced by hybridoma, recombinant, transgenic or other techniques known to those skilled in the art.

A "human" antibody (HuMAb) refers to an Ab having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the Ab contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The human Abs of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). However, the term "human antibody," as used herein, is not intended to include Abs in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. The terms "human" Abs and "fully human" Abs and are used synonymously.

A "humanized" antibody refers to an Ab in which some, most or all of the amino acids outside the CDR domains of a non-human Ab are replaced with corresponding amino acids derived from human immunoglobulins. In one embodiment of a humanized form of an Ab, some, most or all of the amino acids outside the CDR domains have been replaced with amino acids from human immunoglobulins, whereas some, most or all amino acids within one or more CDR regions are unchanged. Small additions, deletions,

insertions, substitutions or modifications of amino acids are permissible as long as they do not abrogate the ability of the Ab to bind to a particular antigen. A "humanized" Ab retains an antigenic specificity similar to that of the original Ab.

A "chimeric antibody" refers to an Ab in which the variable regions are derived from one species and the constant regions are derived from another species, such as an Ab in which the variable regions are derived from a mouse Ab and the constant regions are derived from a human Ab.

An "antigen-binding portion" of an Ab (also called an "antigen-binding fragment") refers to one or more fragments of an Ab that retain the ability to bind specifically to the antigen bound by the whole Ab.

A "cancer" refers a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth divide and grow results in the formation of malignant tumors that invade neighboring tissues and may also metastasize to distant parts of the body through the lymphatic system or bloodstream.

An "immune response" refers to the action of a cell of the immune system (for example, T lymphocytes, B lymphocytes, natural killer (NK) cells, macrophages, eosinophils, mast cells, dendritic cells and neutrophils) and soluble macromolecules produced by any of these cells or the liver (including Abs, cytokines, and complement) that results in selective targeting, binding to, damage to, destruction of, and/or elimination from a vertebrate's body of invading pathogens, cells or tissues infected with pathogens, cancerous or other abnormal cells, or, in cases of autoimmunity or pathological inflammation, normal human cells or tissues.

An "immunoregulator" refers to a substance, an agent, a signaling pathway or a component thereof that regulates an immune response. "Regulating," "modifying" or "modulating" an immune response refers to any alteration in a cell of the immune system or in the activity of such cell. Such regulation includes stimulation or suppression of the immune system which may be manifested by an increase or decrease in the number of various cell types, an increase or decrease in the activity of these cells, or any other changes which can occur within the immune system. Both inhibitory and stimulatory immunoregulators have been identified, some of which may have enhanced function in the cancer microenvironment.

The term "immunotherapy" refers to the treatment of a subject afflicted with, or at risk of contracting or suffering a recurrence of, a disease by a method comprising

inducing, enhancing, suppressing or otherwise modifying an immune response. "Treatment" or "therapy" of a subject refers to any type of intervention or process performed on, or the administration of an active agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, slowing down or preventing the onset, progression, development, severity or recurrence of a symptom, complication, condition or biochemical indicia associated with a disease.

"Potentiating an endogenous immune response" means increasing the effectiveness or potency of an existing immune response in a subject. This increase in effectiveness and potency may be achieved, for example, by overcoming mechanisms that suppress the endogenous host immune response or by stimulating mechanisms that enhance the endogenous host immune response.

A "predetermined threshold value," relating to cell surface PD-L1 expression, refers to the proportion of cells in a test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells above which the sample is scored as being positive for cell surface PD-L1 expression. For cell surface expression assayed by IHC with the mAb 28-8, the predetermined threshold value for cells expressing PD-L1 on the cell surface ranges from at least about 0.01% to at least about 20% of the total number of cells. In preferred embodiments, the predetermined threshold value for cells expressing PD-L1 on the cell surface ranges from at least about 0.1% to at least about 10% of the total number of cells. More preferably, the predetermined threshold value is at least about 5%. Even more preferably, the predetermined threshold value is at least about 1%.

The "Programmed Death-1 (PD-1)" receptor refers to an immunoinhibitory receptor belonging to the CD28 family. PD-1 is expressed predominantly on previously activated T cells *in vivo*, and binds to two ligands, PD-L1 and PD-L2. The term "PD-1" as used herein includes human PD-1 (hPD-1), variants, isoforms, and species homologs of hPD-1, and analogs having at least one common epitope with hPD-1. The complete hPD-1 sequence can be found under GENBANK® Accession No. U64863.

"Programmed Death Ligand-1 (PD-L1)" is one of two cell surface glycoprotein ligands for PD-1 (the other being PD-L2) that downregulate T cell activation and cytokine secretion upon binding to PD-1. The term "PD-L1" as used herein includes human PD-L1 (hPD-L1), variants, isoforms, and species homologs of hPD-L1, and analogs having at least one common epitope with hPD-L1. The complete hPD-L1 sequence can be found under GENBANK® Accession No. Q9NZQ7.

A "signal transduction pathway" or "signaling pathway" refers to the biochemical relationship between a variety of signal transduction molecules that play a role in the transmission of a signal from one portion of a cell to another portion of the cell. A "cell surface receptor" includes, for example, molecules and complexes of molecules that are located on the surface of a cell and are capable of receiving a signal and transmitting such a signal across the plasma membrane of a cell. An example of a cell surface receptor of the present invention is the PD-1 receptor, which is located on the surface of activated B cells, activated T cells and myeloid cells, and transmits a signal that results in a decrease in tumor-infiltrating lymphocytes and a decrease in T cell proliferation. An "inhibitor" of signaling refers to a compound or agent that antagonizes or reduces the initiation, reception or transmission of a signal, be that signal stimulatory or inhibitory, by any component of a signaling pathway such as a receptor or its ligand.

A "subject" includes any human or nonhuman animal. The term "nonhuman animal" includes, but is not limited to, vertebrates such as nonhuman primates, sheep, dogs, cats, rabbits, ferrets, rodents such as mice, rats and guinea pigs, avian species such as chickens, amphibians, and reptiles. In preferred embodiments, the subject is a mammal such as a nonhuman primate, sheep, dog, cat, rabbit, ferret or rodent. In more preferred embodiments, the subject is a human. The terms, "subject," "patient" and "individual" are used interchangeably herein.

A "therapeutically effective amount" or "therapeutically effective dosage" of a drug or therapeutic agent, such as an Ab of the invention, is any amount of the drug that, when used alone or in combination with another therapeutic agent, protects a subject against the onset of a disease or promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. The ability of a therapeutic agent to promote disease regression can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.

By way of example, an anti-cancer agent promotes cancer regression in a subject. In preferred embodiments, a therapeutically effective amount of the drug promotes cancer regression to the point of eliminating the cancer. "Promoting cancer regression" means that administering an effective amount of the drug, alone or in combination with an anti-neoplastic agent, results in a reduction in tumor growth or size, necrosis of the tumor, a

decrease in severity of at least one disease symptom, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. In addition, the terms "effective" and "effectiveness" with regard to a treatment includes both pharmacological effectiveness and physiological safety. Pharmacological effectiveness refers to the ability of the drug to promote cancer regression in the patient. Physiological safety refers to the level of toxicity, or other adverse physiological effects at the cellular, organ and/or organism level (adverse effects) resulting from administration of the drug.

By way of example for the treatment of tumors, a therapeutically effective amount of the drug preferably inhibits cell growth or tumor growth by at least about 20%, more preferably by at least about 40%, even more preferably by at least about 60%, and still more preferably by at least about 80% relative to untreated subjects. In other preferred embodiments of the invention, tumor regression may be observed and continue for a period of at least about 20 days, more preferably at least about 40 days, or even more preferably at least about 60 days. Notwithstanding these ultimate measurements of therapeutic effectiveness, evaluation of immunotherapeutic drugs must also make allowance for "immune-related" response patterns.

An "immune-related" response pattern refers to a clinical response pattern often observed in cancer patients treated with immunotherapeutic agents that produce antitumor effects by inducing cancer-specific immune responses or by modifying native immune processes. This response pattern is characterized by a beneficial therapeutic effect that follows an initial increase in tumor burden or the appearance of new lesions, which in the evaluation of traditional chemotherapeutic agents would be classified as disease progression and would be synonymous with drug failure. Accordingly, proper evaluation of immunotherapeutic agents may require long-term monitoring of the effects of these agents on the target disease.

A therapeutically effective amount of a drug includes a "prophylactically effective amount," which is any amount of the drug that, when administered alone or in combination with an anti-neoplastic agent to a subject at risk of developing a cancer (*e.g.*, a subject having a pre-malignant condition) or of suffering a recurrence of cancer, inhibits the development or recurrence of the cancer. In preferred embodiments, the prophylactically effective amount prevents the development or recurrence of the cancer entirely. "Inhibiting" the development or recurrence of a cancer means either lessening

the likelihood of the cancer's development or recurrence, or preventing the development or recurrence of the cancer entirely.

A "tumor-infiltrating inflammatory cell" is any type of cell that typically participates in an inflammatory response in a subject and which infiltrates tumor tissue. Such cells include tumor-infiltrating lymphocytes (TILs), macrophages, monocytes, eosinophils, histiocytes and dendritic cells.

The use of the alternative (*e.g.*, "or") should be understood to mean either one, both, or any combination thereof of the alternatives. As used herein, the indefinite articles "a" or "an" should be understood to refer to "one or more" of any recited or enumerated component.

The terms "about" or "comprising essentially of" refer to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, *i.e.*, the limitations of the measurement system. For example, "about" or "comprising essentially of" can mean within 1 or more than 1 standard deviation per the practice in the art. Alternatively, "about" or "comprising essentially of" can mean a range of up to 20%. Furthermore, particularly with respect to biological systems or processes, the terms can mean up to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the application and claims, unless otherwise stated, the meaning of "about" or "comprising essentially of" should be assumed to be within an acceptable error range for that particular value or composition.

As described herein, any concentration range, percentage range, ratio range or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated.

Various aspects of the invention are described in further detail in the following subsections.

Antibodies of the Invention

Abs of the present invention include a variety of Abs having structural and functional properties described herein, including high-affinity binding to PD-1 or PD-L1, respectively. These Abs may be used, for example, as therapeutic Abs to treat subjects afflicted with disease or as reagents in diagnostic assays to detect their cognate antigens.

Human mAbs (HuMAbs) that bind specifically to PD-1 (*e.g.*, bind to human PD-1 and may cross-react with PD-1 from other species, such as cynomolgus monkey) with high affinity have been disclosed in U.S. Patent No. 8,008,449, and HuMAbs that bind specifically to PD-L1 with high affinity have been disclosed in U.S. Patent No. 7,943,743. The Abs of the invention include, but are not limited to, all of the anti-PD-1 and anti-PD-L1 Abs disclosed in U.S. Patent Nos. 8,008,449 and 7,943,743, respectively. Other anti-PD-1 mAbs have been described in, for example, U.S. Patent Nos. 7,488,802 and 8,168,757, and anti-PD-L1 mAbs have been described in, for example, U.S. Patent Nos. 7,635,757 and 8,217,149, and U.S. Publication No. 2009/0317368. To the extent these anti-PD-1 and anti-PD-L1 mAbs exhibit the structural and functional properties disclosed herein for antibodies of the invention, they too are included as antibodies of the invention.

Anti-PD-1 Antibodies of the Invention

Each of the anti-PD-1 HuMAbs disclosed in U.S. Patent No. 8,008,449 has been demonstrated to exhibit one or more of the following characteristics: (a) binds to human PD-1 with a K_D of 1 x 10^{-7} M or less, as determined by surface plasmon resonance using a BIACORE® biosensor system; (b) does not substantially bind to human CD28, CTLA-4 or ICOS; (c) increases T-cell proliferation in a Mixed Lymphocyte Reaction (MLR) assay; (d) increases interferon-γ production in an MLR assay; (e) increases IL-2 secretion in an MLR assay; (f) binds to human PD-1 and cynomolgus monkey PD-1; (g) inhibits the binding of PD-L1 and/or PD-L2 to PD-1; (h) stimulates antigen-specific memory responses; (i) stimulates Ab responses; and (j) inhibits tumor cell growth *in vivo*. Anti-PD-1 Abs of the present invention include mAbs that bind specifically to human PD-1 and exhibit at least one, preferably at least five, of the preceding characteristics.

U.S. Patent No. 8,008,449 exemplifies seven anti-PD-1 HuMAbs: 17D8, 2D3, 4H1, 5C4 (also referred to herein as nivolumab or BMS-936558), 4A11, 7D3 and 5F4. Isolated DNA molecules encoding the heavy and light chain variable regions of these Abs have been sequenced, from which the amino acid sequences of the variable regions were deduced. The V_H amino acid sequences of 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 and 5F4 are provided herein as SEQ ID NOs. 1, 2, 3, 4, 5, 6 and 7, respectively. The V_L amino acid sequences of 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 and 5F4 are provided herein as SEQ ID NOs. 8, 9, 10, 11, 12, 13 and 14, respectively.

Preferred anti-PD-1 Abs of the present invention include the anti-PD-1 HuMAbs 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 and 5F4. These preferred Abs bind specifically to human PD-1 and comprise: (a) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 1 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 8; (b) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 2 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 9; (c) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 3 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 10; (d) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 4 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 11; (e) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 5 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 12; (f) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 6 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 13; or (g) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 7 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 14.

Given that each of these Abs can bind to PD-1, the V_H and V_L sequences can be "mixed and matched" to create other anti-PD-1 Abs of the invention. PD-1 binding of such "mixed and matched" Abs can be tested using binding assays, *e.g.*, enzyme-linked immunosorbent assays (ELISAs), western blots, radioimmunoassays and BIACORE® analysis that are well known in the art (*see, e.g.*, U.S. Patent No. 8,008,449). Preferably, when V_H and V_L chains are mixed and matched, a V_H sequence from a particular V_H/V_L pairing is replaced with a structurally similar V_H sequence. Likewise, preferably a V_L sequence from a particular V_H/V_L pairing is replaced with a structurally similar V_L sequence. Accordingly, anti-PD-1 Abs of the invention include an isolated mAb or antigen-binding portion thereof comprising: (a) a heavy chain variable region comprising

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an amino acid sequence selected from the group consisting of SEQ ID NOs. 1, 2, 3, 4, 5, 6 and 7, and (b) a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs. 8, 9, 10, 11, 12, 13 and 14, wherein the Ab specifically binds PD-1, preferably human PD-1.

The CDR domains of the above Abs have been delineated using the Kabat system, and these Abs may also be defined by combinations of their 3 heavy chain and 3 light chain CDRs (*see* U.S. Patent No. 8,008,449). Since each of these Abs can bind to PD-1 and antigen-binding specificity is provided primarily by the CDR1, CDR2, and CDR3 regions, the V_H CDR1, CDR2, and CDR3 sequences and V_κ CDR1, CDR2, and CDR3 sequences can be "mixed and matched" (*i.e.*, CDRs from different Abs can be mixed and match, although each Ab must contain a V_H CDR1, CDR2, and CDR3 and a V_κ CDR1, CDR2, and CDR3) to create other anti-PD-1 Abs that also constitute Abs of the invention. PD-1 binding of such "mixed and matched" Abs can be tested using the binding assays described above (*e.g.*, ELISAs, western blots, radioimmunoassays and BIACORE® analysis).

Abs of the invention also include isolated Abs that bind specifically to PD-1 and comprise a heavy chain variable region derived from a particular germline heavy chain immunoglobulin and/or a light chain variable region derived from a particular germline light chain immunoglobulin. Specifically, in certain embodiments, Abs of the invention include isolated Abs comprising: (a) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 3-33 or 4-39 germline sequence, and/or a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L6, or L15 germline sequence. The amino acid sequences of the V_H and V_κ regions encoded by the V_H 3-33, V_H 4-39, V_κ L6 and V_κ L15 germline genes are provided in U.S. Patent No. 8,008,449.

As used herein, an Ab can be identified as comprising a heavy or a light chain variable region that is "derived from" a particular human germline immunoglobulin by comparing the amino acid sequence of the human Ab to the amino acid sequences encoded by human germline immunoglobulin genes, and selecting the human germline immunoglobulin sequence that is closest in sequence (*i.e.*, greatest percentage of sequence identity) to the sequence of the human Ab. A human Ab that is "derived from" a particular human germline immunoglobulin may contain amino acid differences as compared to the germline sequence, due to, for example, naturally-occurring somatic mutations or intentional introduction of site-directed mutation. However, a selected

human Ab is generally at least 90% identical in amino acids sequence to an amino acid sequence encoded by a human germline immunoglobulin gene and contains amino acid residues that identify the human Ab as being human when compared to the germline immunoglobulin amino acid sequences of other species (*e.g.*, murine germline sequences). In certain cases, a human Ab may be at least 95%, or even at least 96%, 97%, 98%, or 99% identical in amino acid sequence to the amino acid sequence encoded by the germline immunoglobulin gene.

In certain embodiments, the sequence of a human Ab derived from a particular human germline sequence will display no more than 10 amino acid differences from the amino acid sequence encoded by the human germline immunoglobulin gene. In other embodiments, the human Ab may display no more than 5, or even no more than 4, 3, 2, or 1 amino acid differences from the amino acid sequence encoded by the germline immunoglobulin gene.

Preferred Abs of the invention also include isolated Abs or antigen-binding portions thereof comprising: (a) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 3-33 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L6 germline sequence; or (b) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 4-39 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L15 germline sequence. Examples of Abs having a V_H and a V_κ derived from V_H 3-33 and V_κ L6 germline sequences, respectively, include 17D8, 2D3, 4H1, 5C4, and 7D3. Examples of Abs having V_H and V_κ regions derived from V_H 4-39 and V_κ L15 germline sequences, respectively, include 4A11 and 5F4.

In yet other embodiments, anti-PD-1 Abs of the invention comprise heavy and light chain variable regions having amino acid sequences that are highly similar or homologous to the amino acid sequences of the preferred anti-PD-1 Abs described herein, wherein the Ab retains the functional properties of the preferred anti-PD-1 Abs of the invention. For example, Abs of the invention include mAbs comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises consecutively linked amino acids having a sequence that is at least 80% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs. 1, 2, 3, 4, 5, 6 and 7, and the light chain variable region comprises consecutively linked

amino acids having a sequence that is at least 80% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs. 8, 9, 10, 11, 12, 13 and 14. In other embodiments, the V_H and/or V_L amino acid sequences may exhibit at least 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to the sequences set forth above.

As used herein, the percent sequence identity (also referred to as the percent sequence homology) between two sequences (amino acid or nucleotide sequences) is a function of the number of identical positions shared by the sequences relative to the length of the sequences compared (*i.e.*, % identity = number of identical positions/total number of positions being compared x 100), taking into account the number of any gaps, and the length of each such gap, introduced to maximize the degree of sequence identity between the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using mathematical algorithms that are well know to those of ordinary skill in the art (*see, e.g.*, U.S. Patent No. 8,008,449).

Antibodies having very similar amino acid sequences are likely to have essentially the same functional properties where the sequence differences are conservative modifications. As used herein, "conservative sequence modifications" refer to amino acid modifications that do not significantly affect the binding characteristics of the Ab containing the amino acid sequence. Such conservative modifications include amino acid substitutions, additions and deletions. Conservative amino acid substitutions are substitutions in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Thus, for example, one or more amino acid residues within the CDR regions of an Ab of the invention can be replaced with other amino acid residues from the same side chain family and the altered Ab can be tested for retained function using functional assays that are well known in the art. Accordingly, certain embodiments of the anti-PD-1 Abs of the invention comprise heavy and light chain variable regions each comprising CDR1, CDR2 and CDR3 domains, wherein one or more of these CDR domains comprise consecutively linked amino acids having sequences that are the same as the CDR sequences of the preferred anti-PD-1 Abs described herein (*e.g.*, 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 or 5F4), or conservative modifications thereof, and wherein the Abs retain the desired functional properties of the preferred anti-PD-1 Abs of the invention.

Further, it is well known in the art that the heavy chain CDR3 is the primary determinant of binding specificity and affinity of an Ab, and that multiple Abs can predictably be generated having the same binding characteristics based on a common

CDR3 sequence (*see, e.g.*, Klimka *et al.*, 2000; Beiboer *et al.*, 2000; Rader *et al.*, 1998; Barbas *et al.*, 1994; Barbas *et al.*, 1995; Ditzel *et al.*, 1996; Berezov *et al.*, 2001; Igarashi *et al.*, 1995; Bourgeois *et al.*, 1998; Levi *et al.*, 1993; Polymenis *et al.*, 1994; and Xu *et al.*, 2000). The foregoing publications demonstrate that, in general, once the heavy chain CDR3 sequence of a given Ab is defined, variability in the other five CDR sequences will not greatly affect the binding specificity of that Ab. Thus, Abs of the invention comprising 6 CDRs can be defined by specifying the sequence of the heavy chain CDR3 domain.

Anti-PD-1 Abs of the invention also include isolated Abs that bind specifically to human PD-1 and cross-compete for binding to human PD-1 with any of HuMAbs 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 and 5F4. Thus, anti-PD-1 Abs of the invention include isolated Abs or antigen-binding portions thereof that cross-compete for binding to PD-1 with a reference Ab or a reference antigen-binding portion thereof comprising: (a) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 1 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 8; (b) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 2 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 9; (c) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 3 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 10; (d) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 4 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 11; (e) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 5 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 12; (f) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 6 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 13; or (g) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set

forth in SEQ ID NO: 7 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEO ID NO: 14.

The ability of Abs to cross-compete for binding to an antigen indicates that these Abs bind to the same epitope region (*i.e.*, the same or an overlapping epitope) of the antigen and sterically hinder the binding of other cross-competing Abs to that particular epitope region. Thus, the ability of a test Ab to competitively inhibit the binding of, for example, 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 or 5F4, to human PD-1 demonstrates that the test Ab binds to the same epitope region of human PD-1 as 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 or 5F4, respectively. All isolated Abs that bind to the same epitope region of human PD-1 as does HuMAb 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 or 5F4 are included among the Abs of the invention. These cross-competing Abs are expected to have very similar functional properties by virtue of their binding to the same epitope region of PD-1. For example, cross-competing anti-PD-1 mAbs 5C4, 2D3, 7D3, 4H1 and 17D8 have been shown to have similar functional properties (*see* U.S. Patent No. 8,008,449 at Examples 3-7). The higher the degree of cross-competition, the more similar will the functional properties be. Further, cross-competing Abs can be readily identified based on their ability to cross-compete with 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 or 5F4 in standard PD-1 binding assays. For example, BIACORE® analysis, ELISA assays or flow cytometry may be used to demonstrate cross-competition with the Abs of the invention (*see, e.g.*, Examples 1 and 2). In preferred embodiments, the Abs that cross-compete for binding to human PD-1 with, or bind to the same epitope region of human PD-1 as, 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 or 5F4 are mAbs, preferably chimeric Abs, or more preferably humanized or human Abs. Such human mAbs can be prepared and isolated as described in U.S. Patent No. 8,008,449. Data provided in Example 1 show that 5C4 or a Fab fragment thereof cross-competes with each of 2D3, 7D3, 4H1 or 17D8 for binding to hPD-1 expressed on the surface of a cell, indicating that all five anti-PD-1 mAbs bind to the same epitope region of hPD-1 (Figures 1A-1C).

An anti-PD-1 Ab of the invention further can be prepared using an Ab having one or more of the V_H and/or V_L sequences disclosed herein as starting material to engineer a modified Ab, which modified Ab may have altered properties from the starting Ab. An Ab can be engineered by modifying one or more residues within one or both variable regions (*i.e.*, V_H and/or V_L), for example within one or more CDR regions and/or within one or more framework regions. Additionally or alternatively, an Ab can be engineered by modifying residues within the constant region(s), for example, to alter the effector

function(s) of the Ab. Specific modifications to Abs include CDR grafting, site-specific mutation of amino acid residues within the V_H and/or V_κ CDR1, CDR2 and/or CDR3 regions to thereby improve one or more binding properties (*e.g.*, affinity) of the Ab, site-specific mutation of amino acid residues within the V_H and/or V_κ framework regions to decrease the immunogenicity of the Ab, modifications within the Fc region, typically to alter one or more functional properties of the Ab, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity, and chemical modification such as pegylation or alteration in glycosylation patterns to increase or decrease the biological (*e.g.*, serum) half life of the Ab. Specific examples of such modifications and methods of engineering Abs are described in detail in U.S. Patent No. 8,008,449. Anti-PD-1 Abs of the invention include all such engineered Abs that bind specifically to human PD-1 and are obtained by modification of any of the above-described anti-PD-1 Abs.

Anti-PD-1 Abs of the invention also include antigen-binding portions of the above Abs. It has been amply demonstrated that the antigen-binding function of an Ab can be performed by fragments of a full-length Ab. Examples of binding fragments encompassed within the term "antigen-binding portion" of an Ab include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and C_{H1} domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_{H1} domains; and (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an Ab.

These fragments, obtained initially through proteolysis with enzymes such as papain and pepsin, have been subsequently engineered into monovalent and multivalent antigen-binding fragments. For example, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker peptide that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules known as single chain variable fragments (scFv). Divalent or bivalent scFvs (di-scFvs or bi-scFvs) can be engineered by linking two scFvs in within a single peptide chain known as a tandem scFv which contains two V_H and two V_L regions. ScFv dimers and higher multimers can also be created using linker peptides of fewer than 10 amino acids that are too short for the two variable regions to fold together, which forces the scFvs to dimerize and produce diabodies or form other multimers. Diabodies have been shown to bind to their cognate

antigen with much higher affinity than the corresponding scFvs, having dissociation constants up to 40-fold lower than the K_D values for the scFvs. Very short linkers (≤ 3 amino acids) lead to the formation of trivalent triabodies or tetravalent tetrabodies that exhibit even higher affinities for to their antigens than diabodies. Other variants include minibodies, which are scFv-C_{H3} dimers, and larger scFv-Fc fragments (scFv-C_{H2}-C_{H3} dimers), and even an isolated CDR may exhibit antigen-binding function. These Ab fragments are engineered using conventional recombinant techniques known to those of skill in the art, and the fragments are screened for utility in the same manner as are intact Abs. All of the above proteolytic and engineered fragments of Abs and related variants (*see* Hollinger *et al.*, 2005; Olafsen *et al.*, 2010, for further details) are intended to be encompassed within the term "antigen-binding portion" of an Ab.

Anti-PD-L1 Antibodies of the Invention

Each of the anti-PD-L1 HuMAbs disclosed in U.S. Patent No. 7,943,743 has been demonstrated to exhibit one or more of the following characteristics (a) binds to human PD-L1 with a K_D of 1 x 10^{-7} M or less; (b) increases T-cell proliferation in a Mixed Lymphocyte Reaction (MLR) assay; (c) increase interferon-γ production in an MLR assay; (d) increase IL-2 secretion in an MLR assay; (e) stimulates Ab responses; (f) inhibits the binding of PD-L1 to PD-1; and (g) reverses the suppressive effect of T regulatory cells on T cell effector cells and/or dendritic cells. Anti-PD-L1 Abs of the present invention include mAbs that bind specifically to human PD-L1 and exhibit at least one, preferably at least four, of the preceding characteristics.

U.S. Patent No. 7,943,743 exemplifies ten anti-PD-1 HuMAbs: 3G10, 12A4 (also referred to herein as BMS-936559), 10A5, 5F8, 10H10, 1B12, 7H1, 11E6, 12B7, and 13G4. Isolated DNA molecules encoding the heavy and light chain variable regions of these Abs have been sequenced, from which the amino acid sequences of the variable regions were deduced. The V_H amino acid sequences of 3G10, 12A4, 10A5, 5F8, 10H10, 1B12, 7H1, 11E6, 12B7, and 13G4 are shown in SEQ ID NOs. 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24, respectively, whereas their V_L amino acid sequences are shown in SEQ ID NOs. 25, 26, 27, 28, 29, 30, 31, 32, 33 and 34, respectively.

Preferred anti-PD-L1 Abs of the present invention include the anti-PD-L1 HuMAbs 3G10, 12A4, 10A5, 5F8, 10H10, 1B12, 7H1, 11E6, 12B7, and 13G4. These preferred Abs bind specifically to human PD-L1 and comprise: (a) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set

forth in SEQ ID NO: 15 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 25; (b) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 16 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 26; (c) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 17 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 27; (d) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 18 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 28; (e) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 19 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 29; (f) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 20 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 30; (g) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 21 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 31; (h) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 22 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 32; (i) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 23 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEO ID NO: 33; or (j) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 24 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 34.

Given that each of these Abs can bind to PD-L1, the V_H and V_L sequences can be "mixed and matched" to create other anti-PD-L1 Abs of the invention. PD-L1 binding of such "mixed and matched" Abs can be tested using binding assays *e.g.*, ELISAs, western

blots, radioimmunoassays and BIACORE® analysis that are well known in the art (*see, e.g.*, U.S. Patent No. 7,943,743). Preferably, when V_H and V_L chains are mixed and matched, a V_H sequence from a particular V_H/V_L pairing is replaced with a structurally similar V_H sequence. Likewise, preferably a V_L sequence from a particular V_H/V_L pairing is replaced with a structurally similar V_L sequence. Accordingly, Abs of the invention also include a mAb, or antigen binding portion thereof, comprising a heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in any of SEQ ID NOs. 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24, and a light chain variable region comprising consecutively linked amino acids having the sequence set forth in any of SEQ ID NOs. 25, 26, 27, 28, 29, 30, 31, 32, 33 or 34, wherein the Ab binds specifically to PD-L1, preferably human PD-L1.

The CDR domains of the above anti-PD-L1 HuMAbs have been delineated using the Kabat system, and these Abs may also be defined by combinations of their 3 heavy chain and 3 light chain CDRs (*see* U.S. Patent No. 7,943,743). Since each of these Abs can bind to PD-L1 and antigen-binding specificity is provided primarily by the CDR1, CDR2, and CDR3 regions, the V_H CDR1, CDR2, and CDR3 sequences and V_κ CDR1, CDR2, and CDR3 sequences can be "mixed and matched" (*i.e.*, CDRs from different Abs can be mixed and match, although each Ab must contain a V_H CDR1, CDR2, and CDR3 and a V_κ CDR1, CDR2, and CDR3) to create other anti-PD-1 Abs that also constitute Abs of the invention. PD-L1 binding of such "mixed and matched" Abs can be tested using, for example, ELISAs, western blots, radioimmunoassays and BIACORE® analysis.

Antibodies of the invention also include Abs that bind specifically to PD-L1 and comprise a heavy chain variable region derived from a particular germline heavy chain immunoglobulin and/or a light chain variable region derived from a particular germline light chain immunoglobulin. Specifically, in certain embodiments, Abs of the invention include Abs comprising: (a) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 1-18, 1-69, 1-3 or 3-9 germline sequence, and/or a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L6, L15, A27 or L18 germline sequence. The amino acid sequences of the V_H and V_κ regions encoded by the V_H 1-18, V_H 1-3, V_H 1-69, V_H 3-9, V_κ L6, V_κ L15 and V_κ A27 germline genes are provided in U.S. Patent No. 7,943,743.

Preferred Abs of the invention include isolated Abs or antigen-binding portions thereof comprising: (a) a heavy chain variable region that comprises consecutively linked

amino acids having a sequence derived from a human V_H 1-18 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L6 germline sequence; (b) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 1-69 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L6 germline sequence; (c) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 1-3 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L15 germline sequence; (d) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 1-69 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ A27 germline sequence; (e) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 3-9 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L15germline sequence; or (f) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 3-9 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L18germline sequence.

An example of an Ab having a V_H and a V_κ derived from V_H 1-18 and V_κ L6 germline sequences, respectively, is 3G10. Examples of Abs having V_H and V_κ regions derived from V_H 1-69 and V_κ L6 germline sequences, respectively, include 12A4, 1B12, 7H1 and 12B7. An example of an Ab having a V_H and a V_κ derived from V_H 1-3 and V_κ L15 germline sequences, respectively, is 10A5. Examples of Abs having V_H and V_κ regions derived from V_H 1-69 and V_κ A27 germline sequences, respectively, include 5F8, 11E6 and 11E6a. An example of an Ab having a V_H and a V_K derived from V_H 3-9 and V_κ L15 germline sequences, respectively, is 10H10. An example of an Ab having a V_H and a V_κ derived from V_H 1-3 and V_κ L15 germline sequences, respectively, is 10A5. An example of an Ab having a V_H and a V_κ derived from V_H 3-9 and V_κ L18 germline sequences, respectively, is 13G4.

In certain embodiments, anti-PD-L1 Abs of the invention comprise heavy and light chain variable regions having amino acid sequences that are highly similar or

homologous to the amino acid sequences of the preferred anti-PD-L1 Abs described herein, wherein the Ab retains the functional properties of the aforementioned anti-PD-L1 Abs of the invention. For example, Abs of the invention include mAbs comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises consecutively linked amino acids having a sequence that is at least 80% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs. 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24, and the light chain variable region comprises consecutively linked amino acids having a sequence that is at least 80% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs. 25, 26, 27, 28, 29, 30, 31, 32, 33, and 34. In other embodiments, the V_H and/or V_L amino acid sequences may exhibit at least 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to the sequences set forth above.

Certain embodiments of the anti-PD-L1 Abs of the invention comprise heavy and light chain variable regions each comprising CDR1, CDR2 and CDR3 domains, wherein one or more of these CDR domains comprise consecutively linked amino acids having sequences that are the same as the CDR sequences of the preferred anti-PD-L1 Abs described herein (*e.g.*, 3G10, 12A4, 10A5, 5F8, 10H10, 1B12, 7H1, 11E6, 12B7 and 13G4), or conservative modifications thereof, and wherein the Abs retain the desired functional properties of the preferred anti-PD-L1 Abs of the invention.

On the basis of the evidence that the heavy chain CDR3 is the primary determinant of binding specificity and affinity of an Ab, it is generally true that once the heavy chain CDR3 sequence of a given Ab is defined, variability in the other five CDR sequences does not greatly affect the binding specificity of that Ab. Accordingly, anti-PD-L1 Abs of the invention include isolated Abs comprising 6 CDRs, wherein the Abs are defined by specifying the sequence of the heavy chain CDR3 domain.

Anti-PD-L1 Abs of the invention also include isolated Abs that bind specifically to human PD-L1 and cross-compete for binding to human PD-L1 with any of HuMAbs 3G10, 12A4, 10A5, 5F8, 10H10, 1B12, 7H1, 11E6, 12B7 and 13G4. Thus, anti-PD-L1 Abs of the invention include isolated Abs or antigen-binding portions thereof that cross-compete for binding to PD-L1 with a reference Ab or a reference antigen-binding portion thereof comprising: (a) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 15 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 25; (b) a human heavy chain variable region comprising

consecutively linked amino acids having the sequence set forth in SEQ ID NO: 16 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 26; (c) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 17 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 27; (d) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 18 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 28; (e) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 19 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 29; (f) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 20 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 30; (g) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 21 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEO ID NO: 31; (h) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 22 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 32; (i) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 23 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEO ID NO: 33; or (j) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 24 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 34.

The ability of an Ab to cross-compete with any of 3G10, 12A4, 10A5, 5F8, 10H10, 1B12, 7H1, 11E6, 12B7 and 13G4 for binding to human PD-L1 demonstrates that such Ab binds to the same epitope region of each of 3G10, 12A4, 10A5, 5F8, 10H10, 1B12, 7H1, 11E6, 12B7 and 13G4, respectively. All isolated Abs that bind to the same epitope region of human PD-L1 as does HuMAb 3G10, 12A4, 10A5, 5F8, 10H10, 1B12, 7H1, 11E6, 12B7 or 13G4 are included among the Abs of the invention. These cross-

competing Abs are expected to have very similar functional properties by virtue of their binding to the same epitope region of PD-L1. For example, cross-competing anti-PD-L1 mAbs 3G10, 1B12, 13G4, 12A4 (BMS-936559), 10A5, 12B7, 11E6 and 5F8 have been shown to have similar functional properties (*see* U.S. Patent No. 7,943,743 at Examples 3-11), whereas mAb 10H10, which binds to a different epitope region, behaves differently (U.S. Patent No. 7,943,743 at Example 11). The higher the degree of cross-competition, the more similar will the functional properties be. Further, cross-competing Abs can be identified in standard PD-L1 binding assays, *e.g.*, BIACORE® analysis, ELISA assays or flow cytometry, that are well known to persons skilled in the art. In preferred embodiments, the Abs that cross-compete for binding to human PD-1 with, or bind to the same epitope region of human PD-L1 as, 3G10, 12A4, 10A5, 5F8, 10H10, 1B12, 7H1, 11E6, 12B7 or 13G4 are mAbs, preferably chimeric Abs, or more preferably humanized or human Abs. Such human mAbs can be prepared and isolated as described in U.S. Patent No. 7,943,743.

Data provided in Example 2 show that each of the anti-PD-L1 HuMAbs 5F8, 7H1, 1B12, 3G10, 10A5, 11E6, 12A4, 12B7 and 13G4, *i.e.*, all of the HuMAbs tested except 10H10, substantially blocked binding of mAbs 3G10, 10A5, 11E6, 12A4 and 13G4 to Chinese Hamster Ovary (CHO) cells expressing PD-L1 cells. HuMAb 10H10 substantially blocked the binding only of itself to CHO/PD-L1 cells. These data show that 3G10, 10A5, 11E6, 12A4 and 13G4 cross-compete with all of the HuMAbs tested, except for 10H10, for binding to the same epitope region of human PD-L1 (Figures 2A-F).

Data provided in Example 3 show that the binding of HuMAb 12A4 to ES-2 ovarian carcinoma cells expressing PD-L1 cells was substantially blocked by 12A4 itself and by 1B12 and 12B7, and was moderately to significantly blocked by mAbs 5F8, 10A5, 13G4 and 3G10, but was not blocked by mAb 10H10. These data, largely consistent with the data in Example 2, show that 12A4 itself, and 2 other HuMabs, 12B7 and 1B12, substantially cross-compete with 12A4 for binding to the same epitope region, possibly the same epitope, of human PD-L1; 5F8, 10A5, 13G4 and 3G10, exhibit a significant but lower level of cross-competition with 12A4, suggesting that these mAbs may bind to epitopes that overlap the 12A4 epitope; whereas 10H10 does not cross-compete at all with 12A4 (Figure 3), suggesting that this mAb binds to a different epitope region from 12A4.

Anti-PD-L1 Abs of the invention also include Abs engineered starting from Abs having one or more of the V_H and/or V_L sequences disclosed herein, which engineered

Abs may have altered properties from the starting Abs. An anti-PD-L1 Ab can be engineered by a variety of modifications as described above for the engineering of modified anti-PD-1 Abs of the invention.

Anti-PD-L1 Abs of the invention also include isolated Abs selected for their ability to bind to PD-L1 in formalin-fixed, paraffin-embedded (FFPE) tissue specimens. The use of FFPE samples is essential for the long-term follow-up analysis of the correlation between PD-L1 expression in tumors and disease prognosis or progression. Yet, studies on measuring PD-L1 expression have often been conducted on frozen specimens because of the difficulty in isolating anti-human PD-L1 Abs that can be used to stain PD-L1 in FFPE specimens by IHC in general (Hamanishi *et al.*, 2007) and, in particular, Abs that bind specifically to membranous PD-L1 in these tissues. The use of different Abs to stain PD-L1 in frozen versus FFPE tissues, and the ability of certain Abs to distinguish membranous and/or cytoplasmic forms of PD-L1, may account for some of the disparate data reported in the literature correlating PD-L1 expression with disease prognosis (Hamanishi *et al.*, 2007; Gadiot *et al.*, 2011). This disclosure provides several rabbit mAbs that bind with high affinity specifically to membranous human PD-L1 in FFPE tissue samples comprising tumor cells and tumor-infiltrating inflammatory cells.

Rabbit and mouse anti-hPD-L1 mAbs were produced as described in the Examples. Out of almost 200 rabbit Ab multiclones and purified mouse subclones screened, only ten rabbit multiclone Abs were found to specifically detect the membranous form of PD-L1, and the top five multiclones (designated Nos. 13, 20, 28, 29 and 49) were subsequently subcloned. The clone that produced the most robust detection specifically of membranous PD-L1, rabbit clone 28-8, was selected for the IHC assays. The sequences of the variable regions of mAb 28-8 are set forth in SEQ ID NOs. 35 and 36, respectively. Rabbit clones 28-1, 28-12, 29-8 and 20-12 were the next best mAbs in terms of robust detection of membranous PD-L1 in FFPE tissues.

Anti-PD-L1 Abs of the invention also include antigen-binding portions of the above Abs, including Fab, $F(ab')_2$ Fd, Fv, and scFv, di-scFv or bi-scFv, and scFv-Fc fragments, diabodies, triabodies, tetrabodies, and isolated CDRs (*see* Hollinger *et al.*, 2005; Olafsen *et al.*, 2010, for further details).

Nucleic Acid Molecules Encoding Antibodies of the Invention

Another aspect of the present disclosure pertains to isolated nucleic acid molecules that encode any of the Abs of the invention. These nucleic acids may be

present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid of the invention can be, for example, DNA or RNA, and may or may not contain intronic sequences. In a preferred embodiment, the nucleic acid is a cDNA.

Nucleic acids of the invention can be obtained using standard molecular biology techniques. For Abs expressed by hybridomas (*e.g.*, hybridomas prepared from transgenic mice carrying human immunoglobulin genes as described further below), cDNAs encoding the light and heavy chains of the Ab made by the hybridoma can be obtained by standard PCR amplification or cDNA cloning techniques. Nucleic acids encoding Abs obtained from an immunoglobulin gene library (*e.g.*, using phage display techniques) can be recovered from the library.

Preferred nucleic acids molecules of the invention are those encoding the V_H and V_κ sequences of the anti-PD-1 HuMAbs, 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 and 5F4 (disclosed in U.S. Patent No. 8,008,449), and those encoding the V_H and V_κ sequences of the anti-PD-L1 HuMAbs, 3G10, 12A4, 10A5, 5F8, 10H10, 1B12, 7H1, 11E6, 12B7, and 13G4 (disclosed in U.S. Patent No. 7,943,743). An isolated DNA encoding the V_H region can be converted to a full-length heavy chain gene by operatively linking the V_H-encoding DNA to another DNA molecule encoding heavy chain constant regions (C_{H1}, C_{H2} and C_{H3}), the sequences of which are known in the art and can be obtained by standard PCR amplification. The heavy chain constant region can be an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region, but is preferably an IgG1 or IgG4 constant region. Similarly, an isolated DNA encoding the V_L region can be converted to a full-length light chain gene by operatively linking the V_L-encoding DNA to another DNA molecule encoding the light chain constant region (C_L), the sequence of which is known in the art and can be obtained by standard PCR amplification. The light chain constant region can be a kappa or lambda constant region, but most preferably is a kappa constant region.

Pharmaceutical Compositions

Antibodies of the present invention may be constituted in a composition, *e.g.*, a pharmaceutical composition, containing one Ab or a combination of Abs, or an antigen-binding portion(s) thereof, and a pharmaceutically acceptable carrier. As used herein, a "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for

intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (*e.g.*, by injection or infusion). A pharmaceutical composition of the invention may include one or more pharmaceutically acceptable salts, anti-oxidant, aqueous and nonaqueous carriers, and/or adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents.

Dosage regimens are adjusted to provide the optimum desired response, *e.g.*, a therapeutic response or minimal adverse effects. For administration of an anti-PD-1 or anti-PD-L1 Ab, the dosage ranges from about 0.0001 to about 100 mg/kg, usually from about 0.001 to about 20 mg/kg, and more usually from about 0.01 to about 10 mg/kg, of the subject's body weight. Preferably, the dosage is within the range of 0.1-10 mg/kg body weight. For example, dosages can be 0.1, 0.3, 1, 3, 5 or 10 mg/kg body weight, and more preferably, 0.3, 1, 3, or 10 mg/kg body weight. The dosing schedule is typically designed to achieve exposures that result in sustained receptor occupancy (RO) based on typical pharmacokinetic properties of an Ab. An exemplary treatment regime entails administration once per week, once every two weeks, once every three weeks, once every four weeks, once a month, once every 3 months or once every three to 6 months. The dosage and scheduling may change during a course of treatment. For example, dosing schedule may comprise administering the Ab: (i) every two weeks in 6-week cycles; (ii) every four weeks for six dosages, then every three months; (iii) every three weeks; (iv) 3-10 mg/kg body weight once followed by 1 mg/kg body weight every 2-3 weeks. Considering that an IgG4 Ab typically has a half-life of 2-3 weeks, a preferred dosage regimen for an anti-PD-1 or anti-PD-L1 Ab of the invention comprises 0.3-10 mg/kg body weight, preferably 3-10 mg/kg body weight, more preferably 3 mg/kg body weight via intravenous administration, with the Ab being given every 14 days in up to 6-week or 12-week cycles until complete response or confirmed progressive disease.

In some methods, two or more mAbs with different binding specificities are administered simultaneously, in which case the dosage of each Ab administered falls within the ranges indicated. Antibody is usually administered on multiple occasions. Intervals between single dosages can be, for example, weekly, every 2 weeks, every 3 weeks, monthly, every three months or yearly. Intervals can also be irregular as indicated by measuring blood levels of Ab to the target antigen in the patient. In some methods, dosage is adjusted to achieve a plasma Ab concentration of about 1-1000 μg/ml and in some methods about 25-300 μg/ml.

Alternatively, the Ab can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the Ab in the patient. In general, human Abs show the longest half-life, followed by humanized Abs, chimeric Abs, and nonhuman Abs. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and preferably until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being unduly toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts. A composition of the present invention can be administered via one or more routes of administration using one or more of a variety of methods well known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results.

Uses and Methods of the Invention

The Abs, Ab compositions, nucleic acids and methods of the present invention have numerous *in vitro* and *in vivo* utilities including, for example, methods to determine and quantify the expression of PD-1 or PD-L1 comprising binding of the Abs to the target polypeptides or measuring the amount of nucleic acid encoding these polypeptides, and a method for immunotherapy of a subject afflicted with a disease comprising administering to the subject a composition comprising a therapeutically effective amount of a

therapeutic agent that inhibits signaling from an inhibitory immunoregulator. In preferred embodiments of the latter method, the inhibitory immunoregulator is a component of the PD-1/PD-L1 signaling pathway, and the therapeutic agent disrupts signaling of this pathway. More preferably, the therapeutic agent is an Ab that interferes with the interaction between PD-1 and PD-L1. In certain preferred embodiments of this method, the Ab binds specifically to PD-1 and blocks the interaction of PD-1 with PD-L1 and/or PD-L2. In other preferred embodiments, the therapeutic agent is an Ab that binds specifically to PD-L1 and blocks the interaction of PD-L1 with PD-1 and/or B7-1 (CD80). Thus, the disclosure provides methods for potentiating an immune response in a subject comprising administering an anti- PD-1 and/or an anti-PD-L1 Ab in order to disrupt the interaction between PD-1 and PD-L1, and methods of treating diseases mediated by such a potentiation of the immune response. When Abs to PD-1 and PD-L1 are administered together, the two can be administered sequentially in either order or simultaneously. In certain aspects, this disclosure provides methods of modifying an immune response in a subject comprising administering to the subject an anti-PD-1 and/or an anti-PD-L1 Ab of the invention, or antigen-binding portion thereof, such that the immune response in the subject is modified. Preferably, the immune response is potentiated, enhanced, stimulated or up-regulated. In preferred embodiments, the Abs of the present invention are human Abs.

Preferred subjects include human patients in need of enhancement of an immune response. The immunotherapeutic methods disclosed herein are particularly suitable for treating human patients having a disorder that can be treated by potentiating a T-cell mediated immune response. In certain embodiments, the methods are employed for treatment of subjects afflicted with a disease caused by an infectious agent. In preferred embodiments, the methods are employed for treatment of subjects afflicted with, or at risk of being afflicted with, a cancer.

Cancer Immunotherapy

Blockade of PD-1/PD-L1 interaction has been shown to potentiate immune responses *in vitro* (U.S. Patent Nos. 8,008,449 and 7,943,743; Fife *et al.*, 2009) and mediate preclinical antitumor activity (Dong *et al.*, 2002; Iwai *et al.*, 2002). However, the molecular interactions potentially blocked by these two Abs are not identical: anti-PD-1 Abs of the invention disrupt PD-1/PD-L1 and potentially PD-1/PD-L2 interactions; in contrast, whereas anti-PD-L1 Abs of the invention also disrupt PD-1/PD-L1 interactions,

they do not block PD-1/PD-L2 interactions but instead may disrupt the PD-1-independent PD-L1/CD80 interaction, which has also been shown to down-modulate T-cell responses *in vitro* and *in vivo* (Park *et al.*, 2010; Paterson *et al.*, 2011; Yang *et al.*, 2011; Butte *et al.*, 2007; Butte *et al.*, 2008). Thus, it is possible that among these varied ligand-receptor pairings, different interactions may dominate in different cancer types, contributing to dissimilar activity profiles for the two Abs.

Disruption of the PD-1/PD-L1 interaction by antagonistic Abs can enhance the immune response to cancerous cells in a patient. PD-L1 is not expressed in normal human cells, but is abundant in a variety of human cancers (Dong *et al.*, 2002). The interaction between PD-1 and PD-L1 impairs T cell responses as manifested by a decrease in tumor-infiltrating lymphocytes (TILs) and a decrease in T-cell receptor mediated proliferation, resulting in T cell anergy, exhaustion or apoptosis, and immune evasion by the cancerous cells (Zou *et al.*, 2008; Blank *et al.*, 2005; Konishi *et al.*, 2004; Dong *et al.*, 2003; Iwai *et al.*, 2002). Immune suppression can be reversed by inhibiting the local interaction between PD-L1 and PD-1 using an anti-PD-1 and/or an anti-PD-L1 Ab. These Abs may be used alone or in combination to inhibit the growth of cancerous tumors. In addition, either or both of these Abs may be used in conjunction with other immunogenic agents including cytokines, standard cancer chemotherapies, vaccines, radiation, surgery, or other Abs.

Immunotherapy of Cancer Patients Using an Anti-PD-1 Antibody

This disclosure provides a method for immunotherapy of a subject afflicted with cancer, which method comprises administering to the subject a composition comprising a therapeutically effective amount of an Ab or an antigen-binding portion thereof that disrupts the interaction of PD-1 with PD-L1 and/or PD-L2. The disclosure also provides a method of inhibiting growth of tumor cells in a subject, comprising administering to the subject an Ab or an antigen-binding portion thereof that disrupts the interaction of PD-1 with PD-L1 and/or PD-L2 in an amount effective to inhibit growth of the tumor cells. In preferred embodiments, the subject is a human. In other preferred embodiments, the Ab or antigen-binding portion thereof is an anti-PD-1 Ab of the invention or an antigen-binding portion thereof. In certain embodiments, the Ab or antigen-binding portion thereof is of an IgG1 or IgG4 isotype. In certain embodiments, the Ab or antigen-binding portion thereof is a mAb or an antigen-binding portion thereof. In certain other embodiments, the Ab or antigen-binding portion thereof is a chimeric, humanized or

human Ab or an antigen-binding portion thereof. In preferred embodiments for treating human subjects, the Ab or antigen-binding portion thereof is a human Ab or an antigen-binding portion thereof.

The clinical trials described in the Examples employed the anti-PD-1 HuMAb, nivolumab (designated 5C4 in U.S. Patent No. 8,008,449), to treat cancer. While 5C4 was selected as the lead Ab for entering the clinic, it is notable that several anti-PD-1 Abs of the invention share with 5C4 functional properties that are important to the therapeutic activity of 5C4, including high affinity binding specifically to human PD-1, increasing T-cell proliferation, IL-2 secretion and interferon-γ production in an MLR assay, inhibiting the binding of PD-L1 and/or PD-L2 to PD-1, and inhibiting tumor cell growth *in vivo*. Moreover, certain of the anti-PD-1 Abs of the invention, 17D8, 2D3, 4H1 and 7D3 are structurally related to 5C4 in comprising V_H and V_κ regions that have sequences derived from V_H 3-33 and V_κ L6 germline sequences, respectively. In addition, 5C4, 2D3, 7D3, 4H1 and 17D8 all cross-compete for binding to the same epitope region of hPD-1 (Example 1). Thus, the preclinical characterization of nivolumab and other anti-PD-1 HuMabs indicate that the methods of treating cancer provided herein may be performed using different Abs selected from the broad genus of anti-PD-1 Abs of the invention.

Accordingly, certain embodiments of the immunotherapy methods disclosed herein comprise administering to a patient an anti-PD-1 Ab or antigen-binding portion thereof comprising: (a) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 3-33 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L6 germline sequence, or (b) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 4-39 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L15 germline sequence.

In certain other embodiments, the Ab or antigen-binding portion thereof that is administered to the patient cross-competes for binding to PD-1 with a reference Ab or a reference antigen-binding portion thereof comprising: (a) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 1 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 8; (b) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ

ID NO: 2 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 9; (c) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 3 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 10; (d) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 4 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 11; (e) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 5 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 12; (f) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 6 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 13; or (g) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 7 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEO ID NO: 14. In preferred embodiments, the Ab or antigen-binding portion thereof cross-competes for binding to PD-1 with nivolumab.

In certain preferred embodiments of the immunotherapy methods disclosed herein, the anti-PD-1 Ab or antigen-binding portion thereof administered to the patient comprises: (a) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 1 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 8; (b) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 2 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 9; (c) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 3 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 10; (d) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 4 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 11; (e) a human heavy chain variable

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region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 5 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 12; (f) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 6 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 13; or (g) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 7 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEO ID NO: 14. In more preferred embodiments, the anti-PD-1 Ab or antigen-binding portion comprises a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 4 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 11. In yet more preferred embodiments, the anti-PD-1 Ab is nivolumab.

In the clinical trials of anti-PD-1 immunotherapy described in the Examples below, intriguing ORs with durable clinical responses, even in heavily pretreated patients, were observed across multiple tumor types including a substantial proportion of NSCLC, MEL, and RCC patients and in various sites of metastasis including liver, lung, lymph nodes, and bone. *See, also*, Topalian *et al.* (2012b). MEL and RCC are considered to be immunogenic neoplasms, having previously been demonstrated to be responsive to cancer immunotherapy, *e.g.*, IL-2 (McDermott *et al.*, 2006) and/or anti-CTLA-4 Ab (Hodi *et al.*, 2010). In contrast, NSCLC has been considered "non-immunogenic" and poorly responsive to immune-based therapies (Holt *et al.*, 2011). Thus, the results with NSCLC are particularly striking, unexpected and surprising. In NSCLC patients, based on data analyzed up to February 2012, 14 ORs were observed at BMS-936558 doses of 1, 3, or 10 mg/kg with response rates of 6%, 32%, and 18%, respectively. ORs were observed across NSCLC histologies: 6 responders of 18 squamous (33%), 7 of 56 nonsquamous (13%), and 1 of 2 unknown. This level of activity seen with anti-PD-1 in NSCLC patients with significant prior therapy (47% with 3 lines of previous therapy) and across histologies is unique, particularly in the squamous histology patients (*cf.* Gridelli *et al.*, 2008; Miller, 2006), and provides a very favorable benefit/risk dynamic regarding efficacy and safety compared to existing standard-of-care.

Durability of clinical responses to anti-PD-1 in heavily-pretreated cancer patients

The durability of ORs across multiple cancer types in patients treated with the anti-PD-1 Ab is particularly notable. The objective response rate (ORR) in heavily pretreated NSCLC patients receiving anti-PD-1 Ab, including patients with squamous histology, is particularly surprising and unexpected, as standard salvage therapies historically show modest benefit in these patients (Scagliotti *et al.*, 2011). As measured by standard RECIST in this study, ORs were long-lasting, with response durations ≥ 1 year in 20 of 31 responders in the data analyzed up to February 2012. In addition, patterns of tumor regression consistent with immune-related patterns of response were observed.

These findings have established the PD-1 pathway as a new therapeutic focus in oncology (Pardoll, 2012; Topalian *et al.*, 2012c; McDermott *et al.*, 2013). In the current study, in which 47% of patients had progressive disease following 3 or more prior systemic regimens, preliminary analysis has been conducted up to March 2013. This updated analysis has supported and reinforced the data obtained and conclusions reached from the earlier February 2012 analyses. Thus, conventional ORs were documented in patients with NSCLC (16%), MEL (31%) and RCC (29%), and prolonged disease stabilization in others (9%, 6%, and 27%, respectively) across all doses tested (*see* Example 7, Table 2). Additionally, 13 patients (4%) manifested unconventional, "immune-related" response patterns as previously described with anti-CTLA-4 therapy, several of which were sustained (Sharma *et al.*, 2011). The updated analyses again underscored the durability of survival in nivolumab-treated patients, which has not been observed with chemotherapy or small molecule inhibitors to date, but has been observed in patients with advanced melanoma receiving ipilimumab, another immune checkpoint blocking agent (Hodi *et al.*, 2010).

Of particular importance, the objective tumor regression and disease stabilization induced by nivolumab in heavily-pretreated patients with advanced NSCLC, MEL, and RCC translate to survival outcomes that compare very favorably with historical data for these patient populations treated with conventional chemotherapy and/or tyrosine-kinase inhibitor (TKI) treatments. In NSCLC, nivolumab induced median overall survivals of 9.6 and 9.2 months in patients with squamous and non-squamous histologies, respectively. Landmark survival rates of 43% (1-year), 32% (2-year) and 24% (3-year) were achieved (*see* Example 7, Table 2). This high level of efficacy is especially impressive since 55% of these patients had received 3 or more prior therapies. Historically, 2L chemotherapeutics for lung cancer (*i.e.*, docetaxel and pemetrexed) have achieved a

median overall survival of 7.5-8.3 months (Shepherd *et al.*, 2000; Hanna *et al.*, 2004). In a 2/3-L population, erlotinib-treated patients had a median survival of 6.7 months, versus 4.7 months in placebo-treated patients (Shepherd *et al.*, 2005). No therapy is currently approved for use in lung cancer beyond the 3L setting, and minimal data exist to benchmark survival in this patient population.

In nivolumab-treated MEL patients, overall survival (OS) of 16.8 months was achieved, with landmark survival rates of 61% (1-year), 44% (2-year) and 40% (3-year) (*see* Example 7, Table 2). Survival outcomes in pretreated melanoma patients supported the recent PDA approvals of ipilimumab and vemurafenib. In patients with at least one prior treatment for metastatic disease, ipilimumab increased median OS from 6.4 to 10.1 months, compared to a gp100 peptide vaccine (Hodi *et al.*, 2010). In phase 2 trials of ipilimumab in previously treated patients, landmark 2-year survival rates ranged from 24.2-32.8% (Lebbe *et al.*, 2012). Median OS in previously treated MEL patients enrolled on a large phase 2 of vemurafenib was 15.9 months (Sosman *et al.*, 2012).

In nivolumab-treated patients with RCC, among whom 44% received 3 or more prior therapies and 74% received prior anti-angiogenic therapy, the median OS has not been achieved and exceeds 22 months. Landmark survival rates of 70% (1-year), 52% (2-year) and 52% (3-year) were achieved (*see* Example 7, Table 2). In a recent Phase 3 trial enrolling kidney cancer patients whose disease progressed following anti-angiogenic therapy, everolimus was compared with placebo: median OS was 14.8 versus 14.4 months, respectively (Motzer *et al.*, 2008; Motzer *et al.*, 2008). A recent Phase 3 trial comparing sorafenib to temsirolimus in a sunitinib-refractory kidney cancer population yielded median OS of 16.6 and12.3 months, respectively (Hutson *et al.*, 2012). Thus, treatment of a heavily-pretreated patient population with nivolumab has yielded a considerably longer median OS (> 22 months) than treatment of a less refractory population with standard-of-care therapies. Controlled Phase 3 trials with prospective survival endpoints are underway in NSCLC, MEL and RCC (NCT01673867, NCT01721772, NCT01642004, NCT01668784, and NCT01721746 (*see* Clinical Trials Website). The results from these trials are expected to further demonstrate the high efficacy of, and durability of responses to, nivolumab in these cancers compared standard-of-care therapies.

The data disclosed herein demonstrating the high efficacy, durability and broad applicability of anti-PD-1 immunotherapy for treating cancer has led to nivolumab being tested for additional types of cancer. For example, on the basis that increased PD-L1

expression has been reported with various hematologic malignancies and may prevent the host immune response from exerting a beneficial impact on the malignant cells, a trial to confirm the ability of nivolumab to mediate antitumor activity in patients with hematologic malignancies (multiple myeloma, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma/primary mediastinal B-cell lymphoma, and chronic myelogenous leukemia) has been initiated (NCT01592370). Nivolumab is also being tested as a monotherapy in advanced hepatocellular carcinoma (NCT01658878).

In summary, the results of anti-PD-1 immunotherapy disclosed herein are remarkable in at least the following three respects. First, anti-PD-1 has been shown to be highly efficacious compared to historical data for patients on standard-of-care treatments for cancer. Notably, this efficacy has been demonstrated in patient in heavily pretreated populations in which about half of the patients had progressive disease following 3 or more prior systemic regimens. Such patients, afflicted with advanced, metastatic and/or refractory cancers, are notoriously difficult to treat. Accordingly, this disclosure provides methods for immunotherapy of a patient afflicted with an advanced, metastatic and/or refractory cancer, which method comprises administering to the patient a therapeutically effective amount of an Ab or an antigen-binding portion thereof that disrupts the interaction of PD-1 with PD-L1 and/or PD-L2. In certain embodiments of any of the therapeutic methods disclosed herein, the subject has been pre-treated for the cancer; for example, the subject had undergone at least one, two, or three prior lines of therapy for cancer.

Second, the present therapeutic methods have been shown to be applicable to a broad genus of different cancers. Based on the surprising discovery that even a "non-immunogenic" cancer such as NSCLC (Holt *et al.*, 2011) and hard-to-treat cancers such as ovarian and gastric cancers (as well as other cancers tested, including MEL, RCC, and CRC) are amendable to treatment with anti-PD-1 and/or anti-PD-L1 (*see* Examples 7 and 14), this disclosure provides methods for immunotherapy of a patient afflicted with any cancer.

Third, treatment with an anti-PD-1 or anti-PD-L1 Ab has been shown to produce strikingly durable clinical activity in cancer patients. Accordingly, this disclosure provides immunotherapeutic methods of inducing a durable clinical response in a cancer patient comprising administering to the patient a therapeutically effective amount of an Ab or an antigen-binding portion thereof that disrupts the interaction of PD-1 with PD-L1

and/or PD-L2. In preferred embodiments of any of the therapeutic methods described herein, the clinical response is a durable response.

As used herein, a "durable" response is a therapeutic or clinical response that exceeds the anticipated median OS rate in a patient population. The anticipated median OS rate varies with different cancer and different patient populations. In certain embodiments, a durable response exceeds the anticipated median OS rate in the relevant patient population by at least 10%, preferably by at least 20%, more preferably by at least 30%, and even more preferably by at least 50%. A major benefit of immunotherapeutic approaches based on PD-1 pathway blockade may be the functional restoration of exhausted T cells with long-term generation of memory T cells that may maintain antitumor immune surveillance and inhibit tumor growth for prolonged periods extending to many years, even in the absence of continued therapy (Kim *et al.*, 2010). Indeed, long-term follow-up studies on patients following cessation of nivolumab therapy have confirmed that a patient with CRC experienced a complete response which was ongoing after 3 years; a patient with RCC experienced a partial response lasting 3 years off therapy, which converted to a complete response that was ongoing at 12 months; and a patient with melanoma achieved a partial response that was stable for 16 months off therapy, and recurrent disease was successfully treated with reinduction anti-PD-1 therapy (Lipson *et al.*, 2013).

Combination therapy including anti-PD-1 Abs

While monotherapy with anti-PD-1 and anti-PD-L1 Abs has been shown herein to significantly increase the survival of patients with lung cancer, melanoma, kidney cancer, and potentially other malignancies, preclinical evidence indicates that synergistic treatment combinations based on PD-1 pathway blockade could have even more potent effects. Clinical evaluation of nivolumab combined with ipilimumab (anti-CTLA-4), whose mechanism of action is similar yet distinct from nivolumab's (Mellman *et al.*, 2011; Topalian *et al.*, 2012c), is ongoing (Wolchok *et al.*, 2013), as are studies of nivolumab in combination with melanoma vaccines (NCT01176461, NCT01176474; Weber *et al.*, 2013), and BMS-986015, an anti-KIR Ab (NCT01714739).

Anti-PD-1 Abs can be combined with an immunogenic agent, for example a preparation of cancerous cells, purified tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), antigen-presenting cells such as dendritic cells bearing tumor-associated antigens, and/or cells transfected with genes encoding immune

stimulating cytokines (He *et al.*, 2004). Non-limiting examples of tumor vaccines that can be used include peptides of melanoma antigens, such as peptides of gp100, MAGE antigens, Trp-2, MART1 and/or tyrosinase, or tumor cells transfected to express the cytokine GM-CSF. PD-1 blockade may also be effectively combined with standard cancer treatments, including chemotherapeutic regimes, radiation, surgery, hormone deprivation and angiogenesis inhibitors, as well as another immunotherapeutic Ab (*e.g.*, an anti-PD-L1, anti-CTLA-4 and/or anti-LAG-3 Ab).

Immune-related clinical responses

It has become evident that conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. For example, treatment with the anti-CTLA-4 Ab, ipilimumab, has been shown to produce four distinct response patterns, all of which were associated with favorable survival: (a) shrinkage in baseline lesions, without new lesions; (b) durable stable disease (in some patients followed by a slow, steady decline in total tumor burden); (c) response after an increase in total tumor burden; and (d) response in the presence of new lesions. Accordingly, to properly evaluate immunotherapeutic agents, long-term effects on the target disease must also be captured. In this regard, systematic immune-related response criteria (irRC) that make allowances for an early increase in tumor burden and/or the appearance of new lesions, and which seek to enhance the characterization of immune-related response patterns, have been proposed (Wolchok *et al.*, 2009). While the full impact of these unconventional response patterns remains to be defined in randomized trials of nivolumab with survival endpoints, the present observations are reminiscent of findings with ipilimumab in which a significant extension of OS was observed in treated patients (Hodi *et al.*, 2010; Robert *et al.*, 2011).

The overall risk/benefit profile of anti-PD-1 immunotherapy is also favorable, with a low incidence of more severe drug-related adverse events (AEs; > grade 3), the specific events observed to date being consistent with other immunotherapeutic agents. This suggests that anti-PD-1 immunotherapy can be delivered in an outpatient setting with minimal supportive care.

Broad spectrum of cancers treatable by anti-PD-1 immunotherapy

The clinical data presented herein demonstrate that immunotherapy based on PD-1 blockade is not limited to only "immunogenic" tumor types, such as MEL and RCC, but

extends to tumor types not generally considered to be immune-responsive, including NSCLC. The unexpected successes with treatment-refractory metastatic NSCLC underscore the possibility that any neoplasm can be "immunogenic" in the context of proper immune modulation, and suggest that PD-1 blockade as an immunotherapeutic approach is broadly applicable across a very diverse range of tumor types. Cancers that may be treated using the anti-PD-1 Abs of the invention also include cancers typically responsive to immunotherapy. Non-limiting examples of preferred cancers for treatment include NSCLC, MEL, RCC, CRC, CRPC, HCC, squamous cell carcinoma of the head and neck, carcinomas of the esophagus, ovary, gastrointestinal tract and breast, and a hematologic malignancy. Although NSCLC is not generally considered responsive to immunotherapy, data disclosed herein unexpectedly demonstrate that both squamous and non-squamous NSCLC are responsive to treatment with an anti-PD-1 Ab. Additionally, the disclosure provides for the treatment of refractory or recurrent malignancies whose growth may be inhibited using an anti-PD-1 Ab of the invention.

Examples of other cancers that may be treated using an anti-PD-1 Ab in the methods of the present invention, based on the indications of very broad applicability of anti-PD-1 immunotherapy provided herein, include liver cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, breast cancer, lung cancer, cutaneous or intraocular malignant melanoma, renal cancer, uterine cancer, ovarian cancer, colorectal cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, environmentally induced cancers including those induced by asbestos, hematologic malignancies including, for example, multiple myeloma, B-cell lymphoma, Hodgkin lymphoma/primary mediastinal B-cell lymphoma, non-Hodgkin's lymphomas, acute myeloid lymphoma, chronic myelogenous leukemia, chronic lymphoid leukemia, follicular lymphoma, diffuse large B-cell lymphoma, Burkitt's lymphoma, immunoblastic

large cell lymphoma, precursor B-lymphoblastic lymphoma, mantle cell lymphoma, acute lymphoblastic leukemia, mycosis fungoides, anaplastic large cell lymphoma, T-cell lymphoma, and precursor T-lymphoblastic lymphoma, and any combinations of said cancers. The present invention is also applicable to treatment of metastatic cancers.

Medical uses of anti-PD-1 Abs

One aspect of this invention is the use of any anti-PD-1 Ab or antigen-binding portion thereof of the invention for the preparation of a medicament for inhibiting signaling from the PD-1/PD-L1 pathway so as to thereby potentiate an endogenous immune response in a subject afflicted with cancer. Another aspect is the use of any anti-PD-1 Ab or an antigen-binding portion thereof of the invention for the preparation of a medicament for immunotherapy of a subject afflicted with cancer comprising disrupting the interaction between PD-1 and PD-L1. These uses for the preparation of medicaments are broadly applicable to the full range of cancers disclosed herein. In preferred embodiments of these uses, the cancers include squamous NSCLC, non-squamous NSCLC, MEL, RCC, CRC, CRPC, HCC, squamous cell carcinoma of the head and neck, and carcinomas of the esophagus, ovary, gastrointestinal tract and breast, and a hematologic malignancy. This disclosure also provides medical uses of any anti-PD-1 Ab or antigen-binding portion thereof of the invention corresponding to all the embodiments of the methods of treatment employing an anti-PD-1 Ab described herein.

The disclosure also provides an anti-PD-1 Ab or an antigen-binding portion thereof of the invention for use in potentiating an endogenous immune response in a subject afflicted with cancer by inhibiting signaling from the PD-1/PD-L1 pathway. The disclosure further provides an anti-PD-1 Ab or an antigen-binding portion thereof of the invention for use in immunotherapy of a subject afflicted with cancer comprising disrupting the interaction between PD-1 and PD-L1. These Abs may be used in potentiating an endogenous immune response against, or in immunotherapy of, the full range of cancers disclosed herein. In preferred embodiments, the cancers include squamous NSCLC, non-squamous NSCLC, MEL, RCC, CRC, CRPC, HCC, squamous cell carcinoma of the head and neck, and carcinomas of the esophagus, ovary, gastrointestinal tract and breast, and a hematologic malignancy.

Immunotherapy of Cancer Patients Using an Anti-PD-L1 Antibody

PD-L1 is the primary PD-1 ligand up-regulated within solid tumors, where it can inhibit cytokine production and the cytolytic activity of PD-1-positive, tumor-infiltrating

$CD4^+$ and $CD8^+$ T-cells, respectively (Dong *et al.*, 2002; Hino *et al.*, 2010; Taube *et al.*, 2012). These properties make PD-L1 a promising target for cancer immunotherapy. The clinical trials of anti-PD-L1 immunotherapy described in the Examples demonstrate for the first time that mAb blockade of the immune inhibitory ligand, PD-L1, produces both durable tumor regression and prolonged (≥ 24 weeks) disease stabilization in patients with metastatic NSCLC, MEL, RCC and OV, including those with extensive prior therapy. The human anti-PD-L1 HuMAb, BMS-936559, had a favorable safety profile overall at doses up to and including 10 mg/kg, as is evident from the low (9%) incidence of grade 3-4 drug-related AEs. These findings are consistent with the mild autoimmune phenotype seen in PD-$L1^{-/-}$ mice (Dong *et al.*, 2004) and the more severe hyperproliferation seen in CTLA-$4^{-/-}$ mice relative to PD-$1^{-/-}$ mice (Phan *et al.*, 2003; Tivol *et al.*, 1995; Nishimura *et al.*, 1999). Most of the toxicities associated with anti-PD-L1 administration in patients were immune-related, suggesting on-target effects. The spectrum and frequency of adverse events of special interest (AEOSIs) is somewhat different between anti-PD-L1 and anti-CTLA-4, emphasizing the distinct biology of these pathways (Ribas *et al.*, 2005). Infusion reactions were observed with BMS-936559, although they were mild in most patients. Severe colitis, a drug-related AE observed in ipilimumab-treated patients (Beck *et al.*, 2006), was infrequently noted with anti-PD-L1.

As noted above for anti-PD-1 immunotherapy, another important feature of anti-PD-L1 therapy is the durability of responses across multiple tumor types. This is particularly notable considering the advanced disease and prior treatment of patients on the current study. Although not compared directly, this durability appears greater than that observed with most chemotherapies and kinase inhibitors used in these diseases.

Because peripheral blood T-cells express PD-L1, it is possible to assess *in vivo* RO by BMS-963559 as a pharmacodynamic measure. Median RO was 65.8%, 66.2%, and 72.4% for the doses tested. Whereas these studies provide a direct assessment and evidence of target engagement in patients treated with BMS-936559, relationships between RO in peripheral blood and the tumor microenvironment remain poorly understood.

Based on the clinical data disclosed herein, this disclosure provides a method for immunotherapy of a subject afflicted with cancer, which method comprises administering to the subject a composition comprising a therapeutically effective amount of an anti-PD-L1 Ab of the invention or an antigen-binding portion thereof. The disclosure also provides a method of inhibiting growth of tumor cells in a subject, comprising

administering to the subject an anti-PD-L1 Ab of the invention or an antigen-binding portion thereof. In preferred embodiments, the subject is a human. In certain embodiments, the Ab or antigen-binding portion thereof is of an IgG1 or IgG4 isotype. In certain embodiments, the Ab or antigen-binding portion thereof is a mAb or an antigen-binding portion thereof. In certain other embodiments, the Ab or antigen-binding portion thereof is a chimeric, humanized or human Ab or an antigen-binding portion thereof. In preferred embodiments for treating human subjects, the Ab or antigen-binding portion thereof is a human Ab or an antigen-binding portion thereof.

Clinical trials described in the Examples employed the anti-PD-L1 HuMAb BMS-936559 to treat cancer. While BMS-936559 (designated HuMAb 12A4 in U.S. Patent No. 7,943,743) was selected as the lead anti-PD-L1 Ab for entering the clinic, it is notable that several anti-PD-L1 Abs of the invention share with 12A4 functional properties that are important to the therapeutic activity of 12A4, including high affinity binding specifically to human PD-L1, increasing T-cell proliferation, IL-2 secretion and interferon-γ production in an MLR assay, inhibiting the binding of PD-L1 to PD-1, and reversing the suppressive effect of T regulatory cells on T cell effector cells and/or dendritic cells. Moreover, certain of the anti-PD-L1 Abs of the invention, namely 1B12, 7H1 and 12B7 are structurally related to 12A4 in comprising V_H and V_κ regions that have sequences derived from V_H 1-69 and V_κ L6 germline sequences, respectively. In addition, at least 12B7, 3G10, 1B12 and 13G4 cross-compete with 12A4 for binding to the same epitope region of hPD-L1, whereas 5F8 and 10A5 may bind to the same or an overlapping epitope region as 12A4 (Examples 2 and 3). Thus, the preclinical characterization of 12A4 and other anti-PD-L1 HuMabs indicate that the methods of treating cancer provided herein may be performed using any of the broad genus of anti-PD-L1 Abs of the invention.

Accordingly, this disclosure provides immunotherapy methods comprising administering to a patient an anti-PD-L1 Ab or antigen-binding portion thereof comprising (a) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 1-18 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L6 germline sequence; (b) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 1-69 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L6 germline sequence;

(c) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 1-3 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L15 germline sequence; (d) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 1-69 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ A27 germline sequence; (e) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 3-9 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L15germline sequence; or (f) a heavy chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_H 3-9 germline sequence, and a light chain variable region that comprises consecutively linked amino acids having a sequence derived from a human V_κ L18germline sequence.

In certain other embodiments, the anti-PD-L1 Ab or antigen-binding portion thereof administered to the patient cross-competes for binding to PD-L1 with a reference Ab or a reference antigen-binding portion thereof comprising: (a) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 15 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 25; (b) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 16 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 26; (c) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 17 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 27; (d) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 18 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 28; (e) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 19 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 29; (f) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID

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NO: 20 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 30; (g) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 21 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEO ID NO: 31; (h) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 22 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 32; (i) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 23 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEO ID NO: 33; or (j) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 24 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 34. In preferred embodiments, the Ab or antigen-binding portion thereof cross-competes for binding to PD-1 with a reference Ab or reference antigen-binding portion thereof comprising a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 16 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 26.

In certain preferred embodiments of the immunotherapy methods disclosed herein, the anti-PD-L1 Ab or antigen-binding portion thereof administered to the subject comprises: (a) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 15 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 25; (b) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 16 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 26; (c) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 17 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 27; (d) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 18 and a human light chain variable region comprising consecutively linked

amino acids having the sequence set forth in SEQ ID NO: 28; (e) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 19 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 29; (f) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 20 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 30; (g) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 21 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEO ID NO: 31; (h) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 22 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 32; (i) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 23 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEO ID NO: 33; or (j) a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 24 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 34. In more preferred embodiments, the anti-PD-L1 Ab or antigen-binding portion comprises a human heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 16 and a human light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 26.

Broad spectrum of cancers treatable by anti-PD-L1 immunotherapy

The clinical activity of anti-PD-L1 in patients with advanced NSCLC, similar to the activity of anti-PD-1 in these patients, was surprising and unexpected since NSCLC has been considered to be poorly responsive to immune-based therapies (Holt and Disis, 2008; Holt *et al.*, 2011). The present clinical data obtained with BMS-936559, an anti-PD-L1 Ab of the invention, substantiate and extend the evidence obtained using the anti-PD-1 Ab that immunotherapy based on PD-1 blockade is not applicable only to "immunogenic" tumor types, such as MEL and RCC, but is also effective with a broad range of cancers, including treatment-refractory metastatic NSCLC, that are generally not

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considered to be immune-responsive. Preferred cancers that may be treated using the anti-PD-L1 Abs of the invention include MEL (*e.g.*, metastatic malignant melanoma), RCC, squamous NSCLC, non-squamous NSCLC, CRC, ovarian cancer (OV), gastric cancer (GC), breast cancer (BC), pancreatic carcinoma (PC) and carcinoma of the esophagus. Additionally, the invention includes refractory or recurrent malignancies whose growth may be inhibited using the anti-PD-L1 Abs of the invention.

Examples of other cancers that may be treated using an anti-PD-L1 Ab in the methods of the invention, based on the indications of very broad applicability of anti-PD-L1 immunotherapy provided herein, include bone cancer, skin cancer, cancer of the head or neck, breast cancer, lung cancer, cutaneous or intraocular malignant melanoma, renal cancer, uterine cancer, castration-resistant prostate cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, carcinomas of the ovary, gastrointestinal tract and breast, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, multiple myeloma, environmentally induced cancers including those induced by asbestos, metastatic cancers, and any combinations of said cancers. The present invention is also applicable to treatment of metastatic cancers.

Combination therapy with anti-PD-L1 Abs

Optionally, Abs to PD-L1 can be combined with an immunogenic agent, for example a preparation of cancerous cells, purified tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), antigen-presenting cells such as dendritic cells bearing tumor-associated antigens, and cells transfected with genes encoding immune stimulating cytokines (He *et al.*, 2004). Non-limiting examples of tumor vaccines that can be used include peptides of melanoma antigens, such as peptides of gp100,

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MAGE antigens, Trp-2, MART1 and/or tyrosinase, or tumor cells transfected to express the cytokine GM-CSF. PD-1 blockade may also be effectively combined with standard cancer treatments, including chemotherapeutic regimes, radiation, surgery, hormone deprivation and angiogenesis inhibitors, as well as another immunotherapeutic Ab (*e.g.*, an anti-PD-1, anti-CTLA-4 or anti-LAG-3 Ab).

Uses of anti-PD-L1 Abs

This disclosure provides the use of any anti-PD-L1 Ab or antigen-binding portion thereof of the invention for the preparation of a medicament for inhibiting signaling from the PD-1/PD-L1 pathway so as to thereby potentiate an endogenous immune response in a subject afflicted with cancer. The disclosure also provides the use of any anti-PD-L1 Ab or antigen-binding portion thereof of the invention for the preparation of a medicament for immunotherapy of a subject afflicted with cancer comprising disrupting the interaction between PD-1 and PD-L1. The disclosure provides medical uses of any anti-PD-L1 Ab or antigen-binding portion thereof of the invention corresponding to all the embodiments of the methods of treatment employing an anti-PD-L1 Ab described herein.

This disclosure also provides an anti-PD-L1 Ab or an antigen-binding portion thereof of the invention for use in potentiating an endogenous immune response in a subject afflicted with cancer by inhibiting signaling from the PD-1/PD-L1 pathway. The disclosure further provides an anti-PD-L1 Ab or an antigen-binding portion thereof of the invention for use in immunotherapy of a subject afflicted with cancer comprising disrupting the interaction between PD-1 and PD-L1. These Abs may be used in potentiating an endogenous immune response against, or in immunotherapy of, the full range of cancers disclosed herein. In preferred embodiments, the cancers include MEL (*e.g.*, metastatic malignant MEL), RCC, squamous NSCLC, non-squamous NSCLC, CRC, ovarian cancer (OV), gastric cancer (GC), breast cancer (BC), pancreatic carcinoma (PC) and carcinoma of the esophagus.

Validation of Cancer Immunotherapy by Immune Checkpoint Blockade

A major implication of the clinical activity of immune checkpoint blockade is that significant endogenous immune responses to tumor antigens are generated and these responses may be harnessed therapeutically to mediate clinical tumor regression upon checkpoint inhibition. In fact, there is evidence that inhibitory ligands such as PD-L1 are induced in response to immune attack, a mechanism termed adaptive resistance (Gajewski *et al.*, 2010; Taube *et al.*, 2012). This potential mechanism of immune resistance by

tumors suggests that PD-1/PD-L1-directed therapy might synergize with other treatments that enhance endogenous antitumor immunity. Follow-up studies have verified that patients continue to demonstrate tumor control after cessation of PD-1/PD-L1 pathway blockade (Lipson *et al.*, 2013). Such tumor control may reflect a persistent antitumor immune response and the generation of effective immunologic memory to enable sustained control of tumor growth.

The data disclosed herein on the clinical testing of Abs that block the immunoregulatory receptor, PD-1, and also of Abs that block one of its cognate ligands, PD-L1, are unprecedented. These data constitute the largest clinical experience to date with PD-1 pathway-directed cancer immunotherapy, and the first report specifically describing the safety, tolerability, and initial clinical activity of an anti-PD-L1-directed agent. These findings show that both anti-PD-1 and anti-PD-L1 have favorable overall safety profiles and provide clear evidence of clinical activity across diverse cancers, including NSCLC, a tumor not historically considered responsive to immunotherapy, as well as tumors known to respond to immunotherapy, including MEL, RCC and OV. Thus, these data strongly validate the PD-1/PD-L1 pathway as an important target for therapeutic intervention in cancer.

The remarkable similarities observed between the patterns of clinical activity obtained with the anti-PD-1 and anti-PD-L1 mAbs, and among the tumor types analyzed to date, validate the general importance of the PD-1/PD-L1 signaling pathway in tumor immune resistance and as a target for therapeutic intervention. Although the molecular interactions blocked by these two Abs are not identical, it has been clearly demonstrated herein that, irrespective of mechanistic details, both anti-PD-1 and anti-PD-L1 Abs of the invention are effective in treating patients afflicted with a wide variety of cancers, including "immunogenic" cancers such as MEL and RCC as well as treatment-refractory metastatic NSCLC, a tumor that is generally not considered to be immune-responsive. In certain embodiments of the invention, either or both of these Abs can be administered in combination with another therapeutic agent such as a cytokine.

Infectious Diseases

Other methods of the invention are used to treat patients that have been exposed to particular toxins or pathogens. For example, another aspect of the disclosure provides a method of treating an infectious disease in a subject comprising administering to the subject an anti-PD1 or an anti-PD-L1 Ab, or antigen-binding portion thereof, of the

invention such that the subject is treated for the infectious disease. Preferably, the Ab is a human anti-human PD-1 or PD-L1 Ab (such as any of the human Abs described herein). Alternatively, the Ab is a chimeric or humanized Ab.

Similar to its application to tumors as discussed above, Ab-mediated PD-1 or PD-L1 blockade can be used alone, or as an adjuvant, in combination with vaccines, to potentiate an immune response to pathogens, toxins, and/or self-antigens. Examples of pathogens for which this therapeutic approach may be particularly useful include pathogens for which there is currently no effective vaccine, or pathogens for which conventional vaccines are less than completely effective. These include, but are not limited to HIV, Hepatitis (A, B, and C), Influenza, Herpes, Giardia, Malaria, Leishmania, Staphylococcus aureus, Pseudomonas aeruginosa. PD-1 and/or PD-L1 blockade is particularly useful against established infections by agents such as HIV that present altered antigens over the course of an infection. Novel epitopes on these antigens are recognized as foreign at the time of anti-human PD-1 or PD-L1 administration, thus provoking a strong T cell response that is not dampened by negative signals through the PD-1/PD-L1 pathway.

In the above methods, PD-1 or PD-L1 blockade can be combined with other forms of immunotherapy such as cytokine treatment (*e.g.*, administration of interferons, GM-CSF, G-CSF or IL-2).

Kits

Also within the scope of the present invention are kits, including pharmaceutical kits, comprising an anti-PD-1 and/or an anti-PD-L1 Ab of the invention for therapeutic uses, and diagnostic kits comprising an anti-PD-L1 Ab of the invention for assaying membranous PD-L1 expression as a biomarker for screening patients for immunotherapy or for predicting the efficacy of an immunotherapeutic agent. Kits typically include a label indicating the intended use of the contents of the kit and instructions for use. The term label includes any writing, or recorded material supplied on or with the kit, or which otherwise accompanies the kit. In certain embodiments of a pharmaceutical kit, the anti-PD-1 and/or anti-PD-L1 Abs may be co-packaged with other therapeutic agents in unit dosage form. In certain embodiments of a diagnostic kit, the anti-PD-L1 Ab may be co-packaged with other reagents for performing an assay to detect and/or quantify PD-L1 expression.

In certain preferred embodiments, the pharmaceutical kit comprises the anti-human PD-1 HuMAb, nivolumab. In other preferred embodiments, the pharmaceutical kit comprises the anti-human PD-L1 HuMAb, BMS-936559. In certain preferred embodiments, the diagnostic kit comprises the rabbit anti-human PD-L1 mAb, 28-8, comprising the V_H and V_κ regions whose amino acid sequences are set forth in SEQ ID NOs. 35 and 36, respectively. In other preferred embodiments, the diagnostic kit comprises the murine anti-human PD-L1 mAb, 5H1 (Dong *et al.*, 2002).

PD-L1 Biomarker for Predicting anti-PD-1 Efficacy

A particular challenge in cancer immunotherapy has been the identification of mechanism-based predictive biomarkers to enable patient selection and guide on-treatment management. Data disclosed in the Examples below indicate that cell surface PD-L1 expression in tumors is a useful molecular marker for predicting the efficacy of, and selecting patients for, anti-PD-1 immunotherapy.

There are conflicting reports in the literature about the clinical implications of PD-L1 being expressed in tumors. Several studies have concluded that PD-L1 expression in tumors correlates with a poor prognosis for the patient. *See, e.g.*, Hino *et al.*, 2010 (MEL); Hamanishi *et al.*, 2007 (OV); Thompson *et al.*, 2006 (RCC). These findings may be rationalized on the basis that the interaction of PD-L1 on tumor cells and PD-1 on T cells helps abrogate immune responses directed against the tumor, resulting in immune evasion from tumor-specific T cells. However, in contrast to the foregoing studies, Gadiot *et al.*, 2011 and Taube *et al.*, 2012 have recently reported that PD-L1 expression in melanoma tumors correlates with a trend toward better survival. These seemingly contradictory data may reflect the relatively small numbers of patients analyzed, different histologic subtypes studied, or different methodologies used, *e.g.*, the use of different Abs to stain PD-L1, the use of frozen versus paraffin-embedded material for IHC, and the detection of membranous and/or cytoplasmic staining of PD-L1. Taube *et al.*, 2012 note that PD-L1 is a type I transmembrane molecule, and hypothesize that while the cytoplasmic presence of PD-L1 may represent intracellular stores of this polypeptide that may be deployed to the cell surface upon appropriate stimulation, it is cell surface PD-L1 expression of that is biologically relevant as a potential biomarker for predicting clinical response to PD-1 blockade. *See, also*, Brahmer *et al.*, 2010, which describes preliminary evidence, obtained on a small sample size of only 9 patients, of a correlation between membranous PD-L1 expression and anti-PD-1 efficacy. The data described in the Examples below on the use

of membranous PD-L1 expression as a biomarker for anti-PD-1 efficacy, which was obtained from analysis of a much larger sample, substantiate the hypothesis that PD-L1 expression may be used as a biomarker for predicting anti-PD-1 clinical response and for screening patients to identify suitable candidates for immunotherapy with an anti-PD-1 Ab or other inhibitors of inhibitory immunoregulators.

Specifically, membranous PD-L1 expression was assayed using an automated IHC protocol and a rabbit anti-hPD-L1 Ab. Strikingly, in the initial set of data analyzed (*see* Example 8), no patients with cell surface PD-L1-negative tumors (MEL, NSCLC, CRC, RCC and CRPC) experienced an OR following treatment with the anti-PD-1 Ab, nivolumab. In contrast, cell surface expression of PD-L1 on tumor cells in pretreatment biopsies may be associated with an increased rate of OR among patients treated with nivolumab. While tumor cell expression of PD-L1 may be driven by constitutive oncogenic pathways, it may also reflect "adaptive immune resistance" in response to an endogenous antitumor immune response, part of a host inflammatory response, which may remain in check unless unleashed by blockade of the PD-1/PD-L1 pathway (Taube *et al.*, 2012). This emerging concept of adaptive immune resistance in cancer immunology suggests that inhibitory ligands such as PD-L1 are induced in response to immune attack (Gajewski *et al.*, 2010; Taube *et al.*, 2012). A major implication of the clinical activity of immune checkpoint blockade as described herein is that significant endogenous immune responses to tumor antigens are generated and these responses may be harnessed therapeutically to mediate clinical tumor regression upon checkpoint inhibition. This potential mechanism of immune resistance by tumors suggests that PD-1/PD-L1-directed therapy might synergize with other treatments that enhance endogenous antitumor immunity. It also suggests that cell surface expression of PD-L1 in tumors and/or inflammatory cells in the tumor microenvironment may be a marker not just for treatment of cancer patients with an anti-PD-1 Ab, but also for treatment with an anti-PD-L1 Ab as well as treatments targeting inhibitory immunoregulatory pathways other than the PD-1/PD-L1 pathway.

Assaying Cell-Surface PD-L1 Expression by Automated IHC

As described in the Examples, an automated IHC method was developed for assaying the expression of PD-L1 on the surface of cells in FFPE tissue specimens. The disclosure provides methods for detecting the presence of human PD-L1 antigen in a test tissue sample, or quantifying the level of human PD-L1 antigen or the proportion of cells

in the sample that express the antigen, which methods comprise contacting the test sample, and a negative control sample, with a mAb that specifically binds to human PD-L1, under conditions that allow for formation of a complex between the Ab or portion thereof and human PD-L1. Preferably, the test and control tissue samples are FFPE samples. The formation of a complex is then detected, wherein a difference in complex formation between the test sample and the negative control sample is indicative of the presence of human PD-L1 antigen in the sample. Various methods are used to quantify PD-L1 expression.

In a particular embodiment, the automated IHC method comprises: (a) deparaffinizing and rehydrating mounted tissue sections in an autostainer; (b) retrieving antigen using a decloaking chamber and pH 6 buffer, heated to 110ºC for 10 min; (c) setting up reagents on an autostainer; and (d) running the autostainer to include steps of neutralizing endogenous peroxidase in the tissue specimen; blocking non-specific protein-binding sites on the slides; incubating the slides with primary Ab; incubating with a post-primary blocking agent; incubating with NovoLink Polymer; adding a chromogen substrate and developing; and counterstaining with hematoxylin.

For assessing PD-L1 expression in tumor tissue samples, a pathologist examines the number of membrane PD-L1$^+$ tumor cells in each field under a microscope and mentally estimates the percentage of cells that are positive, then averages them to come to the final percentage. The different staining intensities are defined as 0/negative, 1+/weak, 2+/moderate, and 3+/strong. Typically, percentage values are first assigned to the 0 and 3+ buckets, and then the intermediate 1+ and 2+ intensities are considered. For highly heterogeneous tissues, the specimen is divided into zones, and each zone is scored separately and then combined into a single set of percentage values. The percentages of negative and positive cells for the different staining intensities are determined from each area and a median value is given to each zone. A final percentage value is given to the tissue for each staining intensity category: negative, 1+, 2+, and 3+. The sum of all staining intensities needs to be 100%.

Staining is also assessed in tumor-infiltrating inflammatory cells such as macrophages and lymphocytes. In most cases macrophages serve as an internal positive control since staining is observed in a large proportion of macrophages. While not required to stain with 3+ intensity, an absence of staining of macrophages should be taken into account to rule out any technical failure. Macrophages and lymphocytes are assessed for plasma membrane staining and only recorded for all samples as being positive or

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negative for each cell category. Staining is also characterized according to an outside/inside tumor immune cell designation. "Inside" means the immune cell is within the tumor tissue and/or on the boundaries of the tumor region without being physically intercalated among the tumor cells. "Outside" means that there is no physical association with the tumor, the immune cells being found in the periphery associated with connective or any associated adjacent tissue.

In certain embodiments of these scoring methods, the samples are scored by two pathologists operating independently and the scores are subsequently consolidated. In certain other embodiments, the identification of positive and negative cells is scored using appropriate software.

A histoscore is used as a more quantitative measure of the IHC data. The histoscore is calculated as follows:

Histoscore = [(% tumor x 1 (low intensity)) + (% tumor x 2 (medium intensity)) + (% tumor x 3 (high intensity)]

To determine the histoscore, the pathologist estimates the percentage of stained cells in each intensity category within a specimen. Because expression of most biomarkers is heterogeneous the histoscore is a truer representation of the overall expression. The final histoscore range is 0 (no expression) to 300 (maximum expression).

An alternative means of quantifying PD-L1 expression in a test tissue sample IHC is to determine the adjusted inflammation score (AIS) score defined as the density of inflammation multiplied by the percent PD-L1 expression by tumor-infiltrating inflammatory cells (Taube *et al.*, 2012).

Cancer Immunotherapy with Anti-PD-1 Comprising a Patient Selection Step

This disclosure also provides a method for immunotherapy of a subject afflicted with cancer, which method comprises: (a) selecting a subject that is a suitable candidate for immunotherapy, the selecting comprising (i) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells, (ii) assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface, and (iii) selecting the subject as a suitable candidate based on an assessment that the proportion of cells in the test tissue sample that express PD-L1 on the cell surface exceeds a predetermined threshold level; and (b) administering to the selected subject a composition comprising a therapeutically effective amount of an agent that inhibits signaling from an inhibitory immunoregulator.

There is evidence that membranous PD-L1 expression is a surrogate for an endogenous antitumor immune response that is part of a host inflammatory response (Gajewski *et al.*, 2010; Taube *et al.*, 2012). Accordingly, cell surface expression of PD-L1 in tumors and/or tumor-infiltrating inflammatory cells is a marker not just for selecting cancer patients who would benefit from treatment with an anti-PD-1 Ab, but also for treatment with an anti-PD-L1 Ab as well as treatments targeting inhibitory immunoregulatory pathways other than the PD-1/PD-L1 pathway. For example, cell surface expression of PD-L1 in tumors and/or tumor-infiltrating inflammatory cells may be used as a marker for identifying or selecting suitable cancer patients who would benefit from immunotherapy with agents, including Abs, that target, and disrupt or inhibit signaling from, inhibitory immunoregulators such as PD-L1, Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4), B and T Lymphocyte Attenuator (BTLA), T cell Immunoglobulin and Mucin domain-3 (TIM-3), Lymphocyte Activation Gene-3 (LAG-3), Killer cell Lectin-like Receptor G1 (KLRG-1), Natural Killer Cell Receptor 2B4 (CD244), and CD160 (Baitsch *et al.*, 2012). In certain preferred embodiments, the inhibitory immunoregulator is a component of the PD-1/PD-L1 signaling pathway. In other preferred embodiments, the inhibitory immunoregulator is an anti-PD-1 Ab of the invention. In yet other preferred embodiments, the inhibitory immunoregulator is an anti-PD-L1 Ab of the invention.

Although many of the immunotherapy methods below comprising assaying PD-L1 expression, *i.e.*, employing a PD-L1 expression biomarker, are described as comprising the selection of a patient that is, or is not, suitable for anti-PD-1 immunotherapy or as comprising the administration of an anti-PD-1 Ab for immunotherapeutic purposes, it should be understood that these methods apply generally to the selection of a patient that is, or is not, suitable for immunotherapy with, or to the administration of an inhibitor of an inhibitory immunoregulator or a component or ligand thereof. Further, in any the methods comprising the measurement of PD-L1 expression in a test tissue sample, it should be understood that the step comprising the provision of a test tissue sample obtained from a patient is an optional step. That is, in certain embodiments the method includes this step, and in other embodiments, this step is not included in the method. It should also be understood that in certain preferred embodiments the "assessing" step to identify, or determine the number or proportion of, cells in the test tissue sample that express PD-L1 on the cell surface is performed by a transformative method of assaying for PD-L1 expression, for example by performing a

reverse transcriptase-polymerase chain reaction (RT-PCR) assay or an IHC assay. In certain other embodiments, no transformative step is involved and PD-L1 expression is assessed by, for example, reviewing a report of test results from a laboratory. In certain embodiments, the steps of the methods up to, and including, assessing PD-L1 expression provides an intermediate result that may be provided to a physician or other medical practitioner for use in selecting a suitable candidate for immunotherapy and/or administering an immunotherapeutic agent to the patient. In certain embodiments, the steps that provide the intermediate result may be performed by a medical practitioner or someone acting under the direction of a medical practitioner. In other embodiment, these steps are performed by an independent person or laboratory.

The disclosure further provides a method for treatment of a subject afflicted with cancer, which method comprises: (a) selecting a subject that is not suitable for treatment with an agent that inhibits an inhibitory immunoregulator, *e.g.*, anti-PD-1 Ab immunotherapy, the selecting comprising (i) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells; (ii) assessing the proportion of cells in the test tissue sample that express PD-L1 on the surface of the cells; and (iii) selecting the subject as not suitable for immunotherapy with an inhibitor of an inhibitory immunoregulator, *e.g.*, an anti-PD-1 Ab, based on an assessment that the proportion of cells in the test tissue sample that express PD-L1 on the cell surface is less than a predetermined threshold level; and (b) administering a standard-of-care therapeutic other than an inhibitor of an inhibitory immunoregulator, *e.g.*, an anti-PD-1 Ab, to the selected subject.

Measurement of PD-L1 expression

In certain embodiments of any of the present methods, the proportion of cells that express PD-L1 is assessed by performing an assay to determine the presence of PD-L1 RNA. In further embodiments, the presence of PD-L1 RNA is determined by RT-PCR, *in situ* hybridization or RNase protection. In other embodiments, the proportion of cells that express PD-L1 is assessed by performing an assay to determine the presence of PD-L1 polypeptide. In further embodiments, the presence of PD-L1 polypeptide is determined by immunohistochemistry (IHC), enzyme-linked immunosorbent assay (ELISA), *in vivo* imaging, or flow cytometry. In preferred embodiments, PD-L1 expression is assayed by IHC. Flow cytometry may be particularly suitable for assaying PD-L1 expression in cells

of hematologic tumors. In preferred embodiments of all of these methods, cell surface expression of PD-L1 is assayed using, *e.g.*, IHC or *in vivo* imaging.

Imaging techniques have provided important tools in cancer research and treatment. Recent developments in molecular imaging systems, including positron emission tomography (PET), single-photon emission computed tomography (SPECT), fluorescence reflectance imaging (FRI), fluorescence-mediated tomography (FMT), bioluminescence imaging (BLI), laser-scanning confocal microscopy (LSCM) and multiphoton microscopy (MPM), will likely herald even greater use of these techniques in cancer research. Some of these molecular imaging systems allow clinicians to not only see where a tumor is located in the body, but also to visualize the expression and activity of specific molecules, cells, and biological processes that influence tumor behavior and/or responsiveness to therapeutic drugs (Condeelis *et al.*, 2010). Ab specificity, coupled with the sensitivity and resolution of PET, makes immunoPET imaging particularly attractive for monitoring and assaying expression of antigens in tissue samples (McCabe *et al.*, 2010; Olafsen *et al.*, 2010). In certain embodiments of any of the present methods, PD-L1 expression is assayed by immunoPET imaging.

In certain embodiments of any of the present methods, the proportion of cells in a test tissue sample that express PD-L1 is assessed by performing an assay to determine the presence of PD-L1 polypeptide on the surface of cells in the test tissue sample. In certain embodiments, the test tissue sample is a FFPE tissue sample. In certain preferred embodiments, the presence of PD-L1 polypeptide is determined by IHC assay. In further embodiments, the IHC assay is performed using an automated process. In further embodiments, the IHC assay is performed using an anti-PD-L1 mAb to bind to the PD-L1 polypeptide.

Abs that bind specifically to cell-surface-expressed PD-L1 in FFPE tissues

An Ab may bind to an antigen in fresh tissues but completely fail to recognize the antigen in an FFPE tissue sample. This phenomenon, well known in the art, is thought to be due primarily to intra- and inter-molecular cross-linking of polypeptides induced by formalin fixation, which alters the epitope recognized by the Ab (Sompuram *et al.*, 2006). In addition, several factors known to influence staining in FFPE tissue, including variable time to fixation, inadequate fixation period, differences in fixative used, tissue processing, Ab clone and dilution, antigen retrieval, detection system, and interpretation of results using different threshold points are important variables that can affect tissue antigenicity

and IHC measurements (Bordeaux *et al.*, 2010). In particular, a lack of anti-human PD-L1 Abs that stain PD-L1 in FFPE specimens has been noted in the art (Hamanishi *et al.*, 2007). Thus, the contradictory results reported by different groups on the implications of PD-L1 expression for prognosis of a tumor may, in part, reflect the differential abilities of anti-PD-L1 Abs used to detect PD-L1 polypeptide in FFPE tissue samples. Indeed, our analysis of five commercially available anti-hPD-L1 Abs shows that these Abs failed to distinguish FFPE cells expressing PD-L1 from cells that did not express PD-L1 (see Example 9, Table 6). Accordingly, in order to detect hPD-L1 on the surface of cells using an IHC assay on FFPE tissues, there is a need for anti-hPD-L1 Abs that bind specifically to cell surface-expressed PD-L1 in FFPE tissue samples.

This disclosure provides a mAb or an antigen-binding portion thereof that binds specifically to a cell surface-expressed PD-L1 antigen in a FFPE tissue sample. In preferred embodiments, the mAb or antigen-binding portion thereof does not bind to a cytoplasmic PD-L1 polypeptide in the FFPE tissue sample or exhibits a very low level of background binding. In certain other embodiments, the presence or absence of binding specifically to a cell surface-expressed or a cytoplasmic PD-L1 polypeptide is detected by immunohistochemical staining. In certain preferred aspects of the invention, the mAb or antigen-binding portion is a rabbit Ab or a portion thereof. In other preferred embodiments, the mAb is the rabbit mAb designated 28-8, 28-1, 28-12, 29-8 or 20-12. In more preferred embodiments, the mAb is the rabbit mAb designated 28-8 or an antigen-binding portion thereof. In further embodiments, the mAb is an Ab comprising a heavy chain variable region (V_H) comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 35 and a light chain variable region (V_κ) comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 36. In other embodiments, the mAb comprises the CDR1, CDR2 and CDR3 domains in a V_H having the sequence set forth in SEQ ID NO: 35, and the CDR1, CDR2 and CDR3 domains in a V_κ having the sequence set forth in SEQ ID NO: 36.

It is known in the art that rabbit Abs have certain advantages over murine Abs. For example, rabbit Abs generally exhibit more diverse epitope recognition, improved immune response to small-size epitopes, and higher specificity and affinity compared to murine Abs (*see, e.g.*, Fischer *et al.*, 2008; Cheang *et al.*, 2006; Rossi *et al.*, 2005). For example, the rabbit's lower immune dominance and larger B-cell repertoire results in greater epitope recognition compared to murine Abs. Further, the high specificity and novel epitope recognition of rabbit antibodies translates to success with recognition of

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post-translational modifications (Epitomics, 2013). In addition, many protein targets relevant to signal transduction and disease are highly conserved between mice, rats and humans, and can therefore be recognized as self-antigens by a mouse or rat host, making them less immunogenic. This problem is avoided by generating Abs in rabbits. In addition, in applications in which two antigen-specific Abs are required, it is more convenient to have the Abs come from two different species. Thus, for example, it is easier to multiplex a rabbit Ab such as 28-8 with other Abs (likely to be murine Abs since the best immune marking Abs are murine Abs) that can mark immune cells that also express PD-L1 (*e.g.*, macrophages and lymphocytes). Thus, rabbit anti-hPD-L1 mAbs, *e.g.*, 28-8, are particularly suited to IHC assays for detecting surface-expressed PD-L1 in FFPE tissue samples and have distinct advantages over murine Abs, such as 5H1.

As described in Example 9, a large number (185) of antibody multiclones from both rabbit and mouse immunizations were screened, and only ten rabbit Ab, but no mouse Ab, multiclones specifically detected the membranous form of hPD-L1. After further extensive screening by multiple rounds of IHC, 15 purified rabbit subclones were selected based on their specificity and intensity of staining (see Table 4). Following further characterization of the antibodies to determine their binding affinity and cross-competition by surface plasmon resonance, as well as screening by IHC on FFPE tissues, mAb 28-8 was selected as the Ab with the best combination of binding to membranous PDF-L1 with high affinity and specificity, and low background staining.

In certain aspects of this invention, the mAb or antigen-binding portion cross-competes with mouse mAb 5H1 for binding to PD-L1, which indicates that these antibodies bind to the same epitope region of PD-L1. In certain other aspects, the mAb or antigen-binding portion thereof does not cross-compete with mouse mAb 5H1 for binding to PD-L1, indicating that they do not bind to the same epitope region of PD-L1.

The disclosure also provides nucleic acids encoding all of the rabbit anti-hPD-L1 Abs or portions thereof disclosed herein.

Immunotherapeutic methods comprising measurement of cell surface PD-L1 expression

The availability of rabbit Abs that bind with high affinity specifically to membranous PD-L1 in FFPE tissue specimens facilitates methods comprising a step of detecting PD-L1 polypeptide on the surface of cells in FFPE tissue samples. Accordingly, this disclosure also provides a method for immunotherapy of a subject afflicted with

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cancer, which method comprises: (a) selecting a subject that is a suitable candidate for immunotherapy, the selecting comprising: (i) optionally providing a FFPE test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells; (ii) assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface by IHC using a rabbit anti-human PD-L1 Ab, *e.g.*, mAb 28-8, to bind to the PD-L1; and (iii) selecting the subject as a suitable candidate based on an assessment that the proportion of cells in the test tissue sample that express PD-L1 on the cell surface exceeds a predetermined threshold level; and (b) administering a composition comprising a therapeutically effective amount of an anti-PD-1 Ab to the selected subject.

In certain embodiments of methods employing IHC to assay PD-L1 expression in FFPE tissues, an automated IHC assay is used. The automated IHC process is performed on an autostainer and comprises: (a) de-paraffinizing the FFPE sample with xylene and rehydrating the sample; (b) retrieving the antigen using a decloaking chamber; (c) blocking nonspecifc protein binding sites by incubation with a Protein Block; (d) incubating the sample with a primary anti-PD-L1 Ab; (e) adding a polymeric horseradish peroxidase (HRP)-conjugated secondary Ab; (f) detecting the bound secondary Ab comprising staining with a 3,3′-diaminobenzidine (DAB) chromogen; and/or (g) counterstaining with hematoxylin. This automated IHC process has been optimized by minimization of the number of steps, optimization of incubation times, and selection of primary Abs, blocking and detection reagents that produce strong specific staining with a low level of background staining. In preferred embodiments of this automated IHC assay, the primary anti-PD-L1 Ab is rabbit mAb 28-8 or murine mAb 5H1. In certain embodiments of this invention, this IHC assay, and any other IHC assay described herein to measure PD-L1 expression, may be used as part of a method of immunotherapy. In other embodiments, any of the IHC methods described herein is used independently of any therapeutic process requiring the administration of a therapeutic, *i.e.*, solely as a diagnostic method to assay PD-L1 expression.

In certain embodiments any of the immunotherapy methods described herein, the Ab administered to the selected subject is any anti-PD-1 or anti-PD-L1 Ab or antigen-binding portion thereof of the invention. In certain preferred embodiments, the subject is a human. In other preferred embodiments, the Ab is a human Ab or antigen-binding portion thereof. In more preferred embodiments, the anti-PD-1 Ab is nivolumab and the anti-PD-L1 Ab is BMS-936559. In certain other embodiments, the anti-PD-1 Ab is an Ab

or antigen-binding portion thereof that cross-competes with nivolumab for binding to PD-1, and the anti-PD-L1 Ab is an Ab or antigen-binding portion thereof that cross-competes with BMS-936559 for binding to PD-L1. In certain preferred embodiments, the cancer to be treated is selected from the group consisting MEL, RCC, squamous NSCLC, non-squamous NSCLC, CRC, castration-resistant prostate cancer CRPC, HCC, squamous cell carcinoma of the head and neck, carcinomas of the esophagus, ovary, gastrointestinal tract and breast, and a hematological malignancy.

In certain embodiments of the disclosed methods, the predetermined threshold is based on a proportion of (a) tumor cells, (b) tumor-infiltrating inflammatory cells, (c) particular tumor-infiltrating inflammatory cells, *e.g.*, TILs or macrophages, or (d) a combination of tumor cells and tumor-infiltrating inflammatory cells, in a test tissue sample that expresses PD-L1 on the cell surface. In certain embodiments, the predetermined threshold is at least 0.001% of tumor cells expressing membranous PD-L1 as determined by IHC. In other embodiments, the predetermined threshold is at least 0.01%, preferably at least 0.1%, more preferably at least 1% of tumor cells expressing membranous PD-L1, as determined by IHC. In certain embodiments, the predetermined threshold is at least 5% of tumor cells expressing membranous PD-L1 as determined by IHC. In certain embodiments, the predetermined threshold is at least 0.01%, at least 0.1%, at least 1%, or at least 5% of tumor cells expressing membranous PD-L1 as determined by IHC, and/or a single tumor-infiltrating inflammatory cell expressing membranous PD-L1 as determined by IHC. In certain other embodiments, the predetermined threshold is at least 0.01%, at least 0.1%, at least 1%, or at least 5% of a tumor-infiltrating inflammatory cell expressing membranous PD-L1 as determined by IHC. In certain other embodiments, the predetermined threshold is at least 0.01%, at least 0.1%, at least 1%, or at least 5% of a tumor-infiltrating lymphocyte expressing membranous PD-L1 as determined by IHC. In certain other embodiments, the predetermined threshold is at least 0.01%, at least 0.1%, at least 1%, or at least 5% of a tumor-infiltrating macrophage expressing membranous PD-L1 as determined by IHC. In yet other embodiments, the predetermined threshold is at least a single tumor cell or a single tumor-infiltrating inflammatory cell expressing membranous PD-L1 as determined by IHC. Preferably, PD-L1 expression is assayed by automated IHC using mAb 28-8 or 5H1 as the primary Ab.

This disclosure also provides a method for treatment of a subject afflicted with cancer, which method comprises: (a) screening a plurality of subjects to identify a subject that is not a suitable candidate for immunotherapy comprising the administration of an

anti-PD-1 Ab to the subject, the screening comprising: (i) optionally providing test tissue samples from the plurality of subjects, the test tissue samples comprising tumor cells and tumor-infiltrating inflammatory cells; (ii) assessing the proportion of cells in the test tissue samples that express PD-L1 on the surface of the cells; and (iii) selecting the subject as a candidate that is not suitable for anti-PD-1 Ab immunotherapy based on an assessment that the proportion of cells that express PD-L1 on the surface of cells in the subject's test tissue sample is below a predetermined threshold level; and (b) administering a standard-of-care therapeutic other than an anti-PD-1 Ab to the selected subject.

This disclosure also provides a method for immunotherapy of a subject afflicted with cancer, which method comprises: (a) screening a plurality of subjects to identify a subject that is a suitable candidate for immunotherapy, the screening comprising: (i) optionally providing test tissue samples from the plurality of subjects, the test tissue samples comprising tumor cells and tumor-infiltrating inflammatory cells; (ii) assessing the proportion of cells in the test tissue samples that express PD-L1 on the surface of the cells; and (iii) selecting the subject as a candidate that is suitable for anti-PD-1 Ab immunotherapy based on an assessment that the proportion of cells in the test tissue sample that express PD-L1 on the cell surface exceeds a predetermined threshold level; and (b) administering a composition comprising a therapeutically effective amount of an anti-PD-1 Ab to the selected subject.

This disclosure further provides a method for treatment of a subject afflicted with cancer, which method comprises: (a) screening a plurality of subjects to identify a subject that is a suitable candidate for the treatment, the screening comprising: (i) optionally providing test tissue samples from the plurality of subjects, the test tissue samples comprising tumor cells and tumor-infiltrating inflammatory cells; (ii) assessing the proportion of cells in the test tissue samples that express PD-L1 on the surface of the cells, wherein the subject is identified as a suitable candidate for anti-PD-1 Ab immunotherapy if the proportion of cells in the tissue sample that express PD-L1 on the cell surface exceeds a predetermined threshold level, and the subject is identified as a candidate that is not a suitable candidate for anti-PD-1 Ab immunotherapy if the proportion of cells in the tissue sample that express PD-L1 on the cell surface is below a predetermined threshold level; and (b) administering a composition comprising a therapeutically effective amount of an anti-PD-1 Ab to the subject identified as a suitable candidate for anti-PD-1 Ab immunotherapy, or (c) administering a standard-of-care

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therapeutic other than an anti-PD-1 Ab to the subject identified as not a suitable candidate for anti-PD-1 Ab immunotherapy.

One aspect of this invention is a method for immunotherapy of a subject afflicted with cancer, which method comprises: (a) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells; (b) determining that a proportion of cells in the test tissue sample express PD-L1 above a predetermined threshold level on the cell surface; and (c) based on that determination administering a composition comprising a therapeutically effective amount of an anti-PD-1 Ab to the subject. Another aspect of the invention is a method for treatment of a subject afflicted with cancer, which method comprises: (a) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells; (b) determining that the proportion of cells in the test tissue sample that express PD-L1 on the cell surface is below a predetermined threshold level; and (c) based on that determination administering a standard-of-care therapeutic other than an anti-PD-1 Ab to the subject.

Yet another aspect of the invention is a method for immunotherapy of a subject afflicted with cancer, which method comprises: (a) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells; (b) determining that cells in the test tissue sample express PD-L1 on the cell surface; (c) selecting an anti-PD-1 Ab as a treatment for the subject based on the recognition that an anti-PD-1 Ab is effective in patients whose test tissue sample contains a proportion of cells above a predetermined threshold level that express PD-L1 on the cell surface; and (d) administering a composition comprising a therapeutically effective amount of an anti-PD-1 Ab to the subject. In a further aspect, the disclosure provides a method for treatment of a subject afflicted with cancer, which method comprises: (a) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells; (b) determining that cells in the test tissue sample do not express PD-L1 on the cell surface; (c) selecting a standard-of-care therapeutic other than an anti-PD-1 Ab as a treatment for the subject based on the recognition that an anti-PD-1 Ab is ineffective in patients whose test tissue sample contains a proportion of cells that express PD-L1 on the cell surface is below a

predetermined threshold level; and (d) administering the standard-of-care therapeutic to the subject.

This disclosure also provides a method of selecting an immunotherapy for a subject afflicted with cancer, which method comprises: (a) assaying cells of a test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells to assess the proportion of cells in the test tissue sample that express PD-L1; and (b) based on an assessment that the proportion of cells that express membranous PD-L1 is above a predetermined threshold level, selecting an immunotherapy comprising a therapeutically effective amount of an anti-PD-1 Ab for the subject. The disclosure further provides a method of selecting a treatment for a subject afflicted with cancer, which method comprises: (a) assaying cells of a test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells to assess the proportion of cells in the test tissue sample that express PD-L1; and (b) based on an assessment that the proportion of cells that express membranous PD-L1 is below a predetermined threshold level, selecting a standard-of-care treatment other than an anti-PD-1 Ab for the subject.

In addition, the disclosure provides a method for treatment of a subject afflicted with cancer, which method comprises administering to the subject a composition comprising a therapeutically effective amount of an anti-PD-1 Ab, the subject having been selected on the basis that the proportion of cells in a test tissue sample from the subject that express PD-L1 is determined to exceed a predetermined threshold level, wherein the test tissue sample comprises tumor cells and tumor-infiltrating inflammatory cells. This disclosure also provides a method for treatment of a subject afflicted with cancer, which method comprises administering to the subject a standard-of-care treatment other than an anti-PD-1 Ab, the subject having been selected on the basis that the proportion of cells in a test tissue sample from the subject that express PD-L1 is determined to be below a predetermined threshold level, wherein the test tissue sample comprises tumor cells and tumor-infiltrating inflammatory cells.

This disclosure further provides a method for selecting a cancer patient for immunotherapy with an anti-PD-1 Ab, which method comprises: (a) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells; (b) assaying the test tissue sample to determine the proportion of cells therein that express PD-L1 on the cell surface; (c) comparing the proportion of cells that express PD-L1 on the cell surface with a predetermined threshold proportion; and (d) selecting the patient for

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immunotherapy based on an assessment that the proportion of cells in the test tissue sample that express surface PD-L1 is above the predetermined threshold level. In any of the methods described herein comprising a step for assessing PD-L1 expression, the test tissue sample may be a FFPE tissue sample.

In addition, in any method where an immunotherapy is selected or administered based on an assessment that the proportion of cells in a test tissue sample from the subject expresses PD-L1 at a level above a predetermined threshold level, it follows that a complementary method of treatment may be performed wherein a standard-of-care treatment other than the immunotherapy is selected or administered based on an assessment that the proportion of cells in a test tissue sample from the subject expresses PD-L1 at a level below the predetermined threshold level.

This disclosure further provides a method for predicting the therapeutic effectiveness of an anti-PD-1 Ab for treating a cancer patient, which method comprises: (a) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells; (b) assaying the test tissue sample to determine the proportion of cells therein that express PD-L1 on the cell surface; (c) comparing the proportion of cells that express PD-L1 on the cell surface with a predetermined threshold value; and (d) predicting the therapeutic effectiveness of the anti-PD-1 Ab, wherein if the proportion of cells that express PD-L1 on the cell surface exceeds the threshold proportion the Ab is predicted to be effective in treating the patient, and wherein if the proportion of cells that express PD-L1 on the cell surface is below the threshold proportion the Ab is predicted to not be effective in treating the patient.

This disclosure also provides a method for determining an immunotherapeutic regimen comprising an anti-PD-1 Ab for treating a cancer patient, which method comprises: (a) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells; (b) assaying the test tissue sample to determine the proportion of cells therein that express PD-L1 on the cell surface; (c) comparing the proportion of cells that express PD-L1 on the cell surface with a predetermined threshold proportion; and (d) determining an immunotherapeutic regimen comprising an anti-PD-1 Ab based on the determination that the proportion of cells that express PD-L1 on the cell surface exceeds the predetermined threshold proportion.

Standard-of-Care Therapeutics

Several of the methods of treatment described herein comprise the administration of a standard-of-care therapeutic to a patient. As used herein, a "standard-of-care therapeutic" is a treatment process, including a drug or combination of drugs, radiation therapy, surgery or other medical intervention that is recognized by medical practitioners as appropriate, accepted, and/or widely used for a certain type of patient, disease or clinical circumstance. Standard-of-care therapeutics for treating different types of cancer are well known by persons of skill in the art. For example, the National Comprehensive Cancer Network (NCCN), an alliance of 21 major cancer centers in the USA, publishes the NCCN Clinical Practice Guidelines in Oncology (NCCN GUIDELINES®) that provide detailed up-to-date information on the standard-of-care treatments for a wide variety of cancers (*see* NCCN GUIDELINES®, 2013). By way of example, standard-of-care treatments for MEL, RCC and NSCLC are summarized below.

Melanoma

For *in situ* or early-stage MEL, surgical treatment is the primary treatment. Where surgical excision is not feasible for *in situ* melanoma due to comorbidity or cosmetically sensitive tumor location, topical imiquimod and radiotherapy are emerging as treatments, especially for lentigo maligna. Chemotherapeutic agents for treating MEL include dacarbazine, temozolomide, imatinib for melanoma with c-KIT mutation, high-dose interleukin-2, and paclitaxel with or without carboplatin. However, these treatments have modest success, with response rates below 20% in first-line (1L) and second-line (2L) settings.

There is no consensus on the best treatments for metastatic melanoma, though a variety of treatments including excision to clear margins, intralesional injections, laser ablation, radiation and biochemotherapy (combination of chemotherapy and biological agents such as interferon-alpha and IL-2) are being investigated. The therapeutic landscape for metastatic melanoma has recently seen dramatic improvements with the development of novel drugs such as vemurafenib and ipilimumab. Vemurafenib specifically inhibits signaling by a mutated intracellular kinase, BRAF, that is present in about 50% of patients with metastatic melanoma (Flaherty *et al.*, 2010). Ipilimumab is a HuMAb that inhibits the immune checkpoint receptor, CTLA-4, and thereby stimulates a T cell immune response (Hodi *et al.*, 2010). Besides these two agents, no other agent has demonstrated an OS benefit in a Phase 3 randomized study. Dacarbazine is approved by

the FDA and the EMA for treatment of metastatic MEL with a reported objective response rate of 5% to 20% and a median OS of 6.4 months, but these responses are short-lived. Other drugs such as temozolomide and fotemustine have not resulted in significant improvement in survival when compared to dacarbazine. IL-2 has also been approved by the FDA for the treatment of metastatic MEL as it is associated with a 15 to 20% response rate including 4-6% complete responses which can be durable, but it is associated with significant toxicities including hypotension, cardiac arrhythmias, and pulmonary edema. Further details on standard-of-care treatments for melanoma are provided by Garbe *et al.*, 2012. Despite the recent approval of ipilimumab and vemurafenib for advanced MEL, there is still a large unmet need for patients who have progressed on anti-CTLA-4 therapy and a BRAF inhibitor (depending on BRAF status) or patients with previously untreated, unresectable or metastatic BRAF wild-type MEL. The 5-year survival rate for late-stage MEL is currently only 15%.

Renal Cell Carcinoma

For clinically localized RCC (Stage IA and IB), surgical resection, including radical nephrectomy and nephron-sparing surgery, is an effective therapy. Partial nephrectomy is generally not suitable for patients with locally advanced tumors (Stage II and III), in which case radical nephrectomy is preferred. Patients with Stage IV disease may also benefit from surgery, and cytoreductive nephrectomy before systemic therapy is recommended for patients with a potentially surgically resectable primary and multiple resectable metastases.

Until recently, the cytokines IL-2 and IFNα were the only active systemic treatments for advanced or metastatic RCC. However, due to each of these agent's limited clinical benefit and substantial toxicity profile, newer targeted agents have largely replaced cytokines in the treatment of advanced or metastatic renal cell carcinoma. The recognition of the importance of hypoxia inducible factor alpha (HIFα) signaling in the pathogenesis of clear-cell RCC has led to widespread study of two classes of targeted therapies, anti-angiogenic agents and mammalian target of rapamycin (mTOR) inhibitors (Mulders, 2009). Targeting of angiogenesis is rational because constitutive HIFα activation leads to the upregulation or activation of several proteins including vascular endothelial growth factor (VEGF), which can subsequently lead to tumor proliferation and neovasculature formation. Targeting of the mTOR pathway is important because activation of the upstream PI3K/Akt/mTOR signaling pathway is one method by which

constitutive HIFα activation or upregulation occurs (Mulders, 2009). Agents that target angiogenesis include VEGF-receptor (VEGFr) TKIs (*e.g.*, sorafenib, sunitinib, pazopanib, axitinib, and tivozanib) and VEGF-binding mAbs (*e.g.*, bevacizumab), while agents that target the mTOR pathway include the mTOR inhibitors (*e.g.*, everolimus and temsirolimus). However, most patients develop resistance, and overall survival (OS) improvement has only been shown in one Phase 3 trial in poor-risk patients. Everolimus demonstrated a 3-month improvement in median progression-free survival (PFS) versus placebo, with no OS improvement (Motzer *et al.*, 2008). Among the five approved anti-angiogenic agents (sorafenib, sunitinib, bevacizumab, pazopanib, and axitinib) and two approved mTOR inhibitors (temsirolimus, everolimus), only everolimus is approved specifically for use after the failure of treatment with anti-angiogenic therapy. In the US, everolimus is indicated for the treatment of advanced RCC after failure of treatment with sunitinib or sorafenib, whereas in the EU, everolimus is more broadly indicated for patients with advanced RCC, whose disease has progressed on or after treatment with VEGF-targeted therapy.

Non-Small Cell Lung Cancer

NSCLC is the leading cause of cancer death worldwide, exceeding breast, colon and prostate cancer combined. The majority of subjects (approximately 78%) are diagnosed with advanced/recurrent or metastatic disease. NSCLC therapies have incrementally improved OS, but benefit has reached a plateau (median OS for late stage patients is just 1 year). Progression after 1L therapy occurred in nearly all of these subjects and the 5-year survival rate is only 3.6% in the refractory setting.

There is a particular unmet need among patients who have squamous cell NSCLC (representing up to 25% of all NSCLC) as there are few treatment options after 1L therapy. Surgery, radiation therapy (RT) and chemotherapy are the three modalities commonly used to treat NSCLC patients. As a class, NSCLCs are relatively insensitive to chemotherapy, compared to small cell carcinoma. In general, for patients with Stage I or II disease, surgery provides the best chance for cure, with chemotherapy increasingly being used both pre-operatively and post-operatively. RT can also be used as adjuvant therapy for patients with resectable NSCLC, the primary local treatment, or as palliative therapy for patients with incurable NSCLC.

Patients with Stage IV disease who have a good performance status (PS) benefit from chemotherapy. Many drugs, including platinum agents (*e.g.*, cisplatin, carboplatin),

taxanes agents (*e.g.*, paclitaxel, albumin-bound paclitaxel, docetaxel) vinorelbine, vinblastine, etoposide, pemetrexed and gemcitabine are useful for Stage IV NSCLC. Combinations using many of these drugs produce 1-year survival rates of 30% to 40% and are superior to single agents. Specific targeted therapies have also been developed for the treatment of advanced lung cancer. For example, bevacizumab (AVASTIN®) is a mAb that blocks vascular endothelial growth factor A (VEGF-A). Erlotinib (TARCEVA®) is a small-molecule TKI of epidermal growth factor receptor (EGFR). Crizotinib (XALKORI®) is a small-molecule TKI that targets ALK and MET, and is used to treat NSCLC in patients carrying the mutated *ALK* fusion gene. Cetuximab (ERBITUX®) is a mAb that targets EGFR.

Squamous cell carcinoma (SCC) represents one quarter of NSCLC cases and has limited treatment options. Currently, second-line treatment for SCC remains an area of unmet need. Single-agent chemotherapy is standard of care following progression with platinum-based doublet chemotherapy (Pt-doublet), resulting in median OS of approximately 7 months. Docetaxel remains the benchmark treatment in this line of therapy although erlotinib may also used with less frequency. Pemetrexed has also been shown to produce clinically equivalent efficacy outcomes but with significantly fewer side effects compared with docetaxel in the 2L treatment of patients with advanced NSCLC (Hanna *et al.*, 2004). No therapy is currently approved for use in lung cancer beyond the 3L setting. Pemetrexed and bevacizumab are not approved in SCC, and molecularly targeted therapies have limited application.

The present invention is further illustrated by the following examples which should not be construed as further limiting. The contents of all figures and all references, patents and published patent applications cited throughout this application are expressly incorporated herein by reference.

EXAMPLE 1

Cross-Competition between Anti-PD-1 HuMAbs for Binding to CHO Cells Expressing Human PD-1

Chinese Hamster Ovary (CHO) cells transfected to express human PD-1 (CHO/PD-1 cells) were incubated with 10 μg/ml of Fab fragment of the anti-PD-1 HuMAb 5C4 or human IgG1 (hIgG1) isotype control Ab for 30 minutes at 4 ºC before addition of anti-PD-1 HuMAbs 2D3, 7D3 or 4H1 at a concentration of 0.2 μg/ml. Binding of 4H1, 2D3 or 7D3 to CHO/PD-1 cells were detected by fluorescein

isothiocyanate (FITC)-conjugated goat anti-hIgG, Fc-gamma specific Ab. In the case of cross-competition assay with 5C4 and 17D8, CHO/PD-1 cells were incubated with the whole molecule of 5C4 before addition of FITC-labeled 17D8. Binding of 2D3, 7D3, 4H1 or 17D8 to the CHO/PD-1 cells was measured by flow cytometric analysis using a FACS® calibur flow cytometer (Becton Dickinson, San Jose, CA).

The results are depicted in Figure 1. The data show that the 5C4 Fab fragment substantially blocked the binding of mAbs 5C4 itself, as well as the binding of 2D3, 7D3 (Figure 1A) and 4H1 (Figure 1B), while the 5C4 whole mAb substantially blocked the binding of 17D8 (Figure 1C) to CHO/PD-1 cells as measured by mean fluorescent intensity (MFI) of staining.

EXAMPLE 2

Cross-Competition between Anti-PD-L1 HuMAbs for Binding to CHO Cells Expressing Human PD-L1

CHO cells transfected to express hPD-L1 (CHO/PD-L1 cells) were incubated with 10 μg/ml of each of ten unconjugated human anti-PD-L1 mAbs (5F8, 7H1, 10H10, 1B12, 3G10, 10A5, 11E6, 12A4, 12B7, and 13G4) or human IgG1 (hIgG1) isotype control Ab for 20 min at 4 ºC. FITC-conjugated 10H10 (A), 3G10 (B), 10A5 (C), 11E6 (D), 12A4 (E) or 13G4 (F) was added to the cells to a final concentration of 0.09 μg/ml (B, D), 0.27 μg/ml (A, C), 0.91 μg/ml (F), or 2.73 μg/ml (E) for an additional 20 min at 4 ºC without prior washout of unbound, unconjugated Ab. Different quantities of the various FITC-conjugated HuMAbs were used due to differences in binding efficiency following labeling, and the optimal amounts of these FITC-conjugated HuMAbs were previously determined by dose-titration analysis of binding to CHO/PD-L1 cells. Binding of FITC-conjugated 10H10, 3G10, 10A5, 11E6, 12A4 or 13G4 to the CHO/PD-L1 cells was measured by flow cytometry.

The results are depicted in Figure 2. Binding of labeled 10H10 was partially blocked by 10A5, 11E6 and 13G4, but was substantially blocked only by itself (Figure 2A). Conversely, 10H10 substantially blocked the binding only of itself to CHO/PD-L1 cells. Each of anti-PD-L1 HuMAbs 5F8, 7H1, 1B12, 3G10, 10A5, 11E6, 12A4, 12B7 and 13G4 substantially blocked binding of labeled mAbs 3G10 (Figure 2B), 10A5 (Figure 2C), 11E6 (Figure 2D), 12A4 (Figure 2E) and 13G4 (Figure 2F) to CHO/PD-L1 cells as measured by MFI, though mAbs 5F8 and 13G4 generally blocked binding of the labeled mAbs to a slightly lesser extent.

EXAMPLE 3

Cross-Competition between Anti-PD-L1 mAbs for Binding to Ovarian Carcinoma Cells Expressing Human PD-L1

Anti-PD-L1 HuMAbs 5F8, 12B7, 3G10, 1B12, 13G4, 10H10, 10A5 and 12A4, and a human IgG1 (huIgG1) isotype control Ab were serially diluted from 10 μg/ml and incubated with hPD-L1-expressing ES-2 ovarian carcinoma cells for 20 minutes at 4 °C. Without washing, biotinylated-12A4 Ab was added to a final concentration of 0.4 μg/ml for an additional 20 minutes at 4 °C. After washing, bound biotin-12A4 was detected using fluorescent streptavidin-PE secondary reagent and measured by flow cytometry. Figure 3 shows the fluorescence of bound biotin-12A4 plotted against the concentration of unlabeled hPD-L1 HuMAbs. Binding of biotin-12A4 to ES-2 cells was substantially blocked by 12A4 itself and by 1B12 and 12B7, and was moderately to significantly blocked by mAbs 5F8, 10A5, 13G4 and 3G10, but was not blocked by mAb 10H10.

EXAMPLE 4

Design of Phase I Clinical Study of Anti-PD-1 Antibody

A Phase I study was conducted to assess the safety, antitumor activity, and pharmacokinetics of an anti-PD-1 in patients with selected advanced solid tumors. The human anti-PD-1 mAb, BMS-936558 (also referred to herein as nivolumab, and in U.S. Patent No. 8,008,449 as 5C4), was administered as an intravenous infusion every 2 weeks of each 8-week treatment cycle. Patients continued treatment for up to 2 years (12 cycles), unless they experienced complete remission, unacceptable toxicity, disease progression, or withdrew consent. In patients who were otherwise clinically stable, study treatment was continued beyond apparent initial disease progression until further progression was noted as recommended by proposed immune response criteria (Wolchok *et al.*, 2009). Patients with stable disease (SD) or an ongoing objective response (OR: complete [CR] or partial response [PR]) at the end of treatment were followed for 1 year and were offered retreatment for 1 additional year in the event of progression.

Dose escalation

Patients with advanced melanoma (MEL), non-small cell lung (NSCLC), renal cell carcinoma (RCC), castration-resistant prostate (CRPC) and colorectal cancer (CRC) were eligible to enroll. Cohorts of 3-6 patients per dose level were enrolled sequentially at 1.0, 3.0, and 10.0 mg/kg. Dose escalation proceeded when a minimum of 3 patients had completed the safety evaluation period (56 days) at the given dose level, with dose-

limiting toxicity in less than one-third of patients. Intra-patient dose escalation was not permitted.

Cohort expansion

A maximum tolerated dose (MTD) was not reached. Initially, 5 expansion cohorts of approximately 16 patients each were enrolled at 10 mg/kg for MEL, NSCLC, RCC, CRPC and CRC. Based on initial signals of activity, additional expansion cohorts of approximately 16 patients each were enrolled for MEL (at 1.0 and 3.0 mg/kg, followed by cohorts randomized to 0.1, 0.3, or 1.0 mg/kg), NSCLC (squamous or nonsquamous histology cohorts randomized to 1, 3, or 10 mg/kg), and RCC (at 1.0 mg/kg).

Patients

Eligible patients had documented advanced solid tumors; age >18 years; life expectancy >12 weeks; Eastern Cooperative Oncology Group performance status of ≤2; measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST), v1.0 with modification (*see* Topalian *et al.*, 2012b); adequate hematologic, hepatic, and renal function; and received 1-5 prior systemic treatment regimens. Patients with stable treated brain metastases were enrolled. Exclusion criteria included a history of chronic autoimmune disease, prior therapy with T-cell modulating Abs (*e.g.*, anti-CTLA-4), conditions requiring immunosuppressive medications, and chronic infections (HIV, hepatitis B or C).

A total of 296 patients with advanced solid tumors including MEL (n=104), NSCLC (n=122), RCC (n=34), CRPC (n=17), and CRC (n=19) were treated with BMS-936558 for 40 months up to February 2012. By March 2013, 304 patients including patients with non-small cell lung cancer (n=127), melanoma (n=107), RCC (n=34), CRPC (n=17), and CRC (n=19) had been treated with BMS-936558 from October 2008 through March 2012, all with a minimum of one year and up to about 4.4 years of observation. Two patients did not receive a full cycle of treatment and were not considered response-evaluable. The majority of patients were heavily pretreated, with 47% having received at least 3 prior regimens. Notable prior therapies included immunotherapy (64%) and B-RAF inhibitor (8%) in MEL patients; platinum-based chemotherapy (94%) and tyrosine kinase inhibitors (TKIs, 34%) in NSCLC patients; and nephrectomy (94%), immunotherapy (59%), and anti-angiogenic therapy (74%) in RCC patients. Baseline characteristics of the total treated population (N=296) were similar to

those of the efficacy population (response evaluable patients, N=236). Details on the patient pre-treatments are provided in Topalian *et al.*, 2012b.

Statistical analysis

All patients (N=304) treated as of the date of analysis (March 2013) were used for summaries of baseline characteristics and AEs. Pharmacokinetic and molecular-marker populations consisted of treated patients with available data as of the date of analysis. The efficacy population consisted of response-evaluable patients commencing treatment at least 8 months before the date of analysis. Tumor measurements were collected after each treatment cycle (4 doses) by investigators. Individual best objective responses based on the tumor measurements were assessed by the sponsor per modified RECIST v1.0. Objective response was confirmed by at least one sequential tumor assessment. Objective response and stable disease rates were estimated with confidence intervals using the Clopper-Pearson method. Time-to-event endpoints including progression-free survival, overall survival, survival rates, and duration of response, were estimated using the Kaplan-Meier method. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA), version 14.1. AEs of special interest (AEOSIs), with potential immune-related etiologies, defined as adverse events that require more frequent monitoring and/or unique intervention, were identified using a pre-defined list of MeDRA terms. Individual best ORs were derived from investigator-reported data per modified RECIST v1.0. OR was confirmed by at least one sequential tumor assessment and OR rate (ORR=$\{[CR + PR] \div n\} \times 100$) was calculated.

EXAMPLE 5

Safety Evaluations on Patients Treated with Anti-PD-1 Antibody

Safety evaluations, including clinical examination and laboratory assessments, were conducted in all treated patients at baseline and regular intervals up to 100 days following last administration of drug. The severity of AEs was graded based on the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE), v3.0. Computed tomography (CT) or magnetic resonance imaging was performed for tumor assessment at baseline and following each treatment cycle.

A MTD was not defined across the doses of BMS-936558 tested on this study. A relative BMS-936558 dose intensity of 90% or higher was achieved in 87% of patients (*see* Topalian *et al.*, 2012b, for details). AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA), version 14.1. AEOSIs were identified using a pre-

defined list of MeDRA terms. Fifteen of 296 (5%) patients discontinued treatment due to BMS-936558-related AEs. As of the date of analysis, 62 (21%) patients had died, with disease progression being the most common cause of death (Topalian *et al.*, 2012b).

The most common adverse events, regardless of causality included fatigue, decreased appetite, diarrhea, nausea, cough, dyspnea, constipation, vomiting, rash, pyrexia and pruritus (Topalian *et al.*, 2012b). Common BMS-936558-related AEs included fatigue, rash, diarrhea, decreased appetite, and nausea. The majority of the events were low grade, with grade 3-4 drug-related AEs observed in 41 of 296 (14%) patients. Drug-related serious AEs occurred in 32 of 296 (11%) patients (Topalian *et al.*, 2012b). The spectrum, frequency, and severity of BMS-936558-related AEs were generally similar across the dose levels tested. Drug-related AEOSIs, with potential immune-related etiologies, included pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis among others. Hepatic or gastrointestinal AEOSIs were managed with treatment interruption and, as necessary, with administration of corticosteroids. Among patients treated to-date, these AEs (in 13 patients with diarrhea; 11 patients with hepatic AEs) were reversible in all cases. Endocrine AEOSIs were managed with replacement therapy. At the discretion of the treating physician, patients successfully reinitiated treatment with BMS-936558. Drug-related pneumonitis occurred in 9 of 296 (3%) patients. Grade 3-4 pneumonitis developed in 3 patients (1%). No clear relationship between the occurrence of pneumonitis and tumor type, dose level, or the number of doses received was noted. Early grade pneumonitis was generally reversible with treatment discontinuation and corticosteroid administration. In 3 patients with pneumonitis, infliximab and/or mycophenolate were utilized for additional immunosuppression; however, given the small number of patients and variable outcomes, the effectiveness of this treatment is unclear. There were 3 (1%) drug-related deaths due to pneumonitis (2 NSCLC patients, 1 CRC).

EXAMPLE 6

Pharmacokinetics/Pharmacodynamics Analyses on Anti-PD-1 Antibody

For pharmacokinetic (PK) analyses, serial blood samples were collected and serum concentrations of BMS-936558 were quantified using by ELISA. For pharmacodynamic (PD) analysis, peripheral blood mononuclear cells were isolated from patients at baseline and following cycle 1 to estimate PD-1 receptor occupancy (RO) by BMS-936558 on circulating CD3+ T-cells via flow cytometry (Brahmer *et al.*, 2010).

The maximum concentration of BMS-936558 was observed at a median T_{max} of 1-4 hours after the start of infusion. The PK of BMS-936558 was linear with a dose proportional increase in C_{max} and $AUC_{(0\text{-}14\ d)}$ in the dose range of 0.1-10 mg/kg (n=35). BMS-936558 PD was assessed by PD-1 RO on circulating T-cells. PBMCs from 65 MEL patients treated with one cycle of BMS-936558 at 0.1-10 mg/kg biweekly demonstrated median occupancy of PD-1 molecules on circulating $CD3^+$ T-cells by BMS-936558 ranging from 64%-70% (*see* Topalian *et al.*, 2012b, for details).

EXAMPLE 7

Antitumor Efficacy Exhibited by Anti-PD-1 Antibody

Analysis of data obtained since February 2012 is ongoing; thus, unless otherwise noted, the data presented below were obtained as of February 2012. Clinical antitumor activity was observed at all BMS-936558 doses tested. ORs (confirmed CR or PR) were observed in a substantial portion of patients with NSCLC, MEL, and RCC (Tables 1-3; Figure 4), and in various sites of metastatic disease including liver, lung, lymph nodes, and bone (Figures 5-7 and not shown). Tumor regressions followed conventional as well as "immune-related" patterns of response, such as prolonged reduction in tumor burden in the presence of new lesions. Individual best overall responses were derived from investigator-reported data according to modified RECIST v1.0. OR was confirmed by at least one sequential tumor assessment. At the time of data analysis, 2 patients with NSCLC who were treated with 10 mg/kg had unconfirmed responses, and 8 additional patients (with MEL, NSCLC, or RCC) had a persistent reduction in baseline target lesions in the presence of new lesions, *(i.e.*, an "immune-related" response pattern). None of these patients was categorized as a responder for the purpose of calculating OR rates. Antitumor responses and/or prolonged disease stabilization were observed in patients irrespective of prior therapies received (*see* summary of progression free interval for patients with OR and SD in Supplementary Appendix 4 of Topalian *et al.*, 2012b).

In NSCLC patients, 14 ORs were observed at BMS-936558 doses of 1, 3, or 10 mg/kg with response rates of 6%, 32%, and 18%, respectively. ORs were observed across NSCLC histologies: 6 responders of 18 squamous (33%), 7 responders of 56 nonsquamous (13%), and 1 of 2 unknown. All 14 patients with ORs started treatment $\geq$ 24 weeks before data analysis, and of these, 8 had response duration $\geq$ 24 weeks (Table 1). Stable disease (SD) lasting $\geq$ 24 weeks was observed in 5 (7%) NSCLC patients, all with nonsquamous histology. Among MEL patients, 26 ORs were observed at doses

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ranging from 0.1-10 mg/kg, with response rates ranging from 19%-41% per dose level. At the 3 mg/kg dose level, ORs were noted in 7 of 17 (41%) patients. Of 26 MEL patients who achieved an OR, 17 started treatment ≥ 1 year before data analysis, and of these, 13 patients had an OR duration ≥ 1 yr. The remaining 8 patients with OR were on study < 1 year and 6 had responses ranging from 1.9-5.6 months. SD lasting ≥ 24 weeks was observed in 6 (6%) patients. In RCC patients, ORs occurred in 4 of 17 (24%) patients treated with a BMS-936558 dose of 1 mg/kg and 5 of 16 (31%) patients treated with 10 mg/kg. Among 8 RCC patients with OR who started treatment ≥ 1 year prior to data analysis, 5 (63%) had OR duration ≥ 1 yr. SD lasting ≥ 24 weeks was observed in an additional 9 (27%) patients.

Table 1. Clinical Activity of BMS-936558 in the Efficacy Population* (N=236)†

Tumor Type	Dose (mg/kg)	n	ORR‡ No. Patients (%) [95% CI]†	SD ≥ 24 wk No. Patients (%) [95% CI]	PFSR§ at 24 wk (%) [95% CI]
MEL	0.1	14	4 (29) [8-58]	1 (7) [0.2-34]	40 [13-66]
	1.0	27	8 (30) [14-50]	3 (11) [2-29]	45 [26-65]
	3.0	17	7 (41) [18-67]	1 (6) [0.1-29]	55 [30-80]
	10.0	20	4 (20) [6-44]	0	30 [9-51]
ALL MEL		94	26 (28) [19-38]	6 (6) [2-13]	41 [30-51]
NSCLC**					
All	1	18	1 (6) [0.1-27]	1 (6) [0.1-27]	16 [0-34]
Squamous	1	5	0	0	0
Nonsquamous	1	12	0	1 (8) [0.2-39]	14 [0-37]
Unknown	1	1	1(100) [3-100]	0	1
All	3	19	6 (32) [13-57]	2 (11) [1-33]	41 [18-64]
Squamous	3	6	3 (50) [12-88]	0	50 [10-90]
Nonsquamous	3	13	3 (23) [5-54]	2 (15) [2-45]	37 [10-64]
All	10	39	7 (18) [8-34]	2 (5) [0.6-17]	24 [11-38]
Squamous	10	7	3 (43) [10-82]	0	43 [6-80]
Nonsquamous	10	31	4 (13) [4-30]	2 (7) [0.8-21]	21 [6-36]
Unknown	10	1	0	0	0
ALL NSCLC		76	14 (18) [11-29]	5 (7) [2-15]	26 [16-36]

Tumor Type	Dose (mg/kg)	n	ORR[‡] No. Patients (%) [95% CI][†]	SD ≥ 24 wk No. Patients (%) [95% CI]	PFSR[§] at 24 wk (%) [95% CI]
All Squamous		18	6 (33) [13-59]	0	33 [12-55]
All Nonsquamous		56	7 (13) [5-24]	5 (9) [3-20]	22 [11-34]
RCC	1	17	4 (24) [7-50]	4 (24) [7-50]	47 [23-71]
	10	16	5 (31) [11-59][‡]	5 (31) [11-59][¶]	67 [43-91]
ALL RCC		33	9 (27) [13-46]	9 (27) [13-46]	56 [39-73

[*] The efficacy population consists of response-evaluable patients whose treatment was initiated at least 8 months before data analysis in February 2012, and had measurable disease at baseline and one of the following: at least 1 on-treatment scan or clinical evidence of disease progression or death.

[†] CR denotes complete response, MEL melanoma, NSCLC non-small cell lung cancer, ORR objective response rate, PFSR progression-free survival rate, PR partial response, RCC renal cell cancer, SD stable disease, n number of patients.

[‡] Objective response rates ({[CR + PR] ÷ n} × 100) have been calculated based on confirmed responses with confidence intervals calculated using the Clopper-Pearson method. Individual patient responses were adjudicated per RECIST v1.0 with modification (*see* Topalian *et al.*, 2012b).

[§] Progression-free survival rate was the proportion of patients who did not progress and were alive at 24 weeks calculated by the Kaplan-Meier methodology with confidence intervals using the Greenwood method.

[¶] One CR.

**One NSCLC patient who was treated at the 3 mg/kg dose level had an initial evaluation of progressive disease, subsequently had a PR, and was classified as a responder.

Table 2. Clinical Activity of BMS-936558 in the Efficacy Population*

Tumor Type	ORR[a] *No. of patients/total no. of patients (%) [95% CI]*	SD ≥24 wk *No. of patients/total no. of patients (%)* [95% CI]	Median Overall Survival (95% CI)	Overall Survival Rate (95% CI); patients at risk, n		
				1 y	2 y	3 y
NSCLC	20/122 (16.4) [10.3, 24.2]	11/122 (9.0) [4.6, 15.6]	NA	43 (33-53); 24	32 (18-47); 4	24 (7-41); 1
Squamous	9/48 (18.8) [8.9, 32.6]	NA	NA	NA	NA	NA
Non-sq.	11/73 (15.1) [7.8, 25.4]	NA	NA	NA	NA	NA
MEL	33/106 (31.1) [22.5, 40.9]	6/106 (5.7) [2.1, 11.9]	16.8 (12.5, NR)	61 (52-71); 50	44 (33-56); 24	40 (29-52); 1
RCC	10/34 (29.4) [15.1, 47.5]	9/34 (26.5) [12.9, 44.4]	NR (13.6, NR)	70 (55-86); 22	52 (32-72); 7	52 (32-72); 1

* The efficacy population consists of response-evaluable patients up to March 2013

[a] Objective response rate was calculated as {[CR + PR] ÷ n} x 100.

NR - not reached

NA - not available from July 3, 2012 data cut. The percentage of patients with stable disease for ≥ 36 weeks or ≥ 48 weeks [95% CI], median duration of response (months) and median progression-free survival (95% CI) were N/A.

The following results are drawn from preliminary analyses of BMS-936558 clinical efficacy data as of March 2013. Sustained survival, as reflected by median overall survival and 1- and 2-year landmark overall survival rates, was noted in each of the responding patient populations (Table 2). Median overall survivals of 9.6 months for lung cancer, 16.8 months for melanoma, and greater than 22 months for kidney cancer, were

observed. Thirteen patients with melanoma, lung or kidney cancer were characterized as having unconventional response patterns that did not meet RECIST criteria (*e.g.*, persistent reduction in target lesions in the presence of new lesions or following initial progression) (Wolchok *et al*, 2009).

Table 3. Duration of Objective Responses to BMS-936558*

Tumor Type	Dose (mg/kg)	No. of Patients with OR	Duration of Response (months)†
MEL	0.1	4	7.5+, 5.6+, 5.6, 5.6
	0.3	3	3.8+, 2.1+, 1.9+
	1	8	24.9+, 22.9, 20.3+, 19.3+, 18.4+, 7.6+, 5.6+, 5.3+
	3	7	22.4+, 18.3+, 15.2+, 12.9, 11.1, 9.3, 9.2+
	10	4	24.6+, 23.9+, 18.0+, 17.0
NSCLC§	1	1	9.2+
	3	6	30.8+, 7.6+, 5.5+, 3.7+, 1.9+, NA‡
	10	7	14.8+, 7.6+, 7.3+, 6.7, 4.2, 3.7+, 3.7
RCC	1	4	17.5+, 9.2+, 9.2, 5.6+
	10	5	22.3+. 21.7+, 12.9, 12.0, 8.4

*MEL denotes melanoma, NA not applicable, NSCLC non-small cell lung cancer, RCC renal cell cancer.

†Time from first response to time of documented progression, death, or for censored data, time to last tumor assessment.

‡One patient was treated beyond an initial evaluation of progressive disease and subsequently had a PR; this patient was classified as a responder for the purposes of calculating response rates by RECIST v1.0 but was not eligible for calculation of duration of response.

EXAMPLE 8

Measurement of Membranous PD-L1 Expression by Standard IHC Assay

IHC staining of PD-L1 was performed on pretreatment formalin-fixed paraffin-embedded (FFPE) tumor specimens using the murine anti-human PD-L1 mAb 5H1 (Dong *et al.*, 2002) in a standard IHC protocol (Taube *et al.*, 2012; Supp. Materials). Briefly, 5µm-FFPE sections mounted on glass slides were deparaffinized in xylene and antigen retrieval was performed using a Tris-EDTA buffer, pH 9.0 at 120 ºC for 10 min in

a Decloaking Chamber (Biocare Medical). Endogenous peroxidase, biotin and proteins were blocked (CAS system K1500, Dako; Avidin/biotin Blocking Kit, SP-2001, Vector Laboratories; Serotec Block ACE). The primary 5H1 Ab was applied at a concentration of 2 μg/ml and allowed to incubate at 4 °C for 20 h. Secondary Ab (biotinylated anti-mouse IgG1, 553441 BD) was applied at a concentration of 1 μg/ml for 30 min at room temperature (RT). The signal was then developed with amplification according to the manufacturer's protocol (CAS system K1500, Dako). Sections were counterstained with hematoxylin, dehydrated in ethanol and cleared in xylene, and a coverslip was applied.

The percentage of tumor cells exhibiting cell surface staining for PD-L1 was scored by two independent pathologists who were blinded to treatment outcomes. PD-L1 positivity was defined per specimen by a 5% expression threshold (Taube *et al.*, 2012; Thompson *et al.*, 2006), and in cases with multiple specimens, if any specimen met this criterion. A Fisher's exact test was applied to assess the association between PD-L1 expression and OR, noting, however, that this analysis was based in part on optional biopsies from a non-random subset of the population and testing of a statistical hypothesis was not pre-specified.

Sixty-one pretreatment tumor specimens from 42 patients (18 MEL, 10 NSCLC, 7 CRC, 5 RCC, and 2 CRPC) were analyzed for tumor cell surface PD-L1 expression (Figure 8). Biopsy specimens from 25 of 42 patients were positive for PD-L1 expression by IHC. A Fisher's exact test was applied to assess the association between PD-L1 expression and OR in a post-hoc analysis. Among the 42 surface-PD-L1^{+} patients, 9 (36%) achieved an OR. Importantly, among 17 patients with PD-L1^{-} tumors, none achieved an OR**.** Thus, in a subset of patients cell surface expression of PD-L1 on tumor cells in pretreatment biopsies is associated with an increased rate of OR among patients treated with BMS-936558, while no patients with documented PD-L1-negative tumors experienced an OR. These data indicate that tumor PD-L1 expression is a molecular marker that can enable patient selection for anti-PD-1 immunotherapy.

EXAMPLE 9

Isolation of Rabbit mAbs that Detect Membranous hPD-L1 Antigen in FFPE Tissues

Rabbit Abs against human PD-L1 polypeptide were prepared by Epitomics, Inc. (Burlingame, CA) by immunization of rabbits using a recombinant human PD-L1 fusion protein. Antiserum titers were evaluated using standard direct ELISA with the hPD-L1 antigen and cell ELISA using transfected cells overexpressing hPD-L1. These Abs were

also screened for their ability to bind to PD-L1 by IHC assay of FFPE tissue sections. The rabbit with the highest Ab titer was selected for splenectomy. Lymphocytes isolated from the spleen were fused to myeloma cells in 40 x 96-well plates, and screened by ELISA against the immunizing PD-L1 antigen and by cell ELISA against cells overexpressing hPD-L1. Positive clones were expanded into 24-well plates, and confirmatory screens were conducted by direct ELISA and cell ELISA. The supernatants (sups) of clones that were specific to the screening antigen were re-screened by IHC.

A set of mouse anti-hPD-L1 mAbs were also produced by immunization of mice using a protocol similar to that described above for the rabbit mAbs.

Out of a total of 185 multiclones from both rabbit and mouse immunizations screened, only ten rabbit multiclone Abs specifically detected the membranous form of hPD-L1. None of the purified mouse subclones were found to specifically detect cell surface hPD-L1. Sixty subclones from the top five rabbit multiclones (designated Nos. 13, 20, 28, 29 and 49, each comprising 12 subclones) were screened initially by IHC on FFPE low density tissue microarrays (TMAs), followed by confirmation and specificity verification in narrowed 25 subclones. Rabbit IgG was used as a negative isotype control, and mAb 5H1 (Dong *et al.*, 2002) was used as the positive control. Specificity was further verified by antigen preabsorption assay. Through two rounds of IHC, the following 15 purified subclones were selected as the most promising Abs in terms of specificity and intensity of staining: 13-1, 13-3, 13-7, 13-8; 20-5, 20-7, 20-12, 20-6; 28-1, 28-8, 28-12; 49-5, 49-7, 49-9; and 29-8. Immunoreactivity data on these selected Abs are summarized in Table 4.

Additional assays were performed to further characterize the purified Ab clones, including determining binding affinity and cross-competition among the Abs (to identify overlapping versus different epitope regions) by surface plasmon resonance. All the Abs exhibited high binding affinity ($K_D < 10^{-9}$ M). These 15 purified clones were also re-screened by IHC on FFPE low density TMA or regular sections against various cell and tissue types known to be positive or negative for cell surface expression of PD-L1. Rabbit IgG was used as the isotype control, and mAb 5H1 was used as the positive control. At high concentration (10 μg/ml), clones 28-x and 49-x displayed low to moderate levels of background staining in tissues, while clones 13-x exhibited no background staining, which suggests that the 13-x clones have a wider dynamic range. The 20-x clones displayed various degree of background staining which was primarily cytoplasmic and diffuse. The clone with most robust detection specifically of membranous PD-L1, rabbit

clone 28-8 (K_D = 100 p M, as determined by SPR), was selected as the lead Ab for subsequent IHC assays. MAbs 28-1, 28-12, 20-12 and 29-8 had K_D values of 130 pM, 94 pM, 160 pM and 1200 pM, respectively. The sequences of the V_H and V_κ regions of mAb 28-8 are set forth in SEQ ID NOs. 35 and 36, respectively. The 28-8 Ab was shown to recognize a different epitope from mouse mAb 5H1, based on SPR analysis. Clones 28-1, 28-12, 29-8 and 20-12 were the next best Abs in terms of robust detection of membranous PD-L1 in FFPE tissues. Although mAb 13-1 had the best specificity in terms of detection of membranous PD-L1, the maximal detection level was lower than that of the other lead Abs. Western blotting was also performed with plus/minus antigen competition to verify the specificity of the top selected Abs for PD-L1.

Table 4. Immunoreactivity of Rabbit Anti-hPD-L1 mAbs

Antibody Name	Specific Staining		Non-Specific staining
	Pos. vs Neg. Staining on PD-L1 Cells*	Intensity Range on Tissues† (Very High, High, Medium, Low)	Background Staining on Tissues (High, Medium, Low)
13-1	Pos	Low to Very High	None
13-3	Pos	Low to High	None
13-7	Pos	Low to High	None
13-8	Pos	Low to High	None
20-5	Pos	Low to Very High	High
20-6	Pos	Low to High	Medium
20-7	Pos	Low to High	Medium
20-12	Pos	Low to High	Medium
28-1	Pos	Low to Very High	None
28-8	Pos	Medium to Very High	None
28-10	Pos	Medium to Very High	Low
28-12	Pos	Low to Very High	None
49-5	Pos	Low to High	None
49-7	Pos	Low to High	Low
49-9	Pos	Low to High	None
5H1	Pos	High to Very High	None
Rb IgG	Neg	Neg	None

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*PD-L1 stably transfected CHO cells vs. CHO-S control;

†PD-L1 positive tissues included placenta and one non-small cell lung cancer; Detection up to "very high" expression suggests better sensitivity at detecting membranous PD-L1.

The binding of mAbs 5H1 and 28-8 to membranous PD-L1 in FFPE test tissue samples comprising tumor cells and tumor-infiltrating inflammatory cells from different types of tumors was compared. Membranous PD-L1 expression was evaluated using the histoscore method performed by 2 independent pathologists. Four NSCLC, 2 MEL, and 2 RCC tumors were stained with 28-8 at 2 mg/ml and 5H1 at 5 mg/ml. The data are tabulated in Table 5, and shown graphically in Figure 9. The rabbit mAb 28-8 showed better detection (higher histoscores) for 7 out of 10 samples using 2.5-fold less Ab, and in only one sample was the histoscore for 5H1 slightly higher than for mAb 28-8.

Table 5. Comparison of mAbs 28-8 and 5H1 by histoscore analysis

Tissue	Sample I.D.	Histoscore Average (5H1)	Histoscore Average (28-8)
NSCLC	1080754B	245	261
NSCLC	1080766B	103	130
NSCLC	1080790	40	37
NSCLC	1080993B	12	16
Mel	T030668	98	113
Mel	T980744	98	123
Mel	1168657B	0	0
Mel	T980747	1	9
RCC	1164619B	4	4
RCC	1167809B	108	125

Taube *et al.*, 2012 demonstrated by flow cytometry on cultured cells that mAb 5H1 bound to the cell surface, and the specificity of binding to PD-L1 was confirmed using a PD-L1 fusion protein to competitively block binding of the 5H1 mAb to tissue sections. These authors also compared 5H1 with a rabbit polyclonal anti-hPD-L1 Ab, 4059, previously described by Gadiot *et al.*, 2011, and found that whereas 5H1 showed a cell surface staining pattern on FFPE samples, Ab 4059 demonstrated diffuse cytoplasmic

staining. Further, when 5H1 was compared to Ab 4059 by western blot analysis, Ab 4059 bound to multiple proteins in lysates of melanoma cells in addition to a 50 kDa protein corresponding to the expected mass of glycosylated PD-L1, in contrast to 5H1 which specifically detected the 50 kDa band of glycosylated PD-L1 (Taube *et al.*, 2012).

In the present study, an automated IHC assay (*see* Example 10) was used to evaluate the binding of several commercially available anti-PD-L1 Abs and 5H1 (Dong *et al.*, 2002) to FFPE tissue samples containing various cells expressing PD-L1. The results, summarized in Table 6, show that none of the commercially available Abs tested specifically recognized membranous PD-L1 expression in human tissues known to express PD-L1, or to clearly distinguish CHO cells expressing PD-L1 versus the untransfected parent CHO cells that did not express PD-L1. The inability of the polyclonal Ab (pAb) 4059 to bind specifically recognized membranous PD-L1 is consistent with the findings of Taube *et al.*, 2012. The binding of 28-8 was similar to that of 5H1 in this assay, though histoscore analysis suggests that 28-8 performs better than 5H1.

Table 6. Binding of mAbs to FFPE Samples Containing PD-L1-expressing cells

Source	Antibody Types	Clone No. (mAb)/ Catalog No. (pAb)	Pos. vs. Neg. Staining on PD-L1 Cells*	Human Positive Tissues†
MBL	mAb	27A2	Failed	Failed
BioLegend	mAb	29E.2A3	Failed	Failed
eBiosciences	mAb	M1H1	No Staining	No staining
Collaborator	mAb	5H1	Passed	Passed
ProSci	pAb	4059	Failed	Failed
LifeSpan BioSciences	pAb	LS-B480/0604	Failed	Failed

*PD-L1 stably transfected CHO cells vs. parent CHO-S negative control;

†PD-L1 positive tissues included tonsil and/or thymus;

mAb, mouse mAb; pAb, rabbit polyclonal Ab.

EXAMPLE 10

Development of Automated IHC Protocol for Assessing PD-L1 Expression

An automated IHC protocol was developed to assay PD-L1 expression in FFPE specimens. Tissue sections (4 μm) were mounted on slides, deparaffinized in an autostainer (Leica) by soaking twice for 5 min in xylene, and re-hydrated through soaking twice for 2 min each time in 100% EtOH, twice in 95% (v/v) EtOH, once in 70% (v/v) EtOH, and once in de-ionized water (dH_2O). Antigen retrieval was performed using a decloaking chamber (Biocare Medical Decloaking Chamber Plus) and Dako pH 6 buffer, heated to 110ºC (P1) for 10 min, then moved to the next step (P2 FAN ON at 98ºC; FAN OFF at 90ºC). The slides were cooled at room temperature (RT) for 15 min and rinsed with water for about 1 min.

Reagents were set up on an autostainer (BIOGENEX® i6000), using a pap pen to define the tissue area. The IHC assay, run using the autostainer in research mode, comprised the following steps: neutralizing endogenous peroxidase using the Peroxidase Block (Leica) for 10 min, followed by rinsing 3 times with IHC wash buffer (Dako); applying Protein Block (Leica) to the slides, and incubating for 10 min at RT, followed by washing 3 times with wash buffer; applying the primary Ab to the slides (2 μg/ml) and incubating for 1 h at RT, followed by washing 6 times with wash buffer; adding Post Primary Block (NovoLink Kit) to the slides and incubating for 30 min, followed by washing 6 times with wash buffer; adding NovoLink Polymer (NovoLink Kit) to the slides and incubating for 30 min, followed by washing 6 times with wash buffer; adding the DAB chromogen substrates (NovoLink Kit) and developing for 3 min, followed by rinsing 5 times with dH_2O at RT; counterstaining with hematoxylin (NovoLink Kit) for 1 min at RT, followed by washing 3 times with dH_2O for 5 times at RT. The primary Ab was selected from the rabbit anti-PD-L1 Abs shown in Table 4; mAb 28-8 was the preferred Ab. As a negative control, rabbit IgG (Dako) was used. The tissue sections were dehydrated using a Leica autostainer by washing once for 2 min in 70% EtOH, twice for 2 min in 95% EtOH, and three times for 2 min in 70% EtOH, then cleared by washing three times for 5 min in xylene. The sections were permanently mounted with permount to the slide, covered with a coverslip, and transferred to a chemical hood to dry.

EXAMPLE 11

Design of Phase I Clinical Study on Anti-PD-L1 Antibody

Study design

A Phase I study was conducted to assess the safety and tolerability of BMS-936559 (also referred to herein and in U.S. Patent No. 7,943,743 as 12A4) in patients with selected advanced solid tumors. Secondary objectives included initial assessment of the antitumor activity of BMS-936559 and pharmacokinetic evaluation. Pharmacodynamic measures were included under exploratory objectives. Patients were treated in 6-week cycles of BMS-936559 administered as a 60-minute intravenous infusion every 2 weeks on days 1, 15, and 29 of each cycle. Patients continued treatment for up to 16 cycles unless they experienced unacceptable toxicity, disease progression, or withdrew consent. In some patients who were clinically stable, treatment beyond initial disease progression was permitted until further progression was confirmed.

Dose escalation

Patients with advanced NSCLC, MEL, CRC, RCC, ovarian (OV), gastric (GC), breast (BC), and pancreatic (PC) carcinoma were eligible to enroll. Using an accelerated titration design, safety was assessed at doses of 0.3, 1, 3, and 10 mg/kg. One patient was enrolled in each successive cohort until there was a ≥ grade 2 drug-related AE during cycle 1. Two additional patients were then enrolled at that dose level and the study was transitioned to a standard 3+3 design. Intra-patient dose escalation or de-escalation was not permitted. The maximum tolerated dose (MTD) was defined as the highest dose where less than one-third of patients had a dose-limiting toxicity.

Cohort expansion

Initially, 5 expansion cohorts (n=16/cohort) were enrolled at 10 mg/kg for patients with NSCLC, MEL, RCC, OV, and CRC. Based on initial signals of activity, additional expansion cohorts (up to n=16/cohort) were enrolled for MEL (at 1.0 and 3.0 mg/kg), NSCLC (squamous or nonsquamous histology cohorts randomized to 1, 3, or 10 mg/kg), and at 10 mg/kg for PC, BC, and GC.

Patients

Patients were required to have documented advanced NSCLC, MEL, RCC, OV, CRC, PC, GC, or BC, and have failed at least one prior tumor-appropriate therapy for advanced/metastatic disease (except for PC or GC patients who could be treatment-

naïve). Other inclusion criteria included age ≥ 18 years, life expectancy ≥ 12 weeks, Eastern Cooperative Oncology Group performance status of ≤ 2, measurable disease as defined by RECIST v1.0, and adequate hematologic, hepatic, and renal function. Patients with treated brain metastases were allowed, if stable for at least 8 weeks. Major exclusion criteria included a history of autoimmune disease or other diseases requiring systemic steroids or immunosuppressive medication, prior therapy with T cell- modulating Abs (including anti-PD-1, anti-PD-L1 and anti-CTLA-4), history of HIV, or active hepatitis B or C.

In this ongoing study, 207 patients with NSCLC (n=75), MEL (n=55), CRC (n=18), RCC (n=17), OV (n=17), PC (n=14), GC (n=7), or BC (n=4) were treated with BMS-936559 during a 34-month period and are included in the safety data. Efficacy was characterized in 160 response-evaluable patients. The baseline demographic characteristics of the total and response-evaluable patient populations were very similar (Brahmer *et al.*, 2012). Among treated patients, 86% had received prior chemotherapy and 28% immunologic or biological therapy. Prior therapies by tumor type included immunotherapy (56%) and B-RAF inhibitor (9%) in patients with MEL; platinum-based chemotherapy (95%) and tyrosine kinase inhibitors (TKI; 41%) in patients with NSCLC; and nephrectomy (94%), anti-angiogenic therapy (82%), and immunotherapy (41%) in patients with RCC (*see* Brahmer *et al.*, 2012) for more details on patient pre-treatments).

Statistical analysis

All 207 patients commencing treatment as of the date of analysis were used for summaries of baseline characteristics and AEs. The efficacy population consisted of 160 response-evaluable patients who initiated treatment at least 7 months before the date of analysis. AEs were coded using MedDRA v14.1. Individual best overall responses were derived from radiographic scan measurements according to modified RECIST v1.0. ORs were confirmed by at least one sequential tumor assessment. Additional details regarding statistical methods are provided in Brahmer *et al.*, 2012.

EXAMPLE 12

Safety Evaluations on Patients Treated with Anti-PD-L1 Antibody

Safety evaluations (clinical examination and laboratory assessments) were conducted on all treated patients at baseline and regular intervals (weekly during cycle 1 and biweekly thereafter). AE severity was graded based on the NCI CTCAE, v3.0. Disease assessment via computed tomography (CT) scans or magnetic resonance imaging

was performed at baseline and prior to each treatment cycle.

A MTD was not reached up to the highest tested dose of 10 mg/kg of BMS-936559. The median duration of therapy was 12 weeks (range 2.0-111.1 weeks). A relative dose intensity of ≥ 90% was achieved in 86% of patients. Twelve of 207 patients (6%) discontinued treatment due to a BMS-936559-related AE (*see* Brahmer *et al.*, 2012, for details).

AEs regardless of causality (any grade) were reported in 188 of 207 patients. Investigator-assessed BMS-936559-related AEs were noted in 126 of 207 (61%) patients. The most common drug-related AEs were fatigue, infusion reactions, diarrhea, arthralgia, rash, nausea, pruritus, and headache. Most events were low grade with BMS-936559-related grade 3-4 events noted in 19 of 207 (9%) patients (Brahmer *et al.*, 2012). The spectrum, frequency, and severity of BMS-936559-related AEs were similar across the dose levels, with the exception of infusion reactions. Drug-related AEOSIs, with potential immune-related etiologies, were observed in 81 of 207 (39%) of the patients and included rash, hypothyroidism, hepatitis, and single cases each of sarcoidosis, endophthalmitis, diabetes mellitus, and myasthenia gravis (Brahmer *et al.*, 2012). These AEs were predominantly grade 1-2 and generally reversible with treatment interruption or discontinuation. Notably, 9 patients were treated with corticosteroids for the management of AEs. AEs improved or resolved in all patients. Furthermore, 4 of these 9 patients maintained disease control despite treatment with corticosteroids. Endocrine AEs were managed with replacement therapy and patients reinitiated treatment with BMS-936559 at the discretion of the treating physician. Infusion reactions were observed in 21 of 207 (10%) patients, predominantly at 10 mg/kg. They were grade 1-2 with the exception of one grade 3 event at 10 mg/kg. Infusion reactions were generally rapidly reversible with antihistamines and antipyretics and, in some cases, corticosteroids. A prophylactic regimen with antihistamines and antipyretics was implemented during the study. Patients with grade 1-2 infusion reactions were able to continue treatment with BMS-936559 with prophylactic antihistamines and antipyretics and at a reduced infusion rate. BMS-936559-related serious AEs occurred in 11 of 207 (5%) patients. As of the data analysis date, 45 patients (22%) had died (Brahmer *et al.*, 2012); no drug-related deaths were observed.

EXAMPLE 13

Pharmacokinetics/Pharmacodynamics Analyses on Anti-PD-L1 Antibody

For PK analyses, serial blood samples were collected and serum concentrations of BMS-936559 were quantified by ELISA. Peripheral blood mononuclear cells were isolated from patients at baseline and following one treatment cycle to assay PD-L1 RO by BMS-936559 on circulating CD3-positive T-cells via flow cytometry (Brahmer *et al.*, 2010).

Serum concentrations of BMS-936559 increased in a dose-dependent manner from 1-10 mg/kg (n=131). Geometric mean area under the curve (0-14 days) for the 1, 3, and 10 mg/kg dose levels were 2210, 7750, and 36620 μg/mL•hr (coefficient of variation [CV] 34-59%), respectively; geometric mean peak concentrations at these dose levels were 27, 83, and 272 μg/mL (CV 30−34%), respectively, after the first dose. The half-life of BMS-936559 was estimated from population pharmacokinetic data as approximately 15 days. PD-L1 RO on CD3-positive peripheral blood lymphocytes was assessed in 29 MEL patients at the end of 1 cycle of treatment, at BMS-936559 doses from 1-10 mg/kg. Median RO exceeded 65% for all groups (Brahmer *et al.*, 2012).

EXAMPLE 14

Antitumor Efficacy Exhibited by Anti-PD-L1 Antibody

One-hundred and sixty patients out of the 207 treated were evaluable for response and included those with NSCLC, MEL, CRC, RCC, OV, and PC, but not patients with GC or BC. Clinical activity was observed at all doses ≥ 1 mg/kg (Brahmer *et al.*, 2012). ORs (confirmed complete [CR] or partial [PR] responses) were observed in patients with MEL, NSCLC, RCC, and OV (Table 7), as illustrated by representative spider plots and CT scans (Figures 10-13), and many ORs were also durable (Table 8). Four additional patients had a persistent reduction in target lesions in the presence of new lesions, consistent with an "immune-related" pattern of response; however, for the purpose of calculating response rates, they were not categorized as responders. Antitumor responses and/or prolonged stable disease (SD) were observed in patients with a variety of prior therapies received. ORs were observed even in patients with an extensive burden of metastatic disease.

In patients with MEL, there were 9 ORs across the 1, 3, and 10 mg/kg dose levels, with response rates of 6%, 29%, and 19%, respectively. Three MEL patients achieved a CR. All 9 MEL patients who experienced an OR started treatment ≥ 1 year prior to data

analysis; of these 5 had a response duration ≥ 1 year. Additionally 14 MEL patients (27%) had SD lasting ≥ 24 weeks. In patients with NSCLC, there were 5 ORs amongst the 3 and 10 mg/kg dose levels, with response rates of 8% and 16%, respectively. There were ORs in patients with non-squamous (n=4) or squamous histology (n=1). All 5 NSCLC responders started treatment ≥ 24 weeks prior to data analysis; of these, 3 had responses lasting ≥ 24 weeks. Six additional NSCLC patients had SD lasting ≥ 24 weeks. There was 1 PR out of 17 patients with OV (6% response rate) and 3 patients (18%) with SD lasting ≥ 24 weeks, all at the 10 mg/kg dose. In patients with RCC, there were ORs in 2 of 17 (12%) patients treated at 10 mg/kg with responses lasting 4 and 18 months, respectively. Seven additional RCC patients had SD lasting ≥ 24 weeks.

Table 7. Clinical Activity of BMS-936559 in 160 Patients, Response Evaluable*

Tumor Type	Dose (mg/kg)	n	ORR§ No. of patients (%) [95% CI]	SD ≥ 24 wk No. of patients (%) [95% CI]	PFSR** at 24 wk (%) [95% CI]
MEL	0.3	1	0 [0-98]	0 [0-98]	N/A
	1	18	1 (6) [0.1-27]	6 (33) [13-59]	39 [16-61]
	3	17	5 (29)† [10-56]	3 (18) [4-43]	47 [21-72]
	10	16	3 (19)†† [4-46]	5 (31) [11-59]	44 [19-68]
ALL MEL		52	9 (17) (8-30)	14 (27) [16-41]	42 [28-56]
NSCLC§	1	11	0 [0-29]	0 [0-29]	N/A
Squamous	1	1	0 [0-98]	0 [0-98]	N/A
Non-Squamous	1	10	0 [0-31]	0 [0-31]	N/A
	3	13	1 (8) [0.2-36]	1 (8) [0.2-36]	34 [7-60]
Squamous	3	4	0 [0-60]	1 (25) [0.6-81]	50 [1-99]
Non-Squamous	3	9	1 (11) [0.3-48]	0 [0-34]	25 [0-55]
	10	25	4 (16) [5-36]	5 (20) [7-41]	46 [25-67]
Squamous	10	8	1 (13) [0.3-53]	2 (25) [3-65]	47 [10-83]
Non-Squamous	10	17	3 (18) [4-43]	3 (18) [4-43]	46 [20-72]
ALL NCSLC		49	5 (10) [3-22]	6 (12) [5-25]	31 [17-45]
ALL Squamous		13	1 (8) [0.2-36]	3 (23.1) [5-54]	43 [15-71]
ALL Non-Squamous		36	4 (11) [3-26]	3 (8) [2-23]	26 [10-42]

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Tumor Type	Dose (mg/kg)	n	ORR[§] No. of patients (%) [95% CI]	SD ≥ 24 wk No. of patients (%) [95% CI]	PFSR** at 24 wk (%) [95% CI]
OV	3	1	0 [0-98]	0 [0-98]	N/A
	10	16	1 (6) [0.2-30]	3 (19) [4-46]	25 [4-46]
ALL OV		17	1 (6) [0.1-29]	3 (18) [4-43]	22 [2-43]
RCC	10	17	2 (12) [2-36]	7 (41) [18-67]	53 [29-77]

CI denotes Confidence intervals, MEL melanoma, RCC renal cell carcinoma, NSCLC non-small cell lung cancer, OV ovarian cancer, RCC renal cell carcinoma, N/A not applicable, ORR objective response rate (complete response + partial response), SD stable disease, and PFSR progression-free survival rate.

[*]Efficacy population consists of response-evaluable patients who initiated treatment at least 7 months prior to the date of analysis and had measurable disease at a baseline tumor assessment and at least one of the following: an on-study tumor assessment, clinical progression, or death.

[†]Includes two CRs.

[††]Includes one CR.

[§]Objective response rates ({[CR + PR] ÷ n} × 100) are based on confirmed responses only, with confidence intervals calculated using the Clopper-Pearson method.

** Progression-free survival rate was the proportion of patients who did not progress, and were alive at 24 weeks, calculated by the Kaplan-Meier methodology, with confidence intervals using the Greenwood method

Individual patient responses were adjudicated per RECIST v1.0 with modification (see study protocol in Brahmer *et al.* (2012) *N. Engl. J. Med.* (submitted) for additional information).

Table 8. Duration of Objective Responses to BMS-936559*

Tumor Type	Dose (mg/kg)	No. of Patients with OR	Duration of Response (months)[†]
MEL	1	1	6.9

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Tumor Type	Dose (mg/kg)	No. of Patients with OR	Duration of Response (months)†
	3	5	23.5+, 22.9+, 16.2+, 4.1+, 3.5
	10	4	24.6+, 23.9+, 18.0+, 17.0
NSCLC	1	0	9.2+
	3	1	2.3+
	10	4	16.6+, 12.6+, 9.8, 3.5
RCC	10	2	17, 4
OV	10	1	1.3+

*MEL denotes melanoma, NSCLC non-small cell lung cancer, RCC renal cell cancer, OV ovarian cancer.

†Time from first response to time of documented progression, death, or for censored data Denoted by +), time to last tumor assessment.

Sequence Listing Summary

SEQ ID NO:	Description
1	V_H amino acid sequence of 17D8
2	V_H amino acid sequence of 2D3
3	V_H amino acid sequence of 4H1
4	V_H amino acid sequence of 5C4
5	V_H amino acid sequence of 4A11
6	V_H amino acid sequence of 7D3
7	V_H amino acid sequence of 5F4
8	V_L amino acid sequence of 17D8
9	V_L amino acid sequence of 2D3
10	V_L amino acid sequence of 4H1
11	V_L amino acid sequence of 5C4
12	V_L amino acid sequence of 4A11
13	V_L amino acid sequence of 7D3
14	V_L amino acid sequence of 5F4

SEQ ID NO:	Description
15	V_H amino acid sequence of 3G10
16	V_H amino acid sequence of 12A4
17	V_H amino acid sequence of 10A5
18	V_H amino acid sequence of 5F8
19	V_H amino acid sequence of 10H10
20	V_H amino acid sequence of 1B12
21	V_H amino acid sequence of 7H1
22	V_H amino acid sequence of 11E6
23	V_H amino acid sequence of 12B7
24	V_H amino acid sequence of 13G4
25	V_L amino acid sequence of 3G10
26	V_L amino acid sequence of 12A4
27	V_L amino acid sequence of 10A5
28	V_L amino acid sequence of 5F8
29	V_L amino acid sequence of 10H10
30	V_L amino acid sequence of 1B12
31	V_L amino acid sequence of 7H1
32	V_L amino acid sequence of 11E6
33	V_L amino acid sequence of 12B7
34	V_L amino acid sequence of 13G4
35	V_H amino acid sequence of 28-8
36	V_L amino acid sequence of 28-8

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CLAIMS

What is claimed is:

1. A method of treating a subject afflicted with a cancer comprising administering to the subject a therapeutically effective amount of an antibody or an antigen-binding portion thereof that disrupts the interaction between Programmed Death-1 (PD-1) and Programmed Death Ligand-1 (PD-L1).

2. The method of claim 1, wherein the antibody or antigen-binding portion thereof binds specifically to PD-1.

3. The method of claim 1, wherein the antibody or antigen-binding portion thereof binds specifically to PD-L1.

4. The method of claim 1, wherein the subject has been pre-treated for the cancer.

5. The method of claim 1, wherein the cancer is an advanced, metastatic and/or refractory cancer.

6. The method of claim 1, wherein the administration of the antibody or antigen-binding portion thereof induces a durable clinical response in the subject.

7. The method of claim 3, wherein the cancer is selected from the group consisting of melanoma, renal cell carcinoma, squamous non-small cell lung cancer (NSCLC), non-squamous NSCLC, colorectal cancer, castration-resistant prostate cancer, ovarian cancer, gastric cancer, hepatocellular carcinoma, pancreatic carcinoma, squamous cell carcinoma of the head and neck, carcinomas of the esophagus, gastrointestinal tract and breast, and a hematological malignancy.

8. The method of claim 1, wherein the therapeutically effective amount of the antibody or antigen-binding portion thereof comprises a dose ranging from 0.1 to 10.0 mg/kg body weight which is administered at a dosing schedule of once per week, once every two weeks, or once a month.

9. A method for immunotherapy of a subject afflicted with cancer, which method comprises:

   (a) selecting a subject that is a suitable candidate for immunotherapy, the selecting comprising:

      (i) providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells;

      (ii) assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface; and

(iii) selecting the subject as a suitable candidate based on an assessment that the proportion of cells in the test tissue sample that express PD-L1 on the cell surface exceeds a predetermined threshold level; and

(b) administering a composition comprising a therapeutically effective amount of an anti-PD-1 antibody to the selected subject.

10. The method of claim 9, wherein the proportion of cells that express PD-L1 is assessed by performing an assay to determine the presence of PD-L1 polypeptide on the surface of cells in the test tissue sample.

11. The method of claim 9, wherein the test tissue sample is a formalin-fixed paraffin-embedded (FFPE) tissue sample.

12. The method of claim 11, wherein the presence of PD-L1 polypeptide is determined using an automated IHC assay.

13. The method of claim 12, wherein the IHC assay is performed using an anti-PD-L1 monoclonal antibody to bind to the PD-L1 polypeptide, wherein the anti-PD-L1 monoclonal antibody is selected from 28-8, 28-1, 28-12, 29-8, and 5H1.

14. The method of claim 9, wherein the predetermined threshold level is 1% of tumor cells or a single tumor-infiltrating inflammatory cell expressing cell surface PD-L1 as determined by automated IHC using mAb 28-8.

15. A monoclonal antibody or an antigen-binding portion thereof that binds specifically to a cell surface-expressed PD-L1 polypeptide in a formalin-fixed, paraffin-embedded (FFPE) tissue sample.

16. The monoclonal antibody or antigen-binding portion thereof of claim 15, which antibody or portion thereof comprises the CDR1, CDR2 and CDR3 regions in a heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 35, and the CDR1, CDR2 and CDR3 regions in a light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 36.

17. The monoclonal antibody or antigen-binding portion thereof of claim 15, which antibody or portion thereof comprises a heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 35, and a light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 36.

CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING

ABSTRACT

The disclosure provides a method for immunotherapy of a subject afflicted with cancer, comprises administering to the subject a composition comprising a therapeutically effective amount of an antibody that inhibits signaling from the PD-1/PD-L1 signaling pathway. This disclosure also provides a method for immunotherapy of a subject afflicted with cancer comprising selecting a subject that is a suitable candidate for immunotherapy based on an assessment that the proportion of cells in a test tissue sample from the subject that express PD-L1 on the cell surface exceeds a predetermined threshold level, and administering a therapeutically effective amount of an anti-PD-1 antibody to the selected subject. The invention additionally provides rabbit mAbs that bind specifically to a cell surface-expressed PD-L1 antigen in a FFPE tissue sample, and an automated IHC method for assessing cell surface expression in FFPE tissues using the provided anti-PD-L1 Abs.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING
First Named Inventor/Applicant Name:	John P. COGSWELL
Filer:	Ji Eun Kim/Nikiya Alexander
Attorney Docket Number:	3338.0630006/ELE/C-K

Filed as Large Entity

Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	300	300
UTILITY SEARCH FEE	1111	1	660	660
UTILITY EXAMINATION FEE	1311	1	760	760
REQUEST FOR PRIORITIZED EXAMINATION	1817	1	4000	4000
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Electronic Acknowledgement Receipt

EFS ID:	32876611
Application Number:	16006473
International Application Number:	
Confirmation Number:	5731
Title of Invention:	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING
First Named Inventor/Applicant Name:	John P. COGSWELL
Customer Number:	115018
Filer:	Ji Eun Kim/Nikiya Alexander
Filer Authorized By:	Ji Eun Kim
Attorney Docket Number:	3338.0630006/ELE/C-K
Receipt Date:	12-JUN-2018
Filing Date:	
Time Stamp:	17:10:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$5860
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Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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If you need help call the Patent Electronic Business Center at (866)
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: COGSWELL *et al.*	Confirmation No.: 5731
Applicant: Bristol-Myers Squibb Company	Art Unit: *To Be Assigned*
Application No.: 16/006,473	Examiner: *To Be Assigned*
(*Continuation of Appl. No. 14/950,748; Filed: November 24, 2015*)	Atty. Docket: 3338.0630006/ELE/C-K
Filed: June 12, 2018	

Title: **CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING**

Second Preliminary Amendment Under 37 C.F.R. § 1.115

Mail Stop Amendment

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

In advance of prosecution, Applicant submits the following amendments and remarks.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks and Arguments begin on page 5 of this paper.

It is not believed that extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any additional fees required to continue prosecution or appeal of this application (including issue fee, fees for net addition of claims or forwarding to appeal) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

1-17. (Cancelled)

18. (New) A method of treating a tumor in a human subject in need thereof, comprising administering to the subject about 10 mg/kg of an anti-PD-L1 antibody every 2 weeks, wherein the anti-PD-L1 antibody is administered intravenously over 60 minutes infusion; wherein the tumor is derived from a cancer of the urethra, the bladder, the ureter, or the renal pelvis; and wherein the tumor is refractory to a platinum based chemotherapy.

19. (New) The method of claim 18, wherein the tumor is advanced.

20. (New) The method of claim 18, wherein the tumor is locally advanced.

21. (New) The method of claim 18, wherein the tumor is metastatic.

22. (New) The method of claim 18, wherein the treatment lasts more than 12 weeks.

23. (New) The method of claim 18, wherein the anti-PD-L1 antibody is formulated in a pharmaceutical composition.

24. (New) The method of claim 23, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable salt, an anti-oxidant, an aqueous carrier, a non-aqueous carrier, an adjuvant, or any combination thereof.

25. (New) The method of claim 24, wherein the adjuvant comprises a preservative, a wetting agent, an emulsifying agent, a dispersing agent, or any combination thereof.

26. (New) The method of claim 24, wherein the salt comprises a sodium salt.

27. (New) The method of claim 24, wherein the salt comprises sodium chloride.

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28. (New) The method of claim 18, wherein the tumor is derived from a cancer of the urethra.

29. (New) The method of claim 18, wherein the tumor is derived from a cancer of the bladder.

30. (New) The method of claim 18, wherein the tumor is derived from a cancer of the ureter.

31. (New) The method of claim 18, wherein the tumor is derived from a cancer of the renal pelvis.

32. (New) The method of claim 18, wherein the subject is PD-L1 positive.

33. (New) The method of claim 18, wherein the subject is PD-L1 negative.

34. (New) The method of claim 18, further comprising administering an anti-cancer agent.

35. (New) The method of claim 19, further comprising administering an anti-cancer agent.

36. (New) The method of claim 20, further comprising administering an anti-cancer agent.

37. (New) The method of claim 21, further comprising administering an anti-cancer agent.

38. (New) The method of claim 28, further comprising administering an anti-cancer agent.

39. (New) The method of claim 34, wherein the anti-cancer agent is a chemotherapy.

40. (New) The method of claim 34, wherein the anti-cancer agent is a radiotherapy.

41. (New) The method of claim 35, wherein the anti-cancer agent is a chemotherapy.

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42. (New) The method of claim 35, wherein the anti-cancer agent is a radiotherapy.

43. (New) The method of claim 36, wherein the anti-cancer agent is a chemotherapy.

44. (New) The method of claim 36, wherein the anti-cancer agent is a radiotherapy.

45. (New) A method of treating a tumor in a human subject in need thereof, comprising administering to the subject a platinum based chemotherapy, wherein the tumor is refractory to the platinum based chemotherapy, and administering to the subject about 10 mg/kg of an anti-PD-L1 antibody every 2 weeks, wherein the anti-PD-L1 antibody is administered intravenously over 60 minutes infusion; wherein the tumor is derived from a cancer of the urethra, the bladder, the ureter, or the renal pelvis.

46. (New) The method of claim 18, wherein the platinum-based chemotherapy is a platinum-based doublet chemotherapy.

47. (New) The method of claim 18, wherein the platinum-based chemotherapy comprises cisplatin, carboplatin, or both.

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Remarks

Upon entry of the foregoing amendment, claims 18-47 are pending in the application, with claims 18 and 45 being the independent claims. Claims 1-17 are sought to be canceled without prejudice to or disclaimer of the subject matter therein. New claims 18-47 are sought to be added.

Support for new claims 18-47 can be found throughout the specification as filed. In particular, support for new claims 18 and 45 can be found, *inter alia*, at page 16 line 30 to page 17 line 12; page 25 line 12 to page 32 line 30; page 34 lines 6-33; page 35 line 28 to page 36 line 12; page 43 lines 14-18; page 47 line 31 to page 54 line 26; page 53 lines 6-26; page 92 lines 8-10; and page 93 lines 14-19. Support for new claims 19-21 can be found, *inter alia*, at page 43 lines 14-18. Support for new claim 22 can be found, *inter alia*, at page 94 lines 3-4. Support for new claims 23-27 can be found, *inter alia*, at page 33 line 27 to page 34 line 5. Support for new claims 28-31 can be found, *inter alia*, at page 53 lines 7-26. Support for new claims 32 and 33 can be found, *inter alia*, at page 65 line 30 to page 67 line 31. Support for claims 34-44 can be found, *inter alia*, at page 14 line 30 to page 15 line 3; and page 53 line 27 to page 54 line 5. Support for new claims 46 and 47 can be found, *inter alia*, at page 74 line 33; and page 75 lines 13-15.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

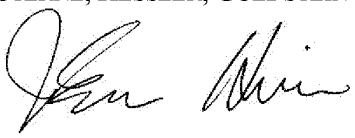
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Conclusion

Prompt and favorable consideration of this Preliminary Amendment is respectfully requested. Applicant believes the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Ji-Eun Kim
Attorney for Applicant
Registration No. 68,504

Date: June 14, 2018

1100 New York Avenue, N.W.
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(202) 371-2600

9454179_1

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 182 of 318

Electronic Patent Application Fee Transmittal

Application Number:	16006473
Filing Date:	
Title of Invention:	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING
First Named Inventor/Applicant Name:	John P. COGSWELL
Filer:	Ji Eun Kim/Jeanette Yando
Attorney Docket Number:	3338.0630006/ELE/C-K

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	10	100	1000
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1000**

Electronic Acknowledgement Receipt

EFS ID:	32898376
Application Number:	16006473
International Application Number:	
Confirmation Number:	5731
Title of Invention:	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING
First Named Inventor/Applicant Name:	John P. COGSWELL
Customer Number:	115018
Filer:	Ji Eun Kim/Jeanette Yando
Filer Authorized By:	Ji Eun Kim
Attorney Docket Number:	3338.0630006/ELE/C-K
Receipt Date:	14-JUN-2018
Filing Date:	
Time Stamp:	15:35:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1000
RAM confirmation Number	061518INTEFSW15361800
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		33380630006-PA.pdf	130523 bc4f12b0d5240b9d1116b2494fcd89d9ff618ea3	yes	6
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Preliminary Amendment		1	1	
	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	6	
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30311 ba4aeca071f2a18355ef51a1406aa7b21e596196	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	160834		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/006,473

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10			OR	x 100 =	1000
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 460 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2720

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/006,473	06/12/2018		2720	3338.0630006/ELE/C-K	30	2

CONFIRMATION NO. 5731

115018
Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DC 20005

FILING RECEIPT

OC000000100603724

Date Mailed: 06/29/2018

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

John P. COGSWELL, Yardley, PA;
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Maria JURE-KUNKEL, Plainsboro, NJ;
Xi-Tao WANG, Wellesley, MA;
Jon M. WIGGINTON, Collegeville, PA;

Applicant(s)

Bristol-Myers Squibb Company, Princeton, NJ;

Assignment For Published Patent Application

Bristol-Myers Squibb Company, Princeton, NJ

Power of Attorney: The patent practitioners associated with Customer Number 115018

Domestic Priority data as claimed by applicant

This application is a CON of 14/950,748 11/24/2015
which is a DIV of 13/892,671 05/13/2013 PAT 9212224
which claims benefit of 61/647,442 05/15/2012
and claims benefit of 61/790,747 03/15/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 06/27/2018

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/006,473**

Projected Publication Date: 10/04/2018

Non-Publication Request: No

Early Publication Request: No

Title

CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/006,473	06/12/2018	John P. COGSWELL	3338.0630006/ELE/C-K	5731

115018 7590 07/20/2018

Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DISTRICT OF COLUMBIA 20005
UNITED STATES OF AMERICA

EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
07/20/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ckim@sternekessler.com
e-office@sternekessler.com
pduffy@sternekessler.com

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 16/006,473	**Applicant(s)** COGSWELL et al.	
	Examiner JoAnne Burke	**Art Unit** OPET	**AIA (First Inventor to File) Status** No

1. THE REQUEST FILED 12 June 2018 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☑ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to JoAnne Burke at (571)272-4584. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/JOANNE L BURKE/ Paralegal Specialist, OPET	

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 14

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	US1	2009/0317368	12-24-2009	Chen	
	US2	6,803,192	10-12-2004	Chen	
	US3	6,808,710	10-26-2004	Wood et al.	
	US4	6,984,720	01-10-2006	Korman et al.	
	US5	7,635,757	12-22-2009	Freeman et al.	
	US6	7,943,743	05-17-2011	Korman et al.	
	US7	8,008,449	08-30-2011	Korman et al.	
	US8	8,168,757	05-01-2012	Finnefrock et al.	
	US9	8,217,149	07-10-2012	Irving et al.	
	US10	US-7595048-B2	09-29-2009	HONJO, Tasuku *et al*.	
	US11	US-8383796-B2	02-26-2013	KORMAN, Alan J. *et al*.	
	US12	US-8779105-B2	07-15-2014	KORMAN, Alan J. *et al*.	
	US13	US-9084776-B2	07-21-2015	KORMAN, Alan J. *et al*.	
	US14	US-9102725-B2	08-11-2015	KORMAN, Alan J. *et al*.	
	US15	US-9212224-B2	12-15-2015	COGSWELL, John *et al.*	
	US16	US-9273135-B2	03-01-2016	KORMAN, Alan J. *et al*.	
	US17	US-9358289-B2	06-07-2016	KORMAN, Alan J. *et al*.	
	US18	US-9387247-B2	07-12-2016	KORMAN, Alan J. *et al*.	
	US19	US-9492539-B2	11-15-2016	KORMAN, Alan J. *et al*.	
	US20	US-9492540-B2	11-15-2016	KORMAN, Alan J. *et al*.	
	US21	US-20060110383-A1	05-25-2006	HONJO, Tasuku *et al*.	
	US22	US-20100015642-A1	01-21-2010	KWON, Eugene D. *et al*.	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 14

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	US23	US-20150125463-A1	05-07-2015	COGSWELL, John P. *et al.*	
	US24	US-20160075782-A1	03-17-2016	KORMAN, Alan J. *et al.*	
	US25	US-20160362495-A1	12-15-2016	KORMAN, Alan J. *et al.*	
	US26	US-8728474-B2	05-20-2014	HONJO, Tasuku *et al.*	
	US27	US-20170088626-A1	03-30-2017	JURE-KUNKEL, Maria *et al.*	
	US28	US-9856320-B2	01-02-2018	COGSWELL; John P. et al.	
	US29	20030039653-A1	02-27-2003	Chen *et al.*	
	US30	20090215812-A1	08-27-2009	Bedrosian *et al.*	
	US31	20110269948-A1	11-03-2011	Sanjuan *et al.*	
	US32	20110206701-A1	08-25-2011	Afar *et al.*	
	US33	20100151447-A1	06-17-2010	Ely; Scott	
	US34	20090217401-A1	08-27-2009	Korman *et al.*	
	US35	20110008369-A1	01-13-2011	Finnefrock *et al.*	
	US36	2017/0028040 A1	02-02-2017	Lan *et al.*	
	US37	9,856,320 B2	01-02-2018	Cogswell *et al.*	
	US38	US-20160090417-A1	03-31-2016	Cogswell *et al.*	
	US39	US-20160362489-A1	04-28-2015	Yang	
	US40	US-20150290316-A1	10-15-2015	GRAZIANO et al.	
	US41	US-20160022814-A1	01-28-2016	PETIT et al.	

Examiner Signature		Date Considered	

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Sheet 3 of 14

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	FP1	WO 00/37504	03-01-2001	Pfizer, Inc. et al..		☐
	FP2	WO 01/14424	03-01-2001	Medarex, Inc.		☐
	FP3	WO 01/14556	03-01-2001	Dana-Farber Cancer Institute, Inc.		☐
	FP4	WO 01/14557	03-29-2001	Dana-Farber Cancer Institute, Inc.		☐
	FP5	WO 01/21631	06-07-2001	Millennium Pharmaceuticals, Inc.		☐
	FP6	WO 01/39722	10-10-2002	Mayo Foundation for Medical Education and Research		☐
	FP7	WO 02/078731	10-10-2002	Wyeth		☐
	FP8	WO 02/079499	10-31-2002	Wyeth et al.		☐
	FP9	WO 02/086083	05-22-2003	Mayo Foundation for Medical Education and Research		☐
	FP10	WO 03/042402	01-15-2004	Dana-Farber Cancer Institute Inc. et al.		☐
	FP11	WO 2004/004771	07-08-2004	Ono Pharmaceutical Co., Ltd.		☒
	FP12	WO 2004/056875	08-26-2004	Wyeth et al.		☐
	FP13	WO 2004/072286	08-26-2004	Ono Pharmaceutical Co., Ltd.		☒
	FP14	WO 2006/042237	04-20-2006	Mayo Foundation for Medical Education and Research		☐

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	FP15	WO 2006/121168	11-16-2006	Ono Pharmaceutical Co., Ltd. et al.		☐
	FP16	WO 2007/005874	01-11-2007	Medarex, Inc.		☐
	FP17	WO2011/066389	06-03-2011	MedImmune, Limited et al.		☐
	FP18	WO 2012/145493	10-26-2012	Amplimmune, Inc.		☐
	FP19	WO 2006/133396 A2	12-14-2006	DANA FARBER CANCER INST INC.		☐
	FP20	CN 101215329 A	07-09-2008	FOURTH MILITARY MEDICAL UNIV.		☒
	FP21	CN 102833441 A	12-19-2012	KONICA MINOLTA BUSINESS TECH		☒

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NON-PATENT LITERATURE DOCUMENTS			
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	NPL1	Androsky, D.J. et al., "Programmed Death Ligand 1 is Expressed by Non-Hodgkin Lymphomas and Inhibits the Activity of Tumor-Associated T Cells", Clinical Cancer Research, Vol. 17, No. 13, pp. 4232-4244 (2011)	☐
	NPL2	Blank, C. et al., "Interaction of PO-L 1 on tumor cells with PD-1 on tumorspecific T cells as a mechanism of immune evasion: implications for tumor immunotherapy", Cancer Immunol. Immunother., Vol. 54, pp. 307-314 (2005)	☐
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	NPL4	Brahmer, J.R. et al., "Phase I Study of Single-Agent Anti-Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates", Journal of Clinical Oncology, Vol. 2S, No. 19, pp. 3167-3175 (2010)	☐
	NPL5	Brahmer, J.R. et al., "Safety and Activity of Anti-PO-L 1 Antibody in Patients with Advanced Cancer", The New England Journal of Medicine, Vol. 366, No. 26, pp. 2455-2465 (2012)	☐
	NPL6	Brown, J.A. et al., "Blockade of Programmed Death-1 Ligands on Dendritic Cells Enhances T Cell Activation and Cytokine Production", The Journal of Immunology, Vol. 170, pp. 1257-1266 (2003)	☐
	NPL7	Carter, L.L. et al., "PD-1:PD-L inhibitory pathway affects both CD4+ and CDS+ T cells and is overcome by IL-2", Eur. J. Immunol., Vol. 32, pp. 634-643 (2002)	☐

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Art Unit	*To Be Assigned*
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	NPL8	Dasanu, C.A. et al., "Immune alterations and emerging immunotherapeutic approaches in lung cancer", Expert Opin. Bioi. Ther., Vol. 12, No. 7, pp. 923-937 (2012)	☐
	NPL9	Dodson, L.F. et al., "Potential targets for pancreatic cancer immunotherapeutics", Immunotherapy, Vol. 3, No.4, pp. 517-537 (2011)	☐
	NPL10	Dong, H. et al., "B7-H1 pathway and its role in the evasion of tumor immunity", J. Mol. Med., Vol. S1, pp. 2S1-2S7 (2003)	☐
	NPL11	Dong, H. et al., "Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion", Nature Medicine, Vol. S, No. S, pp. 793-SOO (2002)	☐
	NPL12	Flies, D. B. et al., "Blockade of the B7-H1/PD-1 Pathway for Cancer Immunotherapy", Yale Journal of Biology and Medicine, Vol. S4, pp. 409-421 (2011)	☐
	NPL13	Freeman, G.J. et al., "Engagement of the PD-1 Immunoinhibitory Receptor by a Novel B7 Family Member Leads to Negative Regulation of Lymphocyte Activation", J. Exp. Med., Vol. 192, No.7, pp. 1027-1034 (2000)	☐
	NPL14	Gadiot, J. et al., "Overall Survival and PO-L 1 Expression in Metastasized Malignant Melanoma", Cancer, Vol. 117, pp. 2192-2201 (2011)	☐
	NPL15	Gajewski, T.F. et al., "Gene Signature in Melanoma Associated with Clinical Activity: A Potential Clue to Unlock Cancer Immunotherapy", The Cancer Journal, Vol. 16, No.4, pp. 399-403 (2010)	☐

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Sheet 7 of 14

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Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

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	NPL16	Garbe, C. et al., "Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline- Update 2012", European Journal of Cancer, Vol. 48, pp. 2375-2390 (2012)	☐
	NPL17	Hamanishi, J. et al., "Programmed cell death 1 ligand 1 and tumor-infiltrating cos+ T lymphocytes are prognostic factors of human ovarian cancer", Proc. Natl. Acad. Sci., Vol. 104, No.9, pp. 3360-3365 (2007)	☐
	NPL18	Hamid, 0. et al., "Anti-programmed death-1 and anti-programmed deathligand 1 antibodies in cancer therapy", Expert Opin. Bioi. Ther., Vol. 13, No. 6, pp. 847-861 (2013)	☐
	NPL19	He, Y.-F. et al., "Blocking Programmed Death-1 Ligand-PD-1 Interactions by Local Gene Therapy Results in Enhancement of Antitumor Effect of Secondary Lymphoid Tissue Chemokine", The Journal of Immunology, Vol. 173, pp. 4919-4928 (2004)	☐
	NPL20	Hino, R. et al., "Tumor Cell Expression of Programmed Cell Death-1 Ligand 1 is a Prognostic Factor for Malignant Melanoma", Cancer, Vol. 116, pp. 1757-1766 (2010)	☐
	NPL21	Hirano, F. et al., "Blockade of B7-H1 and PD-1 by Monoclonal Antibodies Potentiates Cancer Therapeutic Immunity", Cancer Res., Vol. 65, No. 3, pp. 1 089-1 096 (2005)	☐
	NPL22	Holt, G. E. et al., "Immune Modulation as a Therapeutic Strategy for Non-Small-Cell Lung Cancer", Clinical Lung Cancer, Vol. 9, Suppl. 1, pp. S13-S19 (2008)	☐
	NPL23	Holt, G. E. et al., "Immunotherapy as a strategy for the treatment of nonsmall-cell lung cancer", Therapy, Vol. 8, No. 1, pp. 43-54 (2011)	☐

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	NPL24	Iwai, Y. et al., "Involvement of PO-L 1 on tumor cells in the escape from host immune system and tumor immunotherapy by PO-L 1 blockade", Proc. Natl. Acad. Sci., Vol. 99, No. 19, pp. 12293-12297 (2002)	☐
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	NPL26	Kim, P.S. et al., "Features of responding T cells in cancer and chronic infection", Current Opinion in Immunology, Vol. 22, pp. 223-230 (2010)	☐
	NPL27	Konishi, J. et al., "B7-H1 Expression on Non-Small Cell Lung Cancer Cells and Its Relationship with Tumor-Infiltrating Lymphocytes and Their PD-1 Expression", Clinical Cancer Research, Vol. 10, pp. 5094-5100 (2004)	☐
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	NPL29	Mellman, I. et al., "Cancer immunotherapy comes of age", Nature, Vol. 480, pp. 480-489 (2011)	☐
	NPL30	Pardoll, D.M., "The blockade of immune checkpoints in cancer immunotherapy", Nature Reviews: Cancer, Vol. 12, pp. 252-264 (2012)	☐
	NPL31	Parry, R.V. et al., "CTLA-4 and PD-1 Receptors Inhibit T-Cell Activation by Distinct Mechanisms", Molecular and Cellular Biology, Vol. 25, No. 21, pp. 9543-9553 (2005)	☐

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	NPL32	Schreiber, R.D. et al., "Cancer Immunoediting: Integrating Immunity's Roles in Cancer Suppression and Promotion", Science, Vol. 331, pp. 1565-1570 (2011)	☐
	NPL33	Sharma, P. et al., "Novel cancer immunotherapy agents with survival benefit: recent successes and next steps", Nature Reviews: Cancer, Vol. 11, pp. 805-812 (2011)	☐
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	NPL36	Taube, J.M. et al., "Colocalization of Inflammatory Response with B7-H1 Expression in Human Melanocytic Lesions Supports an Adaptive Resistance Mechanism of Immune Escape", Science Translational Medicine, Vol. 4, No. 127, 127ra37 (2012), and Supplementary Materials, http:l/stm.sciencemag.org/content/suppl/2012/03/26/4.127 .127ra37 .DC 1. Html	☐
	NPL37	Topalian, S.L. et al., "Cancer Immunotherapy Comes of Age", Journal of Clinical Oncology, Vol. 29, No. 36, pp. 4828-4836 (2011)	☐
	NPL38	Topalian, S.L. et al., "Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer", The New England Journal of Medicine, Vol. 366, No. 26, pp. 2443-2454 (2012)	☐

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	NPL39	Topalian, S.L. et al. "Targeting the PD-1/B7-H1 (PO-L 1) pathway to activate anti-tumor immunity", Current Opinion in Immunology, Vol. 24, pp. 207-212 (2012)	☐
	NPL40	Wolchok, J.D. et al., "Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study", Lancet Oncol., Vol. 11, pp. 155-164 (2010)	☐
	NPL41	Wong, R.M. et al., "Programmed death-1 blockade enhances expansion and functional capacity of human melanoma antigen-specific CTLs", International Immunology, Vol. 19, No. 10, pp. 1223-1234 (2007)	☐
	NPL42	Zou, W. et al., "Inhibitory 87-family molecules in the tumour microenvironment", Nature Reviews: Immunology, Vol. 8, pp. 467-477 (2008)	☐
	NPL43	International Preliminary Report on Patentability and Written Opinion for International Application No. PCT/US2013/040764, The International Bureau of WIPO, Geneva, Switzerland, issued on November 18, 2014, 10 pages.	☐
	NPL44	International Search Report for International Application No. PCT/US2013/040764, European Patent Office, Netherlands, mailed on October 31, 2013, 8 pages.	☐
	NPL45	ASCIERTO, P.A., et al., "Clinical experiences with anti-CD137 and anti-PD1 therapeutic antibodies," Semin Oncol 37(5):508-516, Elsevier Inc., United States (2010).	☐
	NPL46	National Institutes of Health Clinical Center, Clinical Trial Identifier NCT01024231 entitled "Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma," ClinicalTrials.gov, available at https://clinicaltrials.gov/ct2/show/NCT01024231?term=NCT01024231&rank=1, last accessed on June 30, 2017, 7 pages (same clinical trial accessed on April 27, 2017 by Examiner in related US Application No. 14/400,667, filed November 12, 2014).	☐

Examiner Signature		Date Considered	

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If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 11 of 14

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	NPL47	CURRAN, M.A., et al., "PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors," Proc Natl Acad Sci USA 107(9):4275-4280, National Academy of Sciences, United States (2010).	☐
	NPL48	MAY Jr., K.F., et al., "Prostate Cancer Immunotherapy," Clinical Cancer Research 17(16):5233-5238, American Association of Cancer Research, United States (2011).	☐
	NPL49	NATARAJAN, N., et al., "Novel immunotherapeutic agents and small molecule antagonists of signalling kinases for the treatment of metastatic melanoma," Drugs 71(10):1233-1250, Springer International, New Zealand (2011).	☐
	NPL50	Office Action mailed November 9, 2017 in United States Patent Application No. 14/950,748, inventor Cogswell, J.P., et al., filed November 24, 2015, 11 pages.	☐
	NPL51	POSTOW, M.A., et al., "Targeting Immune Checkpoints: Releasing the Restraints on Anti-tumor Immunity for Patients With Melanoma," Cancer Journal 18(2):153-159, Lippincott Williams & Wilkins, United States (2012).	☐
	NPL52	SZNOL, M., "Advances in the treatment of metastatic melanoma: new immunomodulatory agents," Semin Oncol. 39(2):192-203, Elsevier Inc., United States (2012).	☐
	NPL53	WOLCHOK, J.D., "Immunobiology of immune checkpoints," Pigment Cell Research 24:1005, John Wiley & Sons A/S, United States (2011).	☐
	NPL54	National Institutes of Health, "Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma," ClinicalTrials.gov Identifier NCT01024231, accessed at https://web.archive.org/web/20111023232455/https://clinicaltrials.gov/ct2/show/NCT01024231 , accessed on September 22, 2017, 3 pages.	☐

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Sheet 12 of 14

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
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	NPL55	SHIBAYAMA, S. and YOSHIDA, T., "Development of ONO-4538, fully human anti-PD-1 antibody for malignant tumors," Medical Science Digest 36(12):1120-1123, New Science Co., Japan (2010).	☐
	NPL56	WANG, G. et al., "A Therapeutic strategy of targeting PD1/PDL signal pathway," Chinese Bulletin of Life Sciences 23:86-89, (2011)	☐
	NPL57	GAO, Q., et al., "Overexpression of PD-L1 Significantly Associates with Tumor Aggressiveness and Postoperative Recurrence in Human Hepatocellular Carcinoma," Clinical Cancer Research 15(3);971-979, American Association for Cancer Research, United States (2009)	☐
	NPL58	GHEBEH, H., et al., "The B7-H1 (PD-L1) T Lymphocyte-Inhibitory molecule Is Expressed in Breast cancer Patients with Infiltrating Ductal Carcinoma: Correlation with Important high-Risk Prognostic Factors Neoplasia 8(3):190-198, Elsevier, Netherlands (2006)	☐
	NPL59	ROTH, T., et al., "B7-H3 Ligand Expression by Prostate Cancer: A Novel Marker of Prognosis and Potential Target for Therapy," Cancer Res 67(16):7893-7900, American Association for Cancer, United States (2007)	☐
	NPL60	National Institutes of Health Clinical Center, Clinical Trial Identifier NCT01024231 entitled "Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma," ClinicalTrials.gov, available at https://clinicaltrials.gov/archive/NCT01024231/2012_04_30, last accessed on July 18, 2017, 4 pages (same clinical trial accessed on April 27, 2017 by Examiner in same application).	☐
	NPL61	Study NCT01024231 , "Dose-Escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects with Unrespectable Stage III or Stage IV Malignant Melanoma," April 18, 2012, 3 pages.	☐

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Sheet 13 of 14

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	NPL62	SIMEONE, E., et al., "Immunotreatment of metastatic melanoma: the experience with anti-CTLA-4," *Journal of Immunotoxicology 9(3)*:21-247, Taylor & Francis, United Kingdom (2012)	☐
	NPL63	WOLCHOK, J.D., et a., " Nivolumab Plus Ipilimumab in Advanced Melanoma," *New England Journal of Medicine 369(2)*:122-133, Massachusettes Medical Society, United States (2012)	☐
	NPL64	Phase 3 study of Nivolumab, or Nivolumab Plus Ipilimumab Versus Ipilimumab alone in Previously Untreated Advanced Melanoma (Checkmate 067), last updated December 18, 2017	☐
	NPL65	Co-pending Application, U.S. Application No. 16/006,365, inventors COGSWELL, John, P., filed on June 12, 2018 (NOT PUBLISHED)	☐
	NPL66	Co-pending Application, U.S. Application No. 16/006,493, inventors COGSWELL, John, P., filed on June 12, 2018 (NOT PUBLISHED)	☐
	NPL67	Co-pending Application, U.S. Application No. 16/024,333, inventors COGSWELL, John, P., filed on June 29, 2018 (NOT PUBLISHED)	☐
	NPL68	Co-pending Application, U.S. Application No. 16/024,340, inventors COGSWELL, John, P., filed on June 29, 2018 (NOT PUBLISHED)	☐
	NPL69	KUENEN, B., et al., "A Phase 1 Pharmacologic Study of Necitumumab (IMC-11F8), a Fully Human IgG1 Monoclonal Antibody Directed Against EGFR in Patients with Advanced Solid Malignancies," Clinical Cancer Research 16:1915-1923, American Association for Cancer Research, United States (2010)	☐
	NPL70	SEIWERT, T.Y., et al., "Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE 0-12): an open-label, multicenter, phase 1b trial." Lancet Oncology 17:956-965, Elsevier, Netherlands (2016)	☐

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Sheet 14 of 14

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Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

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	NPL71	WANG, D., et al., "Fixed Dosing Versus Body Size-based Dosing of Monoclonal Antibodies in Adult Clinical Trials," J. Clin Pharmacol 49:1012-1024, John Wiley & Sons, United States (2009)	☐

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Electronic Acknowledgement Receipt

EFS ID:	33238889
Application Number:	16006473
International Application Number:	
Confirmation Number:	5731
Title of Invention:	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING
First Named Inventor/Applicant Name:	John P. COGSWELL
Customer Number:	115018
Filer:	Ji Eun Kim/Jeanette Yando
Filer Authorized By:	Ji Eun Kim
Attorney Docket Number:	3338.0630006/ELE/C-K
Receipt Date:	25-JUL-2018
Filing Date:	12-JUN-2018
Time Stamp:	15:34:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	NPL61_NCT01024231.pdf	169360 5265193366 3a143b6da1505334f5b5fd54025db9	no	3

Warnings:

Information:					
2	Non Patent Literature	NPL62_Simeon.pdf	950017 6983048585ed5ec4b8e866c3e0142cb4524 6eab6	no	23
Warnings:					
Information:					
3	Non Patent Literature	NPL63_Wolchok.pdf	1103121 3df4299e77cca9f222cce6c279554c3a2b20 b2f7	no	12
Warnings:					
Information:					
4	Non Patent Literature	NPL64_Phase3Study.pdf	422039 c0dc55998d856cea65bf8329ce1602b6177 1dcc2	no	10
Warnings:					
Information:					
5	Non Patent Literature	NPL50_OA_1450748.pdf	310027 cfd465a64884e1692ec0d5a4da6ce78607c 628ec	no	11
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Information:					
6	Non Patent Literature	NPL69_Kuenen.pdf	938235 199d878ab771894a0eba16b8d6015c9eef2 a0fdd	no	11
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Information:					
7	Non Patent Literature	NPL70_Seiwert.PDF	1698512 97c38afb3e4616f469508d3e219cc1d30219 cbb1	no	10
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9	Transmittal Letter	33380630006-IDS.pdf	128651 98c31dbc5ef944ae7a7c3bcf10af4ff4efaed6e1	no	4
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10	Information Disclosure Statement (IDS) Form (SB08)	33380630006-IDSSB08A-B.pdf	249227 1de0cf9f6af0caca1248eaa28369943adba08aff	no	14
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		Total Files Size (in bytes):	7331011		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: COGSWELL *et al.*	Confirmation No.: 5731
Applicant: Bristol-Myers Squibb Company	Art Unit: *To Be Assigned*
Application No.: 16/006,473	Examiner: *To Be Assigned*
(*Continuation of Appl. No. 14/950,748; Filed: November 24, 2015*)	
Filing Date: June 12, 2018	Atty. Docket: 3338.0630006/ELE/C-K

Title: **CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING**

Information Disclosure Statement

Mail Stop Amendment

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

Listed on accompanying IDS Forms PTO/SB/08a and PTO/SB/08b equivalent are documents for consideration in view of 37 C.F.R. §1.56 and in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.97 and 1.98.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicant has listed publication dates on the attached IDS Forms based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicant reserves the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

This is a filing under 37 C.F.R. § 1.97(b). This Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. No statement or fee is required.

A concise explanation of the relevance of the non-English language documents appears below in accordance with 37 C.F.R. § 1.98(a)(3).

Document **FP11**, WO 2004/004771, is in a foreign language. An English language abstract was previously appended to the face page of document **FP11**. Additionally, document **US10**, is believed to be an English language equivalent of document **FP11**.

Document **FP13**, WO 2004/072286, is in a foreign language. An English language abstract was previously appended to the face page of document **FP13**.

Document **FP20**, CN 101215329 A, is in a foreign language. An English language abstract was previously appended to the face page of document **FP20**.

Document **FP21**, CN 102833441 A, is in a foreign language. An English language abstract was previously appended to the face page of document **FP21**.

Copies of documents **NPL50**, **NPL61-NPL64,** and **NPL69-71** are submitted. However, in accordance with 37 C.F.R. § 1.98(a)(2)(ii), no copies of U.S. patents and patent application publications cited as documents **US1-US41** on the attached IDS Forms are submitted. Additionally, copies of unpublished U.S. applications **NPL65-NPL68**, cited on the attached IDS Forms, are not provided in accordance with the U.S. Patent and Trademark Office Official Gazette notice of

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 213 of 318

October 19, 2004, which states: "the requirement in 37 C.F.R. § 1.98(a)(2)(iii) for a legible copy of the specification, including the claims, and drawings of each cited pending unpublished U.S. patent application (or portion of the application which caused it to be listed) is sua sponte waived where the cited pending application is stored in the USPTO's IFW system."

Copies of the **FP1-FP21**, **NPL1-NPL49,** and **NPL51-NPL60** documents were cited by or submitted to the Office in an IDS that complies with 37 C.F.R. § 1.98(a)-(c) in Application No. 14/950,748, filed November 24, 2015, which is relied upon for an earlier filing date under 35 U.S.C. § 120. Thus, copies of these documents are not attached. 37 C.F.R. § 1.98(d).

It is expected that the examiner will review the prosecution and cited art in the Parent Application No. 14/950,748, filed November 24, 2015, in accordance with MPEP 2001.06(b), and indicate in the next communication from the office that the art cited in the earlier prosecution history has been reviewed in connection with the present application.3

In accordance with the Federal Circuit decision in *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358 (Fed. Cir. 2003), Applicant submits herewith an Office Action from the co-pending U.S. Patent Application No. 14/950,748, filing date November 24, 2015, as document **NPL50**.

The identification of this Office Action is not to be construed as a waiver of secrecy as to that application now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited applications and the art cited therein during examination.

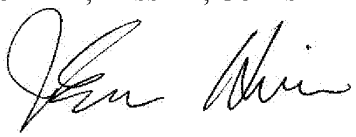
Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 214 of 318

It is respectfully requested that the Examiner initial and return a copy of the enclosed IDS Forms, and indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Ji-Eun Kim
Attorney for Applicant
Registration No. 68,504

Date: July 24, 2018

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
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Atty. Dkt. No. 3338.0630006/ELE/C-K

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/006,473	06/12/2018	John P. COGSWELL	3338.0630006/ELE/C-K	5731

115018 7590 08/07/2018

Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DISTRICT OF COLUMBIA 20005
UNITED STATES OF AMERICA

EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
08/07/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ckim@sternekessler.com
e-office@sternekessler.com
pduffy@sternekessler.com

Office Action Summary	Application No. 16/006,473	Applicant(s) COGSWELL et al.	
	Examiner ILIA I OUSPENSKI	Art Unit 1644	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 06/14/2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 18-47 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 18-47 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 06/12/2018 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

2. Applicant's preliminary amendment filed on 06/14/2018 is acknowledged. Claims 18-47 are pending.

4. The following is a quotation of **35 U.S.C. 112** (pre-AIA), **second paragraph**:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 24-27 and 32-33 are rejected under **35 U.S.C. 112** (pre-AIA), **second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

(i) Claims 24 and 25 is indefinite, because the use of the term “adjuvant” appears to be inconsistent with the context of the claim. As one of skill in the art is aware, an adjuvant, when administered in combination with an antigen, is intended to stimulate an antibody response against the antigen. In the instant case, an anti-PD-L1 antibody is administered to a cancer patient so that it can bind to the PD-L1 molecule to prevent the binding of PD-L1 to its receptor PD-1 on T cells, thereby inhibiting the suppressive effect of PD-L1/PD-1 signaling in T cells anti-tumor activity. Administering the anti-PD-L1 antibody in combination with an adjuvant is expected to promote generation of anti-PD-L1 antibodies in the subject, which is clearly undesirable. Therefore, it is unclear what types of agents are encompassed by the term “adjuvant” within the claim, and thus the meets and bounds of the claims cannot be unequivocally interpreted by a person of ordinary skill in the art.

(ii) Claims 32 and 33 are indefinite, because it is unclear what types of cells or tissues of the subject must be PD-L1 positive or PD-L1 negative for the subject to be encompassed by the claim. As one of skill in the art is aware, PD-L1 signaling activity plays a role in a variety of conditions, including suppression of the immune system during pregnancy, tissue allografts, autoimmune diseases, certain infections and inflammatory diseases such as hepatitis. In these conditions, PD-L1 is expressed in a number of different tissues and cell types. Therefore, in the absence of clarity as to which cell types of tissues must express PD-L1 to a given subject to be included in the claimed method, the subject population is not defined.

(iii) Claims 26 and 27 are indefinite, because they encompass the indefinite limitations of the claims on which they depend.

In view of the above, a person of ordinary skill in the art cannot unequivocally interpret the metes and bounds of the claim so as to understand how to avoid infringement. Applicant is reminded that any amendment must point to a basis in the specification so as not to add New Matter. See MPEP 714.02 and 2163.06.

5. The following is a quotation of the **first paragraph** of pre-AIA **35 U.S.C. 112**:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 18-47 are rejected under **35 U.S.C. 112** (pre-AIA), **first paragraph**, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventors, at the time the application was filed, had possession of the claimed invention. *This is a New Matter rejection.*

Applicant asserts that no New Matter has been added and points to the specification at page 16 line 30 to page 17 line 12; page 25 line 12 to page 32 line 30; page 34 lines 6-33; page 35 line 28 to page 36 line 12; page 43 lines 14-18; page 47 line 31 to page 54 line 26; page 53 lines 6-26; page 92 lines 8-10; and page 93 lines 14-19 for support for the newly added claims 18 and 45.

However, the specification does not appear to provide an adequate written description of a method of treating a urethra, bladder, ureter, or renal pelvis-derived tumor which is refractory to platinum based chemotherapy.

While the specification lists the above types of cancer among many others potentially treatable with anti-PD-L1 antibodies (page 53 lines 6-26), there does not appear to be any mention of treating these cancers with platinum based agents. Platinum-based chemotherapy is mentioned as a standard-of-care in stage IV of squamous cell carcinoma as a subset of non-small cell lung cancer (NSCLC; p. 74 line 32 to p. 75 line 15), but not other types of cancer.

The specification further discloses a working example of a clinical study wherein cancer patients were treated according to the regimen recited in claims 18 and 45, among others. The description of the patient population presented in Example 11 states that the study included patients with NSCLC who previously received platinum-based chemotherapy (p. 93 lines 14-16). The patient population did not include any patients having tumors derived from cancer of the urethra, the bladder or the ureter; the only subset of patients within the scope of the instant claims is those with renal cell carcinoma (RCC), which is encompassed by the recitation of cancer of the renal pelvis. These patients had been pre-treated with nephrectomy, anti-angiogenic therapy or immunotherapy (p. 93 lines 18-19), but not with platinum-based chemotherapy.

Accordingly, the specification does not disclose patients having a tumor derived from a cancer of the urethra, the bladder, the ureter or the renal pelvis who received a treatment with platinum-based chemotherapy, or who are refractory to such therapy, or

the refractory patients subsequently treated with anti-PD-L1 therapy. Thus, the amended claims now recite limitations which were not clearly disclosed in the specification or claims as filed, and change the scope of the instant disclosure as filed. These limitations introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the New Matter in the response to this Office Action. Alternatively, Applicant is invited to clearly point out the written support for the newly added limitations.

7. Claim 45 is rejected under **35 U.S.C. 112** (pre-AIA), **first paragraph**, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide a sufficient enabling description of a method of treating a tumor which is refractory to a platinum based chemotherapy by administering a platinum based chemotherapy.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to make and use the claimed invention.

Claim 45 is directed to a method of treating a tumor in a human subject comprising administering to the subject a platinum based chemotherapy, wherein the

tumor is refractory to the platinum based chemotherapy. The skilled artisan would readily recognize that such treatment, by definition, would be unsuccessful, and as such unnecessary, improper, and undue.

8. Conclusion: no claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA I OUSPENSKI whose telephone number is (571)272-2920. The examiner can normally be reached 8:30 AM – 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Kolker can be reached at 571-272-3181. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ILIA I OUSPENSKI/
Primary Examiner, Art Unit 1644

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/006,473	COGSWELL et al.
	Examiner	Art Unit
	ILIA I OUSPENSKI	1644

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Priority and related applications, including prosecution history	08/02/2018	io
WEST: attached	08/02/2018	io
ProQuest: same as WEST	08/02/2018	io
Inventor search	08/02/2018	io

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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BIB DATA SHEET

CONFIRMATION NO. 5731

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/006,473	06/12/2018 RULE	424	1644	3338.0630006/ELE/C-K

APPLICANTS

Bristol-Myers Squibb Company, Princeton, NJ;

INVENTORS

John P. COGSWELL, Yardley, PA;
Stacie M. GOLDBERG, Potomac, MD;
Ashok K. GUPTA, Clarksburg, MD;
Maria JURE-KUNKEL, Plainsboro, NJ;
Xi-Tao WANG, Wellesley, MA;
Jon M. WIGGINTON, Collegeville, PA;

**** CONTINUING DATA ***************************

This application is a CON of 14/950,748 11/24/2015
which is a DIV of 13/892,671 05/13/2013 PAT 9212224
which claims benefit of 61/647,442 05/15/2012
and claims benefit of 61/790,747 03/15/2013

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

06/27/2018

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
❑ Yes ☑ No	❑ Yes ☑ No	/ILIA I OUSPENSKI/ Examiner's Signature	❑ Initials	PA	24	30	2

ADDRESS

Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DC 20005
UNITED STATES

TITLE

CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
2720	No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

BIB (Rev. 05/07).

WEST Search History

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DATE: Thursday, August 02, 2018

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☐	L5	L4 and ((cogswell-j$ or goldberg-s$ or gupta-a$ or jure-kunkel-m$ or wang-x$ or wigginton-j$).in. or Bristol$.as. or Bristol$.aanm.)	4
☐	L4	L3 same L2	59
☐	L3	L1 same (uret$ or bladder$ or renal$ or pelvi$ or rcc)	737
☐	L2	(platin$ or cisplatin$ or cis-platin$ or oxaliplatin$ or eloxatin$ or carboplatin$ or paraplatin$)	1043245
☐	L1	(("anti-pd-l1$" or anti-pdl1$ or anti-b7-h1$ or anti-b7h1$ or anti-b7-4$ or anti-cd274$ or ".alpha.pd-l1$" or ".alpha.pdl1" or ".alpha.b7-h1$" or ".alpha.b7h1" or ".alpha.b7-4$" or ".alpha.cd274$" or "PD-L1$" or pdl1$ or b7-h1$ or b7h1$ or b7-4$ or cd274$) same (treat$ or administ$ or contact$ or pharmaceut$ or deliver$) same (cancer$ or tumor$ or tumour$ or malignan$ or neoplas$ or metasta$ or onco$))	2959

END OF SEARCH HISTORY

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Dana-Farber v. BMS, IPR2023-00252
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 14

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	US1	2009/0317368	12-24-2009	Chen	
	US2	6,803,192	10-12-2004	Chen	
	US3	6,808,710	10-26-2004	Wood et al.	
	US4	6,984,720	01-10-2006	Korman et al.	
	US5	7,635,757	12-22-2009	Freeman et al.	
	US6	7,943,743	05-17-2011	Korman et al.	
	US7	8,008,449	08-30-2011	Korman et al.	
	US8	8,168,757	05-01-2012	Finnefrock et al.	
	US9	8,217,149	07-10-2012	Irving et al.	
	US10	US-7595048-B2	09-29-2009	HONJO, Tasuku *et al.*	
	US11	US-8383796-B2	02-26-2013	KORMAN, Alan J. *et al.*	
	US12	US-8779105-B2	07-15-2014	KORMAN, Alan J. *et al.*	
	US13	US-9084776-B2	07-21-2015	KORMAN, Alan J. *et al.*	
	US14	US-9102725-B2	08-11-2015	KORMAN, Alan J. *et al.*	
	US15	US-9212224-B2	12-15-2015	COGSWELL, John *et al.*	
	US16	US-9273135-B2	03-01-2016	KORMAN, Alan J. *et al.*	
	US17	US-9358289-B2	06-07-2016	KORMAN, Alan J. *et al.*	
	US18	US-9387247-B2	07-12-2016	KORMAN, Alan J. *et al.*	
	US19	US-9492539-B2	11-15-2016	KORMAN, Alan J. *et al.*	
	US20	US-9492540-B2	11-15-2016	KORMAN, Alan J. *et al.*	
	US21	US-20060110383-A1	05-25-2006	HONJO, Tasuku *et al.*	
	US22	US-20100015642-A1	01-21-2010	KWON, Eugene D. *et al.*	

Examiner Signature		Date Considered	

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Sheet 2 of 14

Complete if Known	
Application Number	16/006,473
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Art Unit	*To Be Assigned*
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Attorney Docket Number	3338.0630006/ELE/C-K

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	US23	US-20150125463-A1	05-07-2015	COGSWELL, John P. *et al.*	
	US24	US-20160075782-A1	03-17-2016	KORMAN, Alan J. *et al.*	
	US25	US-20160362495-A1	12-15-2016	KORMAN, Alan J. *et al.*	
	US26	US-8728474-B2	05-20-2014	HONJO, Tasuku *et al.*	
	US27	US-20170088626-A1	03-30-2017	JURE-KUNKEL, Maria *et al.*	
	US28	US-9856320-B2	01-02-2018	COGSWELL; John P. et al.	
	US29	20030039653-A1	02-27-2003	Chen *et al.*	
	US30	20090215812-A1	08-27-2009	Bedrosian *et al.*	
	US31	20110269948-A1	11-03-2011	Sanjuan *et al.*	
	US32	20110206701-A1	08-25-2011	Afar *et al.*	
	US33	20100151447-A1	06-17-2010	Ely; Scott	
	US34	20090217401-A1	08-27-2009	Korman *et al.*	
	US35	20110008369-A1	01-13-2011	Finnefrock *et al.*	
	US36	2017/0028040 A1	02-02-2017	Lan *et al.*	
	US37	9,856,320 B2	01-02-2018	Cogswell *et al.*	
	US38	US-20160090417-A1	03-31-2016	Cogswell *et al.*	
	US39	US-20160362489-A1	04-28-2015	Yang	
	US40	US-20150290316-A1	10-15-2015	GRAZIANO et al.	
	US41	US-20160022814-A1	01-28-2016	PETIT et al.	

Examiner Signature		Date Considered	

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Sheet 3 of 14

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	FP1	WO 00/37504	03-01-2001	Pfizer, Inc. et al..		☐
	FP2	WO 01/14424	03-01-2001	Medarex, Inc.		☐
	FP3	WO 01/14556	03-01-2001	Dana-Farber Cancer Institute, Inc.		☐
	FP4	WO 01/14557	03-29-2001	Dana-Farber Cancer Institute, Inc.		☐
	FP5	WO 01/21631	06-07-2001	Millennium Pharmaceuticals, Inc.		☐
	FP6	WO 01/39722	10-10-2002	Mayo Foundation for Medical Education and Research		☐
	FP7	WO 02/078731	10-10-2002	Wyeth		☐
	FP8	WO 02/079499	10-31-2002	Wyeth et al.		☐
	FP9	WO 02/086083	05-22-2003	Mayo Foundation for Medical Education and Research		☐
	FP10	WO 03/042402	01-15-2004	Dana-Farber Cancer Institute Inc. et al.		☐
	FP11	WO 2004/004771	07-08-2004	Ono Pharmaceutical Co., Ltd.		☒
	FP12	WO 2004/056875	08-26-2004	Wyeth et al.		☐
	FP13	WO 2004/072286	08-26-2004	Ono Pharmaceutical Co., Ltd.		☒
	FP14	WO 2006/042237	04-20-2006	Mayo Foundation for Medical Education and Research		☐

Examiner Signature		Date Considered	

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Sheet 4 of 14

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	FP15	WO 2006/121168	11-16-2006	Ono Pharmaceutical Co., Ltd. et al.		☐
	FP16	WO 2007/005874	01-11-2007	Medarex, Inc.		☐
	FP17	WO2011/066389	06-03-2011	MedImmune, Limited et al.		☐
	FP18	WO 2012/145493	10-26-2012	Amplimmune, Inc.		☐
	FP19	WO 2006/133396 A2	12-14-2006	DANA FARBER CANCER INST INC.		☐
	FP20	CN 101215329 A	07-09-2008	FOURTH MILITARY MEDICAL UNIV.		☒
	FP21	CN 102833441 A	12-19-2012	KONICA MINOLTA BUSINESS TECH		☒

Examiner Signature		Date Considered	

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Sheet 5 of 14

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	NPL1	Androsky, D.J. et al., "Programmed Death Ligand 1 is Expressed by Non-Hodgkin Lymphomas and Inhibits the Activity of Tumor-Associated T Cells", Clinical Cancer Research, Vol. 17, No. 13, pp. 4232-4244 (2011)	☐
	NPL2	Blank, C. et al., "Interaction of PO-L 1 on tumor cells with PD-1 on tumorspecific T cells as a mechanism of immune evasion: implications for tumor immunotherapy", Cancer Immunol. Immunother., Vol. 54, pp. 307-314 (2005)	☐
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	NPL5	Brahmer, J.R. et al., "Safety and Activity of Anti-PO-L 1 Antibody in Patients with Advanced Cancer", The New England Journal of Medicine, Vol. 366, No. 26, pp. 2455-2465 (2012)	☐
	NPL6	Brown, J.A. et al., "Blockade of Programmed Death-1 Ligands on Dendritic Cells Enhances T Cell Activation and Cytokine Production", The Journal of Immunology, Vol. 170, pp. 1257-1266 (2003)	☐
	NPL7	Carter, L.L. et al., "PD-1:PD-L inhibitory pathway affects both CD4+ and CDS+ T cells and is overcome by IL-2", Eur. J. Immunol., Vol. 32, pp. 634-643 (2002)	☐

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First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

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	NPL8	Dasanu, C.A. et al., "Immune alterations and emerging immunotherapeutic approaches in lung cancer", Expert Opin. Bioi. Ther., Vol. 12, No. 7, pp. 923-937 (2012)	☐
	NPL9	Dodson, L.F. et al., "Potential targets for pancreatic cancer immunotherapeutics", Immunotherapy, Vol. 3, No.4, pp. 517-537 (2011)	☐
	NPL10	Dong, H. et al., "B7-H1 pathway and its role in the evasion of tumor immunity", J. Mol. Med., Vol. S1, pp. 2S1-2S7 (2003)	☐
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	NPL12	Flies, D. B. et al., "Blockade of the B7-H1/PD-1 Pathway for Cancer Immunotherapy", Yale Journal of Biology and Medicine, Vol. S4, pp. 409-421 (2011)	☐
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	NPL14	Gadiot, J. et al., "Overall Survival and PO-L 1 Expression in Metastasized Malignant Melanoma", Cancer, Vol. 117, pp. 2192-2201 (2011)	☐
	NPL15	Gajewski, T.F. et al., "Gene Signature in Melanoma Associated with Clinical Activity: A Potential Clue to Unlock Cancer Immunotherapy", The Cancer Journal, Vol. 16, No.4, pp. 399-403 (2010)	☐

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Sheet 7 of 14

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

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	NPL16	Garbe, C. et al., "Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline- Update 2012", European Journal of Cancer, Vol. 48, pp. 2375-2390 (2012)	☐
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	NPL20	Hino, R. et al., "Tumor Cell Expression of Programmed Cell Death-1 Ligand 1 is a Prognostic Factor for Malignant Melanoma", Cancer, Vol. 116, pp. 1757-1766 (2010)	☐
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	NPL22	Holt, G. E. et al., "Immune Modulation as a Therapeutic Strategy for Non-Small-Cell Lung Cancer", Clinical Lung Cancer, Vol. 9, Suppl. 1, pp. S13-S19 (2008)	☐
	NPL23	Holt, G. E. et al., "Immunotherapy as a strategy for the treatment of nonsmall-cell lung cancer", Therapy, Vol. 8, No. 1, pp. 43-54 (2011)	☐

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Sheet 8 of 14

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

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	NPL24	Iwai, Y. et al., "Involvement of PO-L 1 on tumor cells in the escape from host immune system and tumor immunotherapy by PO-L 1 blockade", Proc. Natl. Acad. Sci., Vol. 99, No. 19, pp. 12293-12297 (2002)	☐
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Sheet 9 of 14

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Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
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	NPL32	Schreiber, R.D. et al., "Cancer Immunoediting: Integrating Immunity's Roles in Cancer Suppression and Promotion", Science, Vol. 331, pp. 1565-1570 (2011)	☐
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	NPL37	Topalian, S.L. et al., "Cancer Immunotherapy Comes of Age", Journal of Clinical Oncology, Vol. 29, No. 36, pp. 4828-4836 (2011)	☐
	NPL38	Topalian, S.L. et al., "Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer", The New England Journal of Medicine, Vol. 366, No. 26, pp. 2443-2454 (2012)	☐

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	NPL39	Topalian, S.L. et al. "Targeting the PD-1/B7-H1 (PO-L 1) pathway to activate anti-tumor immunity", Current Opinion in Immunology, Vol. 24, pp. 207-212 (2012)	☐
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	NPL41	Wong, R.M. et al., "Programmed death-1 blockade enhances expansion and functional capacity of human melanoma antigen-specific CTLs", International Immunology, Vol. 19, No. 10, pp. 1223-1234 (2007)	☐
	NPL42	Zou, W. et al., "Inhibitory 87-family molecules in the tumour microenvironment", Nature Reviews: Immunology, Vol. 8, pp. 467-477 (2008)	☐
	NPL43	International Preliminary Report on Patentability and Written Opinion for International Application No. PCT/US2013/040764, The International Bureau of WIPO, Geneva, Switzerland, issued on November 18, 2014, 10 pages.	☐
	NPL44	International Search Report for International Application No. PCT/US2013/040764, European Patent Office, Netherlands, mailed on October 31, 2013, 8 pages.	☐
	NPL45	ASCIERTO, P.A., et al., "Clinical experiences with anti-CD137 and anti-PD1 therapeutic antibodies," Semin Oncol 37(5):508-516, Elsevier Inc., United States (2010).	☐
	NPL46	National Institutes of Health Clinical Center, Clinical Trial Identifier NCT01024231 entitled "Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma," ClinicalTrials.gov, available at https://clinicaltrials.gov/ct2/show/NCT01024231?term=NCT01024231&rank=1, last accessed on June 30, 2017, 7 pages (same clinical trial accessed on April 27, 2017 by Examiner in related US Application No. 14/400,667, filed November 12, 2014).	☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 11 of 14

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	NPL47	CURRAN, M.A., et al., "PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors," Proc Natl Acad Sci USA 107(9):4275-4280, National Academy of Sciences, United States (2010).	☐
	NPL48	MAY Jr., K.F., et al., "Prostate Cancer Immunotherapy," Clinical Cancer Research 17(16):5233-5238, American Association of Cancer Research, United States (2011).	☐
	NPL49	NATARAJAN, N., et al., "Novel immunotherapeutic agents and small molecule antagonists of signalling kinases for the treatment of metastatic melanoma," Drugs 71(10):1233-1250, Springer International, New Zealand (2011).	☐
	NPL50	Office Action mailed November 9, 2017 in United States Patent Application No. 14/950,748, inventor Cogswell, J.P., et al., filed November 24, 2015, 11 pages.	☐
	NPL51	POSTOW, M.A., et al., "Targeting Immune Checkpoints: Releasing the Restraints on Anti-tumor Immunity for Patients With Melanoma," Cancer Journal 18(2):153-159, Lippincott Williams & Wilkins, United States (2012).	☐
	NPL52	SZNOL, M., "Advances in the treatment of metastatic melanoma: new immunomodulatory agents," Semin Oncol. 39(2):192-203, Elsevier Inc., United States (2012).	☐
	NPL53	WOLCHOK, J.D., "Immunobiology of immune checkpoints," Pigment Cell Research 24:1005, John Wiley & Sons A/S, United States (2011).	☐
	NPL54	National Institutes of Health, "Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma," ClinicalTrials.gov Identifier NCT01024231, accessed at https://web.archive.org/web/20111023232455/https://clinicaltrials.gov/ct2/show/NCT01024231 , accessed on September 22, 2017, 3 pages.	☐

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 12 of 14

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	NPL55	SHIBAYAMA, S. and YOSHIDA, T., "Development of ONO-4538, fully human anti-PD-1 antibody for malignant tumors," Medical Science Digest 36(12):1120-1123, New Science Co., Japan (2010).	☐
	NPL56	WANG, G. et al., "A Therapeutic strategy of targeting PD1/PDL signal pathway," Chinese Bulletin of Life Sciences 23:86-89, (2011)	☐
	NPL57	GAO, Q., et al., "Overexpression of PD-L1 Significantly Associates with Tumor Aggressiveness and Postoperative Recurrence in Human Hepatocellular Carcinoma," Clinical Cancer Research 15(3);971-979, American Association for Cancer Research, United States (2009)	☐
	NPL58	GHEBEH, H., et al., "The B7-H1 (PD-L1) T Lymphocyte-Inhibitory molecule Is Expressed in Breast cancer Patients with Infiltrating Ductal Carcinoma: Correlation with Important high-Risk Prognostic Factors Neoplasia 8(3):190-198, Elsevier, Netherlands (2006)	☐
	NPL59	ROTH, T., et al., "B7-H3 Ligand Expression by Prostate Cancer: A Novel Marker of Prognosis and Potential Target for Therapy," Cancer Res 67(16):7893-7900, American Association for Cancer, United States (2007)	☐
	NPL60	National Institutes of Health Clinical Center, Clinical Trial Identifier NCT01024231 entitled "Dose-escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma," ClinicalTrials.gov, available at https://clinicaltrials.gov/archive/NCT01024231/2012_04_30, last accessed on July 18, 2017, 4 pages (same clinical trial accessed on April 27, 2017 by Examiner in same application).	☐
	NPL61	Study NCT01024231 , "Dose-Escalation Study of Combination BMS-936558 (MDX-1106) and Ipilimumab in Subjects with Unrespectable Stage III or Stage IV Malignant Melanoma," April 18, 2012, 3 pages.	☐

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(Use as many sheets as necessary)

Sheet 13 of 14

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Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	NPL62	SIMEONE, E., et al., "Immunotreatment of metastatic melanoma: the experience with anti-CTLA-4," *Journal of Immunotoxicology 9(3)*:21-247, Taylor & Francis, United Kingdom (2012)	☐
	NPL63	WOLCHOK, J.D., et a., " Nivolumab Plus Ipilimumab in Advanced Melanoma," *New England Journal of Medicine 369(2)*:122-133, Massachusettes Medical Society, United States (2012)	☐
	NPL64	Phase 3 study of Nivolumab, or Nivolumab Plus Ipilimumab Versus Ipilimumab alone in Previously Untreated Advanced Melanoma (Checkmate 067), last updated December 18, 2017	☐
	NPL65	Co-pending Application, U.S. Application No. 16/006,365, inventors COGSWELL, John, P., filed on June 12, 2018 (NOT PUBLISHED)	☐
	NPL66	Co-pending Application, U.S. Application No. 16/006,493, inventors COGSWELL, John, P., filed on June 12, 2018 (NOT PUBLISHED)	☐
	NPL67	Co-pending Application, U.S. Application No. 16/024,333, inventors COGSWELL, John, P., filed on June 29, 2018 (NOT PUBLISHED)	☐
	NPL68	Co-pending Application, U.S. Application No. 16/024,340, inventors COGSWELL, John, P., filed on June 29, 2018 (NOT PUBLISHED)	☐
	NPL69	KUENEN, B., et al., "A Phase 1 Pharmacologic Study of Necitumumab (IMC-11F8), a Fully Human IgG1 Monoclonal Antibody Directed Against EGFR in Patients with Advanced Solid Malignancies," Clinical Cancer Research 16:1915-1923, American Association for Cancer Research, United States (2010)	☐
	NPL70	SEIWERT, T.Y., et al., "Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE 0-12): an open-label, multicenter, phase 1b trial." Lancet Oncology 17:956-965, Elsevier, Netherlands (2016)	☐

Examiner Signature		Date Considered	

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Sheet 14 of 14

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Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

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	NPL71	WANG, D., et al., "Fixed Dosing Versus Body Size-based Dosing of Monoclonal Antibodies in Adult Clinical Trials," J. Clin Pharmacol 49:1012-1024, John Wiley & Sons, United States (2009)	☐

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Examiner Signature	/ILIA I OUSPENSKI/	Date Considered	08/02/2018

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: COGSWELL *et al.*	Confirmation No.: 5731
Applicant: Bristol-Myers Squibb Company	Art Unit: *To Be Assigned*
Application No.: 16/006,473	Examiner: *To Be Assigned*
(*Continuation of Appl. No. 14/950,748; Filed: November 24, 2015*)	
Filing Date: June 12, 2018	Atty. Docket: 3338.0630006/ELE/C-K

Title: **CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING**

Information Disclosure Statement

Mail Stop Amendment

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

Listed on accompanying IDS Forms PTO/SB/08a and PTO/SB/08b equivalent are documents for consideration in view of 37 C.F.R. §1.56 and in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.97 and 1.98.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicant has listed publication dates on the attached IDS Forms based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicant reserves the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /I.I.O/

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

This is a filing under 37 C.F.R. § 1.97(b). This Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. No statement or fee is required.

A concise explanation of the relevance of the non-English language documents appears below in accordance with 37 C.F.R. § 1.98(a)(3).

Document **FP11**, WO 2004/004771, is in a foreign language. An English language abstract was previously appended to the face page of document **FP11**. Additionally, document **US10**, is believed to be an English language equivalent of document **FP11**.

Document **FP13**, WO 2004/072286, is in a foreign language. An English language abstract was previously appended to the face page of document **FP13**.

Document **FP20**, CN 101215329 A, is in a foreign language. An English language abstract was previously appended to the face page of document **FP20**.

Document **FP21**, CN 102833441 A, is in a foreign language. An English language abstract was previously appended to the face page of document **FP21**.

Copies of documents **NPL50**, **NPL61-NPL64,** and **NPL69-71** are submitted. However, in accordance with 37 C.F.R. § 1.98(a)(2)(ii), no copies of U.S. patents and patent application publications cited as documents **US1-US41** on the attached IDS Forms are submitted. Additionally, copies of unpublished U.S. applications **NPL65-NPL68**, cited on the attached IDS Forms, are not provided in accordance with the U.S. Patent and Trademark Office Official Gazette notice of

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Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 241 of 318

October 19, 2004, which states: "the requirement in 37 C.F.R. § 1.98(a)(2)(iii) for a legible copy of the specification, including the claims, and drawings of each cited pending unpublished U.S. patent application (or portion of the application which caused it to be listed) is sua sponte waived where the cited pending application is stored in the USPTO's IFW system."

Copies of the **FP1-FP21**, **NPL1-NPL49,** and **NPL51-NPL60** documents were cited by or submitted to the Office in an IDS that complies with 37 C.F.R. § 1.98(a)-(c) in Application No. 14/950,748, filed November 24, 2015, which is relied upon for an earlier filing date under 35 U.S.C. § 120. Thus, copies of these documents are not attached. 37 C.F.R. § 1.98(d).

It is expected that the examiner will review the prosecution and cited art in the Parent Application No. 14/950,748, filed November 24, 2015, in accordance with MPEP 2001.06(b), and indicate in the next communication from the office that the art cited in the earlier prosecution history has been reviewed in connection with the present application.3

In accordance with the Federal Circuit decision in *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358 (Fed. Cir. 2003), Applicant submits herewith an Office Action from the co-pending U.S. Patent Application No. 14/950,748, filing date November 24, 2015, as document **NPL50**.

The identification of this Office Action is not to be construed as a waiver of secrecy as to that application now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited applications and the art cited therein during examination.

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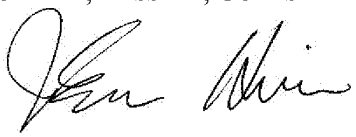
Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 242 of 318

It is respectfully requested that the Examiner initial and return a copy of the enclosed IDS Forms, and indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Ji-Eun Kim
Attorney for Applicant
Registration No. 68,504

Date: July 24, 2018

1100 New York Avenue, N.W.
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08/02/2018

/ILIA I OUSPENSKI/

Atty. Dkt. No. 3338.0630006/ELE/C-K

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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/006,473	06/12/2018	John P. COGSWELL	3338.0630006/ELE/C-K	5731

115018 7590 09/14/2018

Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DC 20005

EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
09/14/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ckim@sternekessler.com
e-office@sternekessler.com
pduffy@sternekessler.com

Applicant-Initiated Interview Summary	**Application No.** 16/006,473	**Applicant(s)** COGSWELL et al.	
	Examiner ILIA I OUSPENSKI	**Art Unit** 1644	**AIA Status** No

All participants (applicant, applicants representative, PTO personnel):

(1) ILIA I. OUSPENSKI.

(3) BRIAN DUDLEY.

(2) JI-EUN KIM.

(4) _____.

Date of Interview: 10 September 2018.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☑112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Discussed the issues of New Matter raised in the preceding Office action, and reviewed the specification for support of the limitations in question..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/ILIA I OUSPENSKI/ Primary Examiner, Art Unit 1644	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/006,473	Filing Date 06/12/2018	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	09/19/2018	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 25	Minus	** 20	= 5	X $100 =	500
	Independent (37 CFR 1.16(h))	* 2	Minus	***2	= 0	X $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**500**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

SLIE
DEIDRE C. KING-WOODWARD

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: COGSWELL *et al.*	Confirmation No.: 5731
Applicant: Bristol-Myers Squibb Company	Art Unit: 1644
Application No.: 16/006,473	Examiner: OUSPENSKI, ILIA I.
Filing Date: June 12, 2018	Atty. Docket: 3338.0630006/ELE/C-K

Title: **CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING**

Amendment and Reply Under 37 C.F.R. § 1.111

Mail Stop Amendment

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

In reply to the Office Action dated August 7, 2018, Applicant submits the following Amendment and Remarks.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks and Arguments begin on page 5 of this paper.

It is not believed that extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any additional fees required to continue prosecution or appeal of this application (including issue fee, fees for net addition of claims or forwarding to appeal) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

1-17. (Cancelled)

18. (Currently Amended) A method of treating a tumor in a human subject in need thereof, comprising administering to the subject about 10 mg/kg of an anti-PD-L1 antibody every 2 weeks, wherein the anti-PD-L1 antibody is administered intravenously over 60 minutes infusion; wherein the tumor is derived from a bladder cancer of ~~the urethra, the bladder, the ureter, or the renal pelvis~~; and wherein the tumor is refractory to a platinum based chemotherapy.

19. (Previously Presented) The method of claim 18, wherein the tumor is advanced.

20. (Previously Presented) The method of claim 18, wherein the tumor is locally advanced.

21. (Previously Presented) The method of claim 18, wherein the tumor is metastatic.

22. (Previously Presented) The method of claim 18, wherein the treatment lasts more than 12 weeks.

23. (Previously Presented) The method of claim 18, wherein the anti-PD-L1 antibody is formulated in a pharmaceutical composition.

24. (Currently Amended) The method of claim 23, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable salt, an anti-oxidant, an aqueous carrier, a non-aqueous carrier, ~~an adjuvant,~~ or any combination thereof.

25. (Cancelled)

26. (Previously Presented) The method of claim 24, wherein the salt comprises a sodium salt.

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27. (Previously Presented) The method of claim 24, wherein the salt comprises sodium chloride.

28-31. (Cancelled)

32. (Currently Amended) The method of claim 18, wherein at least 1% of tumor cells exhibit membrane ~~the subject is~~ PD-L1 expression ~~positive~~.

33. (Currently Amended) The method of claim 18, wherein at least 5% of tumor cells exhibit membrane ~~the subject is~~ PD-L1 expression ~~negative~~.

34. (Previously Presented) The method of claim 18, further comprising administering an anti-cancer agent.

35. (Previously Presented) The method of claim 19, further comprising administering an anti-cancer agent.

36. (Previously Presented) The method of claim 20, further comprising administering an anti-cancer agent.

37. (Previously Presented) The method of claim 21, further comprising administering an anti-cancer agent.

38. (Previously Presented) The method of claim 28, further comprising administering an anti-cancer agent.

39. (Previously Presented) The method of claim 34, wherein the anti-cancer agent is a chemotherapy.

40. (Previously Presented) The method of claim 34, wherein the anti-cancer agent is a radiotherapy.

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41. (Previously Presented) The method of claim 35, wherein the anti-cancer agent is a chemotherapy.

42. (Previously Presented) The method of claim 35, wherein the anti-cancer agent is a radiotherapy.

43. (Previously Presented) The method of claim 36, wherein the anti-cancer agent is a chemotherapy.

44. (Previously Presented) The method of claim 36, wherein the anti-cancer agent is a radiotherapy.

45. (Cancelled)

46. (Previously Presented) The method of claim 18, wherein the platinum-based chemotherapy is a platinum-based doublet chemotherapy.

47. (Previously Presented) The method of claim 18, wherein the platinum-based chemotherapy comprises cisplatin, carboplatin, or both.

48. (New) The method of claims 18, wherein the subject is administered an antihistamine prior to the anti-PD-L1 antibody.

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Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 18-24, 26, 27, 32-44, and 46-48 are pending in the application, with claim 18 being the independent claim. Claims 18, 24, 32, and 33 are sought to be amended; claims 25, 28-31, and 45 are cancelled, without prejudice or disclaimer of the subject matter therein; and new claim 48 is sought to be added.

Support for the amendments to the claims can be found throughout the specification as filed. In particular, support for the amendments to claims 32 and 33 can be found, *inter alia*, at page 65 line 30 to page 67 line 31; and page 88 lines 3-4. In addition, claim 24 is amended for clarity.

Support for new claim 48 can be found throughout the specification as filed, including, *inter alia*, at p. 94, lines 24-28.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Substance of Examiner Interview

In accordance with 37 C.F.R. § 1.133(b), and further to the Applicant-Initiated Interview Summary mailed September 14, 2018, Applicant thanks the Examiner for taking the time to discuss the present application, and Applicant provides the following statement of substance regarding the Examiner Interview. *See* MPEP § 713.04.

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On September 10, 2018, representatives for the Applicant (Ji-Eun Kim and Brian Dudley) met with Examiner Ouspenski to discuss the non-final Office Action, mailed August 7, 2018. In particular, the rejection under 35 U.S.C. § 112, first paragraph was discussed, and Applicant's representatives directed Examiner Ouspenski's attention to support in the specification for the pending claims. It was agreed that the current reply would be considered in light of the interview.

Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected previous claims 24-27, 32, and 33 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Office Action, pp. 2-4. Applicant respectfully disagrees for the following reasons.

Claims 24 and 25

The Examiner rejected claims 24 and 25 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for recitation of the term "adjuvant." Office Action, p. 2. The Examiner contends that it is unclear which types of agents are encompassed by the term "adjuvant." *Id.*

Solely to advance prosecution, and without acquiescing to the Examiner's arguments or characterization of the claims, claim 25 is cancelled, and claim 24 is amended to remove the term "adjuvant." Thus, the claims no longer recite the term objected to by the Examiner, and the Examiner's rejection is rendered moot. A person of ordinary skill in the art at the time the application was filed would have been able to readily identify the metes and bounds of amended claim 24, and thus amended claim 24 is definite. Accordingly, Applicant respectfully requests that the Examiner withdraw this rejection of claims 24 and 25.

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Claims 32 and 33

The Examiner rejected claims 32 and 33 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Office Action, p. 3. In particular, the Examiner contends that "it is unclear what types of cells or tissues of the subject must be PD-L1 positive or PD-L1 negative." *Id.* Applicant respectfully disagrees.

However, solely to advance prosecution, and without acquiescing to the Examiner's arguments, claim 32 is amended to recite that at least 1% of tumor cells exhibit membrane PD-L1 expression, and claim 33 is amended to recite that at least 5% of tumor cells exhibit membrane PD-L1 expression. Amended claims 32 and 33 recite the types of cells that are PD-L1 positive, specifically tumor cells. Therefore, a person of ordinary skill in the art at the time the application was filed would have been able to readily identify the metes and bounds of amended claims 32 and 33. Thus, amended claims 32 and 33 would have been clear and definite to a skilled artisan. Accordingly, Applicant respectfully requests that the Examiner withdraw this rejection of claims 32 and 33.

Claims 26 and 27

The Examiner rejected claims 26 and 27 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite due to their dependency on an allegedly indefinite claim. Office Action, p. 3. Claims 26 and 27 depend directly from amended claim 24, which is definite for the reasons provided above. Therefore, claims 26 and 27 are also definite. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection of claims 26 and 27.

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Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 18-47 under pre-AIA 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement (claims 18-47) and the enablement requirement (claim 45). Office Action, pp. 3-6. Applicant respectfully disagrees for the following reasons.

Written Description – Claims 18-47

The Examiner rejected claims 18-47 under pre-AIA 35 U.S.C. § 112, first paragraph for allegedly lacking written description support in the specification as filed. Office Action, pp. 3-5. The Examiner notes that this is a New Matter Rejection. The Examiner contends that "the specification does not appear to provide an adequate written description of a method of treating a urethra, bladder, ureter, or renal pelvis-derived tumor which is refractory to platinum based chemotherapy." *Id.* at p. 4. Applicant respectfully disagrees.

However, solely to advance prosecution, and without acquiescing to the Examiner arguments or characterization of the claims and/or specification, claims 25, 28-31, and 45 are cancelled, rendering the Examiner rejection of these claims moot. In addition, solely to expedite examination, claim 18 is amended to recite a method of treating a tumor in a human subject in need thereof, comprising administering to the subject about 10 mg/kg of an anti-PD-L1 antibody every 2 weeks, wherein the anti-PD-L1 antibody is administered intravenously over 60 minutes infusion; wherein the tumor is derived from a bladder cancer; and wherein the tumor is refractory to a platinum based chemotherapy.

The specification as filed provides adequate written description support for the full scope of amended claim 18, including treatment of a tumor that is derived from a bladder cancer, wherein the

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tumor is refractory to a platinum based chemotherapy. As the Examiner notes, the specification does specifically exemplify a platinum based chemotherapy as a standard-of-care therapy for non-small cell lung cancer (NSCLC) at pages 74-75. However, the corresponding section of the specification prefaces that disclosure by stating that "[b]y way of example, standard-of-care treatments for MEL, RCC, and NSCLC are summarized below." *Id.* at p. 72, lines 12-13. Thus, the disclosure of platinum based chemotherapy in the context of NSCLC serves merely as an example, and a person of ordinary skill in the art at the time the application was filed would have immediately recognized that the specification as a whole provides adequate written description support for the full scope of amended claim 18.

In particular, the specification clearly discloses treatment of refractory tumor derived from a bladder cancer. The specification provides at p. 43, lines 14-21:

> Accordingly, this disclosure provides methods for immunotherapy of a patient afflicted with an advanced, metastatic and/or **refractory cancer**, which method comprises administering to the patient a therapeutically effective amount of an Ab or an antigen-binding portion thereof that disrupts the interaction of PD-1 with PD-L1 and/or PD-L2. In certain embodiments of any of the therapeutic methods disclosed herein, **the subject has been pre-treated for the cancer**; for example, the subject had undergone at least one, two, or three **prior lines of therapy for cancer**.

Specification, p.43, lines 14-21 (emphasis added). The specification further states that "the invention includes **refractory** or recurrent malignancies whose growth may be inhibited using the anti-PD-L1 Abs of the invention." *Id.* at p. 53, lines 5-6 (emphasis added). The specification continues by listing "cancer of the **bladder** " (*id.* at p. 53, line 20; emphasis added) as an example of "cancers that may be treated using an anti-PD-1 Ab in the methods of the invention, based on the indications of a very broad applicability of anti-PD-L1 immunotherapy provided herein." *See generally id.* at p. 53, lines 7-26.

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Accordingly, the specification provides support for treatment of a tumor derived from a bladder cancer, wherein the tumor is refractory to one or more *prior therapy* to treat the tumor.

Furthermore, the specification defines a standard of care therapy, *e.g.*, a prior therapy, as including any therapy "that is recognized by a medical practitioner as appropriate or accepted" for a given cancer type. *See id.* at p. 72, lines 2-7. In particular, the specification states that:

> As used herein, a "standard-of-care therapeutic" is a treatment process, including a drug or combination of drugs, radiation therapy, surgery or other medical intervention that is **recognized by medical practitioners as appropriate, accepted, and/or widely used for a certain type of patient, disease or clinical circumstance**. Standard-of-care therapeutics for treating different types of cancer are well known by persons of skill in the art. For example, the National Comprehensive Cancer Network (NCCN), an alliance of 21 major cancer centers in the USA, publishes the **NCCN Clinical Practice Guidelines in Oncology** (NCCN GUIDELINES®) that provide detailed up-to-date information on the standard-of-care treatments for a wide variety of cancers (see NCCN GUIDELINES®, 2013). **By way of example**, standard-of care treatments for MEL, RCC and NSCLC are summarized below.

Id. at p. 72, lines 3-13 (emphasis added).

Indeed, the NCCN Clinical Practice Guidelines in Oncology (2013; NPL76; submitted herewith) mentioned in the specification provides a platinum based chemotherapy, cisplatin and/or carboplatin, as part of the recommended standard-of-care for certain types of bladder cancer. The Guidelines disclose under the heading "Principles of Chemotherapy Management" the use of cisplatin (a platinum-based chemotherapy agent) in combination with other chemotherapy drugs to be administered (1) perioperatively as a neoadjuvant or adjuvant, (2) as a first-line or second-line chemotherapy for metastatic disease, and (3) as part of a radiosensitizing chemotherapy regimen. NCCN Guidelines, p. 458. In addition, the Guidelines further provide administering carboplatin (a

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platinum-based chemotherapy agent) as an alternative for first-line and/or second-line chemotherapy of metastatic disease. *Id.*; *see also*, *id.* at pp. 451-452 and 465-470.

Therefore, the specification clearly discloses a method of treating a tumor in a human subject in need thereof, comprising, *inter alia*, administering to the subject an anti-PD-L1 antibody, wherein the tumor is derived from a bladder cancer, wherein the tumor is refractory to one or more prior therapy, such as a platinum based chemotherapy. Thus, the specification provides adequate written description support for the full scope of amended claim 18.

Claims 19-27, 32-44, 46, and 47 depend directly or indirectly from amended claim 18 and thus include every element of amended claim 18. Therefore, the specification also provides adequate written description support for claims 19-27, 32-44, 46, and 47. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection of claims 18-47 under pre-AIA 35 U.S.C. § 112, first paragraph.

Enablement – Claim 45

The Examiner rejected claim 45 under pre-AIA 35 U.S.C. § 112, first paragraph for allegedly lacking enablement in the specification as filed. Office Action, pp. 5-6. Solely to advance prosecution, and without acquiescing to the Examiner's arguments, claim 45 is cancelled, rendering the Examiner's rejection of claim 45 moot. Accordingly, Applicant respectfully requests that the Examiner withdraw this rejection of claim 45.

As the written description and enablement rejections under 35 U.S.C. §112, first paragraph, have been overcome or rendered moot, and as the Examiner has provided no other grounds for rejection, Applicant respectfully requests that the Examiner reconsider the rejections under 35 U.S.C. §112, first paragraph, and allow the present claims. *See* MPEP 2163.06.

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Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/Ji-Eun Kim/

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9920539_1

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Electronic Patent Application Fee Transmittal

Application Number:	16006473
Filing Date:	12-Jun-2018
Title of Invention:	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING
First Named Inventor/Applicant Name:	John P. COGSWELL
Filer:	Ji Eun Kim/Jeanette Yando
Attorney Docket Number:	3338.0630006/ELE/C-K

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt

EFS ID:	33769039
Application Number:	16006473
International Application Number:	
Confirmation Number:	5731
Title of Invention:	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING
First Named Inventor/Applicant Name:	John P. COGSWELL
Customer Number:	115018
Filer:	Ji Eun Kim/Jeanette Yando
Filer Authorized By:	Ji Eun Kim
Attorney Docket Number:	3338.0630006/ELE/C-K
Receipt Date:	19-SEP-2018
Filing Date:	12-JUN-2018
Time Stamp:	17:31:04
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$240
RAM confirmation Number	092018INTEFSW17312600
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	NPL72_Vogel.pdf	2396296 20e087e032aac7a6f3a7efed8329c30eb7f09f09	no	12
Warnings:					
Information:					
2	Non Patent Literature	NPL73_WhatisNonSmallCellLungCancer.pdf	298962 3f7f381197c7181dd7f0ae038eb6f24405929372	no	5
Warnings:					
Information:					
3	Non Patent Literature	NPL74_Atmar.pdf	544968 f50603a007953fb96eae8b22014b2107576e5056	no	3
Warnings:					
Information:					
4	Non Patent Literature	NPL75_Auperin.pdf	1341011 aaf205d5c40203e2e4ae38308cc55880dcac8025	no	10
Warnings:					
Information:					
5	Non Patent Literature	NPL76_Clark.pdf	922327 4da7f4f3e82108c96863378c564e326cf6a0099f	no	30
Warnings:					
Information:					
6	Non Patent Literature	NPL77_Leigh.pdf	740636 8176728ae739d483befd83efccab60bbca9c89b0	no	7
Warnings:					
Information:					

7	Non Patent Literature	NPL78_Lenz.pdf	1445328 638e327352e03591eef7383657b08f3863e17239	no	9
Warnings:					
Information:					
8	Non Patent Literature	NPL79_SafeAdministrationAndMonitoring.pdf	4449410 5682c959fc45739d2d3868c2a535cb362b995c24	no	23
Warnings:					
Information:					
9	Non Patent Literature	NPL80_0630005_OA.pdf	370566 a33c1a5d616f281a6ff5262a64be75d1c031165d	no	9
Warnings:					
Information:					
10	Non Patent Literature	NPL81_OA_630009.pdf	275380 6473ff4009d654ca6e805ad6f04fa49f938dafa0	no	7
Warnings:					
Information:					
11	Non Patent Literature	NPL82_0630007_OA.pdf	368398 8881b45ddd6bbe5dccdae48345f6bfffc46f5497	no	9
Warnings:					
Information:					
12	Non Patent Literature	NPL83_0630008_OA.pdf	422155 70d5702267b2e84bb8b3379c2fbbcaf8afb9346d	no	10
Warnings:					
Information:					
13	Transmittal Letter	2018-09-19-1st-Supp-IDS-3338-0630006.pdf	112992 76ec59982ad35902e80c80f0b2459165149f6b85	no	3
Warnings:					
Information:					

14	Information Disclosure Statement (IDS) Form (SB08)	2018-09-19-SB08A-B-3338-0630006.pdf	91005 9050759f94e69787cab596897ec67a4459435b84	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
15		2018-09-19-Amendment-111-3338-0630006.pdf	144052 2fd640937a93363b4459b6f015cdb5c42566cd94	yes	12

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	12

Warnings:					
Information:					
16	Fee Worksheet (SB06)	fee-info.pdf	30480 6366ca8e1c6faf32c8a1aaef1d97511f910fa811	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	13953966		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: COGSWELL *et al.*	Confirmation No.: 5731
Applicant: Bristol-Myers Squibb Company	Art Unit: 1644
Application No.: 16/006,473	Examiner: OUSPENSKI, ILIA I.
Filing Date: June 12, 2018	Atty. Docket: 3338.0630006/ELE/C-K

Title: **CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING**

First Supplemental Information Disclosure Statement

Mail Stop Amendment

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

Listed on accompanying IDS Forms PTO/SB/08a; PTO/SB/08b equivalent are documents for consideration in view of 37 C.F.R. §1.56 and in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.97 and 1.98. The numbering on this First Supplemental Information Disclosure Statement is a continuation of the numbering in Applicant's Information Disclosure Statement filed on **July 25, 2018** in connection with the above-captioned application.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicant has listed publication dates on the attached IDS Forms based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicant reserves the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

This is a filing under 37 C.F.R. § 1.97(c). This Information Disclosure Statement is being filed more than three months after the U.S. filing date AND after the mailing date of the first Office Action on the merits, but before the mailing date of a Final Rejection, or Notice of Allowance, or an action that otherwise closes prosecution in the application. The required fee is provided through online credit card payment authorization in the amount of $240.00 in payment of the fee under 37 C.F.R. § 1.17(p).

Copies of documents **NPL72-NPL83** are submitted. However, in accordance with 37 C.F.R. § 1.98(a)(2)(ii), no copies of U.S. patent and patent application publications cited as documents **US42-US48** on the attached IDS Forms are submitted.

It is expected that the examiner will review the prosecution and cited art in the Parent Application No. 14/950,748, filed November 24, 2015 (now U.S. Patent No 10,072,082 B2, issued September 11, 2018), in accordance with MPEP 2001.06(b), and indicate in the next communication from the office that the art cited in the earlier prosecution history has been reviewed in connection with the present application.

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 267 of 318

In accordance with the Federal Circuit decision in *Dayco Prods., Inc. v. Total Containment, Inc.* 329 F.3d 1358 (Fed. Cir. 2003), Applicant submits herewith Office Actions from the co-pending U.S. Patent Application Nos.: 16/006,365, filed June 12, 2018, as document **NPL80**; 16/024,340, filed June 29, 2018, as document **NPL81**; 16/006,493, filed June 12, 2018, as document **NPL82**; and 16/024,333, filed June 29, 2018, as document **NPL83**.

The identification of these Office Actions is not to be construed as a waiver of secrecy as to those applications now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited applications and the art cited therein during examination.

It is respectfully requested that the Examiner initial and return a copy of the enclosed IDS Forms, and indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/Ji-Eun Kim/

Ji-Eun Kim
Attorney for Applicant
Registration No. 68,504

Date: September 19, 2018

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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Atty. Dkt. No. 3338.0630006/ELE/C-K

Approved for use through 11/30/2020. OMB 0651-0031
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Substitute for form 1449/PTO

FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	1644
Examiner Name	OUSPENSKI, ILIA I
Attorney Docket Number	3338.0630006/ELE/C-K

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	US42	US-20020102651-A1	08-01-2002	FREEMAN; et al.	
	US43	US-20090055944-A1	02-26-2009	KORMAN; et al.	
	US44	US-20090304711-A1	12-10-2009	PARDOLL; et al.	
	US45	US-20100203056-A1	08-12-2010	IRVING; et al.	
	US46	US-20110244546-A1	10-06-2011	HANSEN; et al.	
	US47	US-20110250201-A1	10-13-2011	SMITH; et al.	
	US48	US-10072082-B2	09-11-2018	COGSWELL; et al.	

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	NPL72	VOGEL, W.H., " Infusion Reactions: Diagnosis, Assessment, and management," Clinical Journal of Oncology Nursing 14(2):E10-E21, Oncology Nursing Society, United States (2010).	☐
	NPL73	American Cancer Society, "What is Non-Small Cell Lung Cancer?," retrieved from https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html, retrieved on August 6, 2018. 5 pages.	☐
	NPL74	ATMAR, J., "Review of the Safety and Feasibility of rapid Infusion of Rituximab," Journal of Oncology Practice 6(2): 91-93, American Society of Clinical Oncology, United States (2010).	☐
	NPL75	AUPERIN, A., et al., "Meta-Analysis of Concomitant versus Sequential Radiochemotherapy in Locally Advanced Non-Small-Cell Lung Cancer," Journal of Clinical Oncology 28(13):2181-2190, American Society of Clinical Oncology Journal, United States (2010).	☐
	NPL76	CLARK, P., et al., "Bladder Cancer," Journal of the National Comprehensive Cancer Network 11(4):446-475, Harborside Press, United States (April 2013).	☐
	NPL77	LEIGHL, N.B., "Treatment paradigms for Patients with metastatic non-small-cell lung cancer: first-, second-, and third-line," Curr Oncol, 19:S52-S58, Multimed Inc., Canada (June 2012).	☐
	NPL78	LENZ, H-J., "Management and Preparedness for Infusion and Hypersensitivity Reactions," The Oncologist 12:601-609, Wiley Online Library, United States (2007)	☐

Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	1644
Examiner Name	OUSPENSKI, ILIA I
Attorney Docket Number	3338.0630006/ELE/C-K

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	NPL79	"Safe Administration and Monitoring of Monoclonal Antibodies in the Treatment of Multiple Sclerosis," International Journal of MScare 9(2): 23 pages, Supplement to the International Journal of MS Care, (April 2007).	☐
	NPL80	Office Action mailed August 10, 2018, in United States Patent Application No. 16/006,365, inventors Cogswell, *et al.,* filed June 12, 2018, 9 pages.	☐
	NPL81	Office Action mailed August 15, 2018, in United States Patent Application No. 16/024,340, inventors Cogswell, *et al.,* filed June 29, 2018, 7 pages.	☐
	NPL82	Office Action mailed August 10, 2018, in United States Patent Application No. 16/006,493, inventors Cogswell, *et al.,* filed June 12, 2018, 9 pages.	☐
	NPL83	Office Action mailed August 15, 2018, in United States Patent Application No. 16/024,333, inventors Cogswell, *et al.,* filed June 29, 2018, 10 pages.	☐

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/006,473	06/12/2018	John P. COGSWELL	3338.0630006/ELE/C-K

CONFIRMATION NO. 5731

115018
Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DC 20005

PUBLICATION NOTICE

OC000000102828475

Title:CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING

Publication No.US-2018-0282413-A1
Publication Date:10/04/2018

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

115018 7590 10/18/2018

Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DC 20005

EXAMINER
OUSPENSKI, ILIA I

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/18/2018

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/006,473	06/12/2018	John P. COGSWELL	3338.0630006/ELE/C-K	5731

TITLE OF INVENTION: CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	01/18/2019

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 272 of 318

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

115018 7590 10/18/2018
Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DC 20005

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/006,473	06/12/2018	John P. COGSWELL	3338.0630006/ELE/C-K	5731

TITLE OF INVENTION: CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	01/18/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
OUSPENSKI, ILIA I	1644	424-172100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1_____
2_____
3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 273 of 318

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/006,473	06/12/2018	John P. COGSWELL	3338.0630006/ELE/C-K	5731

115018 7590 10/18/2018

Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DC 20005

EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/18/2018

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 274 of 318

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/006,473	Applicant(s) COGSWELL et al.	
	Examiner ILIA I OUSPENSKI	Art Unit 1644	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 09/19/2018.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file areply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ILIA I OUSPENSKI/
Primary Examiner, Art Unit 1644

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 276 of 318

Continuation of 3. The allowed claim(s) is/are: 18-24,26-27,32-44 and 46-48

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/006,473	COGSWELL et al.
	Examiner	Art Unit
	ILIA I OUSPENSKI	1644

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Priority and related applications, including prosecution history	08/02/2018	io
WEST: attached	08/02/2018	io
ProQuest: same as WEST	08/02/2018	io
Inventor search	08/02/2018	io
Sequence, WEST and Inventor searches updated	10/15/2018	io

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
See search notes		10/15/2018	io

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 278 of 318

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/006,473	COGSWELL et al.
	Examiner	**Art Unit**
	ILIA I OUSPENSKI	1644

CPC						
Symbol					**Type**	**Version**
C07K	/	16	/	2818	F	2013-01-01
C07K	/	16	/	2827	I	2013-01-01
A61K	/	39	/	3955	I	2013-01-01
C07K	/	16	/	18	I	2013-01-01
C07K	/	16	/	2803	I	2013-01-01
G01N	/	33	/	57492	I	2013-01-01
A61K	/	2039	/	505	A	2013-01-01
A61K	/	2039	/	507	A	2013-01-01
C07K	/	2317	/	76	A	2013-01-01
G01N	/	2333	/	70596	A	2013-01-01
G01N	/	2800	/	52	A	2013-01-01
Y02A	/	50	/	412	A	2018-01-01
Y02A	/	50	/	41	A	2018-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	25	
/ILIA I OUSPENSKI/ Primary Examiner, Art Unit 1644	15 October 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20181015

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 279 of 318

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/006,473	COGSWELL et al.
	Examiner	Art Unit
	ILIA I OUSPENSKI	1644

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C07K	/	16	/	28
A61K	/	39	/	395

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	25	
/ILIA I OUSPENSKI/ Primary Examiner, Art Unit 1644	15 October 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20181015

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 280 of 318

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/006,473	COGSWELL et al.
	Examiner	**Art Unit**
	ILIA I OUSPENSKI	1644

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	18	9	27	14	36		45								
2	19		28	15	37	23	46								
3	20		29	16	38	24	47								
4	21		30	17	39	25	48								
5	22		31	18	40										
6	23	10	32	19	41										
7	24	11	33	20	42										
	25	12	34	21	43										
8	26	13	35	22	44										

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	25	
/ILIA I OUSPENSKI/ Primary Examiner, Art Unit 1644	15 October 2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20181015

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 281 of 318

WEST Search History

Hide Items | Restore | Clear | Close

DATE: Monday, October 15, 2018

Hide?	Set Name	Query	Hit Count
Interference			
		DB=PGPB,USPT; THES=ASSIGNEE; PLUR=YES; OP=ADJ	
☐	L3	L1 and @ pd > 20180731	6
☐	L2	L1 and ((cogswell-j $ or goldberg-s $ or gupta-a $ or jure-kunkel-m $ or wang-x $ or wigginton-j $).in. or Bristol $.as. or Bristol $.aanm.)	1
☐	L1	(("anti-pd-l1$" or anti-pdl1 $ or anti-b7-h1 $ or anti-b7h1 $ or anti-b7-4 $ or anti-cd274 $ or ".alpha.pd-l1$" or ".alpha.pdl1" or ".alpha.b7-h1$" or ".alpha.b7h1" or ".alpha.b7-4$" or ".alpha.cd274$" or "PD-L1$" or pdl1 $ or b7-h1 $ or b7h1 $ or b7-4 $ or cd274 $) same (treat $ or administ $ or contact $ or pharmaceut $ or deliver $) same (cancer $ or tumor $ or tumour $ or malignan $ or neoplas $ or metasta $ or onco $)) same bladder $ same (platin $ or cisplatin $ or cis-platin $ or oxaliplatin $ or eloxatin $ or carboplatin $ or paraplatin $)	44

END OF SEARCH HISTORY

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 282 of 318

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Substitute for form 1449/PTO

FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	1644
Examiner Name	OUSPENSKI, ILIA I
Attorney Docket Number	3338.0630006/ELE/C-K

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	US42	US-20020102651-A1	08-01-2002	FREEMAN; et al.	
	US43	US-20090055944-A1	02-26-2009	KORMAN; et al.	
	US44	US-20090304711-A1	12-10-2009	PARDOLL; et al.	
	US45	US-20100203056-A1	08-12-2010	IRVING; et al.	
	US46	US-20110244546-A1	10-06-2011	HANSEN; et al.	
	US47	US-20110250201-A1	10-13-2011	SMITH; et al.	
	US48	US-10072082-B2	09-11-2018	COGSWELL; et al.	

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	NPL72	VOGEL, W.H., " Infusion Reactions: Diagnosis, Assessment, and management," Clinical Journal of Oncology Nursing 14(2):E10-E21, Oncology Nursing Society, United States (2010).	☐
	NPL73	American Cancer Society, "What is Non-Small Cell Lung Cancer?," retrieved from https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html, retrieved on August 6, 2018. 5 pages.	☐
	NPL74	ATMAR, J., "Review of the Safety and Feasibility of rapid Infusion of Rituximab," Journal of Oncology Practice 6(2): 91-93, American Society of Clinical Oncology, United States (2010).	☐
	NPL75	AUPERIN, A., et al., "Meta-Analysis of Concomitant versus Sequential Radiochemotherapy in Locally Advanced Non-Small-Cell Lung Cancer," Journal of Clinical Oncology 28(13):2181-2190, American Society of Clinical Oncology Journal, United States (2010).	☐
	NPL76	CLARK, P., et al., "Bladder Cancer," Journal of the National Comprehensive Cancer Network 11(4):446-475, Harborside Press, United States (April 2013).	☐
	NPL77	LEIGHL, N.B., "Treatment paradigms for Patients with metastatic non-small-cell lung cancer: first-, second-, and third-line," Curr Oncol, 19:S52-S58, Multimed Inc., Canada (June 2012).	☐
	NPL78	LENZ, H-J., "Management and Preparedness for Infusion and Hypersensitivity Reactions," The Oncologist 12:601-609, Wiley Online Library, United States (2007)	☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /I.I.O/

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	1644
Examiner Name	OUSPENSKI, ILIA I
Attorney Docket Number	3338.0630006/ELE/C-K

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	NPL79	"Safe Administration and Monitoring of Monoclonal Antibodies in the Treatment of Multiple Sclerosis," International Journal of MScare 9(2): 23 pages, Supplement to the International Journal of MS Care, (April 2007).	☐
	NPL80	Office Action mailed August 10, 2018, in United States Patent Application No. 16/006,365, inventors Cogswell, *et al.,* filed June 12, 2018, 9 pages.	☐
	NPL81	Office Action mailed August 15, 2018, in United States Patent Application No. 16/024,340, inventors Cogswell, *et al.,* filed June 29, 2018, 7 pages.	☐
	NPL82	Office Action mailed August 10, 2018, in United States Patent Application No. 16/006,493, inventors Cogswell, *et al.,* filed June 12, 2018, 9 pages.	☐
	NPL83	Office Action mailed August 15, 2018, in United States Patent Application No. 16/024,333, inventors Cogswell, *et al.,* filed June 29, 2018, 10 pages.	☐

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10/15/2018

/ILIA I OUSPENSKI/

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BIB DATA SHEET

CONFIRMATION NO. 5731

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/006,473	06/12/2018 RULE	424	1644	3338.0630006/ELE/C-K

APPLICANTS

Bristol-Myers Squibb Company, Princeton, NJ;

INVENTORS

John P. COGSWELL, Yardley, PA;
Stacie M. GOLDBERG, Potomac, MD;
Ashok K. GUPTA, Clarksburg, MD;
Maria JURE-KUNKEL, Plainsboro, NJ;
Xi-Tao WANG, Wellesley, MA;
Jon M. WIGGINTON, Collegeville, PA;

**** CONTINUING DATA ***************************

This application is a CON of 14/950,748 11/24/2015 PAT 10072082
which is a DIV of 13/892,671 05/13/2013 PAT 9212224
which claims benefit of 61/647,442 05/15/2012
and claims benefit of 61/790,747 03/15/2013

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

06/27/2018

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
❑ Yes ☑ No	❑ Yes ☑ No	/ILIA I OUSPENSKI/ Examiner's Signature	❑ Initials	PA	24	30	2

ADDRESS

Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DC 20005
UNITED STATES

TITLE

CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
2720	No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

BIB (Rev. 05/07).

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

115018 7590 10/18/2018
Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DC 20005

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/006,473	06/12/2018	John P. COGSWELL	3338.0630006/ELE/C-K	5731

TITLE OF INVENTION: CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	01/18/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
OUSPENSKI, ILIA I	1644	424-172100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Sterne, Kessler, Goldstein & Fox P.L.L.C.
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Bristol-Myers Squibb Company

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Princeton, NJ

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ☒ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 19-0036

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Ji-Eun Kim/ Date October 18, 2018

Typed or printed name Ji-Eun Kim Registration No. 68,504

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 286 of 318

Electronic Patent Application Fee Transmittal

Application Number:	16006473
Filing Date:	12-Jun-2018
Title of Invention:	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING
First Named Inventor/Applicant Name:	John P. COGSWELL
Filer:	Ji Eun Kim/Jeanette Yando
Attorney Docket Number:	3338.0630006/ELE/C-K

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1000	1000

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1000**

Electronic Acknowledgement Receipt

EFS ID:	34050261
Application Number:	16006473
International Application Number:	
Confirmation Number:	5731
Title of Invention:	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING
First Named Inventor/Applicant Name:	John P. COGSWELL
Customer Number:	115018
Filer:	Ji Eun Kim/Jeanette Yando
Filer Authorized By:	Ji Eun Kim
Attorney Docket Number:	3338.0630006/ELE/C-K
Receipt Date:	18-OCT-2018
Filing Date:	12-JUN-2018
Time Stamp:	15:42:47
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1000
RAM confirmation Number	101918INTEFSW15431400
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	2018-10-18-Issue-Fee-3338-0630006.PDF	116748 a91f50f52e1494a72685045560c05e3e746d7394	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30417 815f83ade603eaf99becc1c4251297e0a9eea380	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	147165		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: DIST.E.FILE **Document Description: Electronic Terminal Disclaimer - Filed**	PTO/SB/25 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION**
Application Number	16006473
Filing Date	12-Jun-2018
First Named Inventor	John COGSWELL
Attorney Docket Number	3338.0630006/ELE/C-K
Title of Invention	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Bristol-Myers Squibb Company	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

16024333 filed on 06/29/2018

16006493 filed on 06/12/2018

16006365 filed on 06/12/2018

16024340 filed on 06/29/2018

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request. ○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.	
Applicant claims the following fee status: ○ Small Entity ○ Micro Entity ◉ Regular Undiscounted I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.	
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ◉ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application Registration Number 68504 ○ A sole inventor ○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ○ A joint inventor; all of whom are signing this request	
Signature	/Ji-Eun Kim/
Name	Ji-Eun Kim

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	16006473
Filing Date:	12-Jun-2018
Title of Invention:	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING
First Named Inventor/Applicant Name:	John P. COGSWELL
Filer:	Ji Eun Kim/Jeanette Yando
Attorney Docket Number:	3338.0630006/ELE/C-K

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16006473

Filing Date: 12-Jun-2018

Applicant/Patent under Reexamination: COGSWELL

Electronic Terminal Disclaimer filed on October 19, 2018

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	34045965
Application Number:	16006473
International Application Number:	
Confirmation Number:	5731
Title of Invention:	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING
First Named Inventor/Applicant Name:	John P. COGSWELL
Customer Number:	115018
Filer:	Ji Eun Kim/Jeanette Yando
Filer Authorized By:	Ji Eun Kim
Attorney Docket Number:	3338.0630006/ELE/C-K
Receipt Date:	19-OCT-2018
Filing Date:	12-JUN-2018
Time Stamp:	14:00:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$160
RAM confirmation Number	102218INTEFSW14003200
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	36103 0b5873f65bde307b9d32fab4ebc867298383f2a8	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30460 9c210a99aae65561720a4fe9faecda7bed7a0fab	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	66563		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 14

Complete if Known	
Application Number	16/006,473
Filing Date	June 12, 2018
First Named Inventor	COGSWELL; John P.
Art Unit	*To Be Assigned*
Examiner Name	*To Be Assigned*
Attorney Docket Number	3338.0630006/ELE/C-K

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	US23	US-20150125463-A1	05-07-2015	COGSWELL, John P. *et al.*	
	US24	US-20160075782-A1	03-17-2016	KORMAN, Alan J. *et al.*	
	US25	US-20160362495-A1	12-15-2016	KORMAN, Alan J. *et al.*	
	US26	US-8728474-B2	05-20-2014	HONJO, Tasuku *et al.*	
	US27	US-20170088626-A1	03-30-2017	JURE-KUNKEL, Maria *et al.*	
	US28	US-9856320-B2	01-02-2018	COGSWELL; John P. et al.	
	US29	20030039653-A1	02-27-2003	Chen *et al.*	
	US30	20090215812-A1	08-27-2009	Bedrosian *et al.*	
	US31	20110269948-A1	11-03-2011	Sanjuan *et al.*	
	US32	20110206701-A1	08-25-2011	Afar *et al.*	
	US33	20100151447-A1	06-17-2010	Ely; Scott	
	US34	20090217401-A1	08-27-2009	Korman *et al.*	
	US35	20110008369-A1	01-13-2011	Finnefrock *et al.*	
	US36	2017/0028040 A1	02-02-2017	Lan *et al.*	
	US37	9,856,320 B2	01-02-2018	Cogswell *et al.*	
	US38	US-20160090417-A1	03-31-2016	Cogswell *et al.*	
	US39	US-20160362489-A1	~~04-28-2015~~ 12-2016	Yang	
	US40	US-20150290316-A1	10-15-2015	GRAZIANO et al.	
	US41	US-20160022814-A1	01-28-2016	PETIT et al.	

Change(s) applied to document,
/R.F./
10/25/2018

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /I.I.O/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/006,473	11/27/2018	10138299	3338.0630006/ELE/C-K	5731

115018 7590 11/07/2018

Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DC 20005

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

John P. COGSWELL, Yardley, PA;
Bristol-Myers Squibb Company, Princeton, NJ;
Stacie M. GOLDBERG, Potomac, MD;
Ashok K. GUPTA, Clarksburg, MD;
Maria JURE-KUNKEL, Plainsboro, NJ;
Xi-Tao WANG, Wellesley, MA;
Jon M. WIGGINTON, Collegeville, PA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No.: 10,138,299	Confirmation No.: 5731
Date of Patent: November 27, 2018	Art Unit: 1644
Inventors: COGSWELL *et al.*	Atty. Docket: 3338.0630006/ELE/C-K
Patentees: Bristol-Myers Squibb Company	

Title: **CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING**

Request for Certificate of Correction Under 37 C.F.R. § 1.322 and 1.323

Attn: Certificate of Correction Branch

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

Patentee hereby requests that a Certificate of Correction under 37 C.F.R. §§ 1.322 and 1.323 be issued for the above-captioned United States Patent. This Certificate of Correction is being requested due to mistakes which appear in the printed patent. These mistakes were made by both the U.S. Patent and Trademark Office (USPTO) and by Patentee.

Specifically, the printed patent contains the following error for which a Certificate of Correction is respectfully requested:

IN THE SPECIFICATION:

Errors:

1. In Col. 1, Line 4, delete "APPLICTION" and insert - - APPLICATIONS - -, therefor. Support for this correction can be found in the Amendment to the Specification filed on June 12, 2018; page 2, line 3.

2. In Col. 1, Line 9, delete "9,212,442," and insert - - 9,212,224, - -, therefor. Support for this correction can be found in the Amendment to the Specification filed on June 12, 2018; page 2, line 6.
3. In Col. 1, Line 11, delete "U.S" and insert - - U.S. - -, therefor. Support for this correction can be found in the Amendment to the Specification filed on June 12, 2018; page 2, line 7.
4. In Col. 1, Line 12, after "all" insert - - of - -. Support for this correction can be found in the Amendment to the Specification filed on June 12, 2018; page 2, line 8.
5. In Col. 1, Line 21, delete "2018," and insert - - 2018) - -, therefor. Support for this correction can be found in the Amendment to the Specification filed on June 12, 2018; page 2, line 14.
6. In Col. 1, Line 22, delete "entirely." and insert - - entirety. - -, therefor. Support for this correction can be found in the Amendment to the Specification filed on June 12, 2018; page 2, line 14.

IN THE CLAIMS:

Errors:

1. In Col. 101, Line 59, Claim 1, delete "a bladder cancer of;" and insert - - a bladder cancer; - -, therefor.
2. In Col. 101, Line 60, Claim 1, delete "platinum based" and insert - - platinum-based - -, therefor.
3. Claim 16 has been deleted in its entirety (cancelled).

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 301 of 318

4. In Col. 103, Line 11, Claim 17 is renumbered as Claim 16.

5. In Col. 103, Line 13, Claim 18 is renumbered as Claim 17.

6. In Col. 103, Line 15, Claim 19 is renumbered as Claim 18.

7. In Col. 103, Line 17, Claim 20 is renumbered as Claim 19.

8. In Col. 103, Line 19, Claim 21 is renumbered as Claim 20.

9. In Col. 103, Line 21, Claim 22 is renumbered as Claim 21.

10. In Col. 103, Line 23, Claim 23 is renumbered as Claim 22.

11. In Col. 103, Line 25, Claim 24 is renumbered as Claim 23.

12. In Col. 103, Line 27, Claim 25 is renumbered as Claim 24.

13. In Col. 103, Line 27, Claim 25, delete "claims" and insert - - claim - -, therefor. Support for this correction can be found in the Amendment and Reply, filed on September 19, 2018; page 4, claim 48, line 1.

These are errors made by the USPTO and Patentee.

Remarks

The above-noted corrections do not involve such changes in the patent as would constitute new matter or would require reexamination.

A completed Form PTO/SB/44 accompanies this request, with the above-noted correction printed thereon. In addition, per instructions provided by Marietta Joyce of the Office of Data Management, Certificates of Correction Branch on January 7, 2019, Patentee submits herewith a new set of claims with the new and correct numbering and dependencies. The new set of claims

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 302 of 318

reflects the deletion of issued claim 16 as well as the corrections to issued claims 1 and 17-25, as listed above and in the accompanying Form PTO/SB/44. Accordingly, a Certificate of Correction is believed proper and issuance thereof is respectfully requested.

This request is accompanied by payment of the fee set forth in 37 C.F.R. § 1.20(a). Fee payment is provided through online credit card payment. The Commissioner is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/Ji Eun Kim/

Ji Eun Kim
Attorney for Patentee
Registration No. 68,504

Date: January 25, 2019

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
10493052_1.docx

Atty. Docket: 3338.0630006/ELE/C-K

1. A method of treating a tumor in a human subject in need thereof, comprising administering to the subject about 10 mg/kg of an anti-PD-L1 antibody every 2 weeks, wherein the anti-PD-L1 antibody is administered intravenously over 60 minutes infusion; wherein the tumor is derived from a bladder cancer; and wherein the tumor is refractory to a platinum-based chemotherapy.

2. The method of claim 1, wherein the tumor is advanced.

3. The method of claim 1, wherein the tumor is locally advanced.

4. The method of claim 1, wherein the tumor is metastatic.

5. The method of claim 1, wherein the treatment lasts more than 12 weeks.

6. The method of claim 1, wherein the anti-PD-L1 antibody is formulated in a pharmaceutical composition.

7. The method of claim 6, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable salt, an anti-oxidant, an aqueous carrier, a non-aqueous carrier, or any combination thereof.

8. The method of claim 7, wherein the salt comprises a sodium salt.

9. The method of claim 7, wherein the salt comprises sodium chloride.

10. The method of claim 1, wherein at least 1% of tumor cells exhibit membrane PD-L1 expression.

11. The method of claim 1, wherein at least 5% of tumor cells exhibit membrane PD-L1 expression.

12. The method of claim 1, further comprising administering an anti-cancer agent.

13. The method of claim 2, further comprising administering an anti-cancer agent.

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Dana-Farber v. BMS, IPR2023-00252
Page 304 of 318

14. The method of claim 3, further comprising administering an anti-cancer agent.

15. The method of claim 4, further comprising administering an anti-cancer agent.

16. The method of claim 12, wherein the anti-cancer agent is a chemotherapy.

17. The method of claim 12, wherein the anti-cancer agent is a radiotherapy.

18. The method of claim 13, wherein the anti-cancer agent is a chemotherapy.

19. The method of claim 13, wherein the anti-cancer agent is a radiotherapy.

20. The method of claim 14, wherein the anti-cancer agent is a chemotherapy.

21. The method of claim 14, wherein the anti-cancer agent is a radiotherapy.

22. The method of claim 1, wherein the platinum-based chemotherapy is a platinum-based doublet chemotherapy.

23. The method of claim 1, wherein the platinum-based chemotherapy comprises cisplatin, carboplatin, or both.

24. The method of claim 1, wherein the subject is administered an antihistamine prior to the anti-PD-L1 antibody.

Dana-Farber EX1024
Dana-Farber v. BMS, IPR2023-00252
Page 305 of 318

PTO/SB/44 (09-07)
Approved for use through 08/13/2013. OMB 0651-0033
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 10,138,299

APPLICATION NO. : 16/006,473

ISSUE DATE : November 27, 2018

INVENTOR(S) : COGSWELL *et al.*

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

1. In Col. 1, Line 4, delete "APPLICTION" and insert - - APPLICATIONS - -.
2. In Col. 1, Line 9, delete "9,212,442," and insert - - 9,212,224, - -.
3. In Col. 1, Line 11, delete "U.S" and insert - - U.S. - -
4. In Col. 1, Line 12, after "all" insert - - of - -.
5. In Col. 1, Line 21, delete "2018," and insert - - 2018) - -
6. In Col. 1, Line 22, delete "entirely." and insert - - entirety. - -.
7. In Col. 101, Line 59, Claim 1, delete "a bladder cancer of;" and insert - - a bladder cancer; - -.
8. In Col. 101, Line 60, Claim 1, delete "platinum based" and insert - - platinum-based - -.
9. Claim 16 has been deleted in its entirety (cancelled).
10. In Col. 103, Line 11, Claim 17 is renumbered as Claim 16.
11. In Col. 103, Line 13, Claim 18 is renumbered as Claim 17.
12. In Col. 103, Line 15, Claim 19 is renumbered as Claim 18.
13. In Col. 103, Line 17, Claim 20 is renumbered as Claim 19.
14. In Col. 103, Line 19, Claim 21 is renumbered as Claim 20.
15. In Col. 103, Line 21, Claim 22 is renumbered as Claim 21.
16. In Col. 103, Line 23, Claim 23 is renumbered as Claim 22.
17. In Col. 103, Line 25, Claim 24 is renumbered as Claim 23.
18. In Col. 103, Line 27, Claim 25 is renumbered as Claim 24.
19. In Col. 103, Line 27, Claim 25, delete "claims" and insert - - claim - -.

10493050_1.docx

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue, NW
Washington DC 20005-3934

Atty. Dkt. No. 3338.0630006/ELE/C-K

This collection of information is required by 37 CFR 1.322, 1.323 and 1.324. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1.0 hour to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you are required to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Electronic Patent Application Fee Transmittal

Application Number:	16006473
Filing Date:	12-Jun-2018
Title of Invention:	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING
First Named Inventor/Applicant Name:	John P. COGSWELL
Filer:	Ji Eun Kim/Shanova Banks
Attorney Docket Number:	3338.0630006/ELE/C-K

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
CERTIFICATE OF CORRECTION	1811	1	150	150

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**150**

Electronic Acknowledgement Receipt

EFS ID:	34964629
Application Number:	16006473
International Application Number:	
Confirmation Number:	5731
Title of Invention:	CANCER IMMUNOTHERAPY BY DISRUPTING PD-1/PD-L1 SIGNALING
First Named Inventor/Applicant Name:	John P. COGSWELL
Customer Number:	115018
Filer:	Ji Eun Kim/Shanova Banks
Filer Authorized By:	Ji Eun Kim
Attorney Docket Number:	3338.0630006/ELE/C-K
Receipt Date:	25-JAN-2019
Filing Date:	12-JUN-2018
Time Stamp:	15:27:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$150
RAM confirmation Number	012819INTEFSW15294900
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	2019-01-25-Transmittal-3338-0630006.PDF	377217 a93c45809bc0fab68b85741a5faf9f15193ffef1	no	2
Warnings:					
Information:					
2	Request for Certificate of Correction	2019-01-25-Request-COC-3338-0630006.PDF	145111 a0e7eac093f5c5f55ea386c13090e11159c01e79	no	6
Warnings:					
Information:					
3	Request for Certificate of Correction	2019-01-25-COC-Form-3338-0630006.PDF	130899 dbe03b1b86e2ca4a7d4f231f892380ffca272451	no	1
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30526 63419687c3a8390497e8a0c95403d7bfce67158d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	683753		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: TRAN.LET

Document Description: Transmittal Letter

PTO/SB/21 (07-09)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	16/006,473 (USP 10,138,299)
Filing Date	June 12, 2018
First Named Inventor	John P. COGSWELL
Art Unit	1644
Examiner Name	OUSPENSKI, ILIA I.
Attorney Docket Number	3338.0630006/ELE/C-K

Total Number of Pages in This Submission

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
- ☑ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):

$150 payment for Certificate of Correction Fee; and Request for Certificate of Correction Under 37 C.F.R. § 1.322 and 1.323

Remarks

The Office may charge any fee deficiency for any submission made with this transmittal to Deposit Account 19-0036.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.		
Signature	/Ji Eun Kim/		
Printed name	Ji Eun Kim		
Date	January 25, 2019	Reg. No.	68,504

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature			
Typed or printed name		Date	

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and1.14. This collection is estimated to 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/006,473	06/12/2018	John P. COGSWELL	3338.0630006/ELE/C-K	5731

115018 7590 02/11/2019

Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DC 20005

EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
02/11/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ckim@sternekessler.com
e-office@sternekessler.com
pcalvo@sternekessler.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Patent No.: 10138299
Issue Date: 27 November 2018
Appl. No.: 16/006,473
Filed: 12 June 2018

PART (A) RESPONSE FOR CERTIFICATES OF CORRECTION

This is a decision on the Certificate of Correction request filed 25 January 2019.

The request for issuance of Certificate of Correction for the above-identified correction(s) under the provisions of 37 CFR 1.322 and/or 1.323 is hereby:

(Check one)
☑ Approved ☐ Approved in Part ☐ Denied

Comments: ____

PART (B) PETITION UNDER 37 CFR 1.324 OR 37 CFR 1.48

☐ This is a decision on the petition filed ____ to correct inventorship under 37 CFR 1.324.

☐ This is a decision on the request under 37 CFR 1.48, petition filed ____. In view of the fact that the patent has already issued, the request under 37 CFR 1.48 has been treated as a petition to correct inventorship under 37 CFR 1.324.

The petition is hereby: ☐ Granted ☐ Dismissed

Comment: ____

The patented filed is being forwarded to Certificate of Corrections Branch for issuance of a certificate naming only the actual inventor or inventors.

/DANIEL E KOLKER/
Supervisory Patent Examiner, Art Unit 1644
Technology Center 1600
Phone: (571)272-3181

Certificates of Correction Branch email: CustomerServiceCoC@uspto.gov CoC Central Phone Number: (703) 756-1814

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 10,138,299 B2
APPLICATION NO. : 16/006473
DATED : November 27, 2018
INVENTOR(S) : Cogswell et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

Under Abstract, please insert:
-- 24 Claims, 24 Drawing Sheets --

In the Specification
1. In Column 1, Line 4, delete "APPLICTION" and insert -- APPLICATIONS --.
2. In Column 1, Line 9, delete "9,212,442," and insert -- 9,212,224, --.
3. In Column 1, Line 11, delete "U.S" and insert -- U.S. --.
4. In Column 1, Line 12, after "all" insert -- of --.
5. In Column 1, Line 21, delete "2018," and insert -- 2018) --.
6. In Column 1, Line 22, delete "entirely." and insert -- entirety. --.

In the Claims
7. In Column 101, Line 59, Claim 1, delete "a bladder cancer of;" and insert -- a bladder cancer; --.
8. In Column 101, Line 60, Claim 1, delete "platinum based" and insert -- platinum-based --.
9. Claim 16 has been deleted in its entirety.
10. In Column 103, Line 11, Claim 17 is renumbered as Claim 16.
11. In Column 103, Line 13, Claim 18 is renumbered as Claim 17.
12. In Column 103, Line 15, Claim 19 is renumbered as Claim 18.
13. In Column 103, Line 17, Claim 20 is renumbered as Claim 19.
14. In Column 103, Line 19, Claim 21 is renumbered as Claim 20.
15. In Column 103, Line 21, Claim 22 is renumbered as Claim 21.
16. In Column 103, Line 23, Claim 23 is renumbered as Claim 22.
17. In Column 103, Line 25, Claim 24 is renumbered as Claim 23.
18. In Column 103, Line 27, Claim 25 is renumbered as Claim 24.
19. In Column 103, Line 27, Claim 25, delete "claims" and insert -- claim --.

Signed and Sealed this
Thirteenth Day of August, 2019

Andrei Iancu
Director of the United States Patent and Trademark Office

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/17/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
Bristol-Myers Squibb Co. and E. R. Squibb & Sons, L.L.C.	AstraZeneca Pharmaceuticals LP and AstraZeneca UK Ltd.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	See Attached		
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 9,580,505 B2	2/28/2017	E. R. Squibb & Sons, L.L.C.
2	US 9,580,507 B2	2/28/2017	E. R. Squibb & Sons, L.L.C.
3	US 10,138,299 B2	11/27/2018	Bristol-Myers Squibb Company
4	US 10,308,714 B2	6/4/2019	Bristol-Myers Squibb Company
5	US 10,266,594 B1	4/23/2019	Bristol-Myers Squibb Company
6	US 10,266,595 B2	4/23/2019	Bristol-Myers Squibb Company
7	US 10,266,596 B1	4/23/2019	Bristol-Myers Squibb Company
8	US 10,323,092 B2	6/18/2019	Bristol-Myers Squibb Company