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UTILITY PATENT APPLICATION TRANSMITTAL <i>(Only for new nonprovisional applications under 37 CFR 1.53(b))</i>	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Attorney Docket No.</td> <td>3338.0330003/ELE/C-K/BMD</td> </tr> <tr> <td>First Named Inventor</td> <td>Arvin YANG</td> </tr> <tr> <td>Title</td> <td>TREATMENT OF PD-L1 NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY</td> </tr> <tr> <td>Priority Mail Express® Label No.</td> <td></td> </tr> </table>	Attorney Docket No.	3338.0330003/ELE/C-K/BMD	First Named Inventor	Arvin YANG	Title	TREATMENT OF PD-L1 NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY	Priority Mail Express® Label No.	
Attorney Docket No.	3338.0330003/ELE/C-K/BMD								
First Named Inventor	Arvin YANG								
Title	TREATMENT OF PD-L1 NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY								
Priority Mail Express® Label No.									

APPLICATION ELEMENTS <i>See MPEP chapter 600 concerning utility patent application contents.</i>	ADDRESS TO: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
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 <u>64</u>] 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 <u>6</u>] 6. ☒ Inventor's Oath or Declaration [Total Pages <u>1</u>] (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	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) ASCII text file of Sequence Listing _____ This patent application is being submitted under 37 C.F.R. § 1.53(b) without the required fees and without payment of any claim fees _____

***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: <u>115018</u> OR ☐ Correspondence address below					
Name _____					
Address _____					
City _____		State _____		Zip Code _____	
Country _____		Telephone _____		Email _____	
Signature		/Brian M. Dudley/ Brian M. Dudley, Reg. No. 777,546, for		Date	
				January 4, 2019	
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.

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.

Electronic Acknowledgement Receipt	
EFS ID:	34766325
Application Number:	16240316
International Application Number:	
Confirmation Number:	4170
Title of Invention:	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY
First Named Inventor/Applicant Name:	Arvin YANG
Customer Number:	115018
Filer:	Ji Eun Kim/Jeanette Yando
Filer Authorized By:	Ji Eun Kim
Attorney Docket Number:	3338.0330003/ELE/C-K/BMD
Receipt Date:	04-JAN-2019
Filing Date:	
Time Stamp:	16:48:14
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	Authorization for Extension of Time all replies	2019-01-04-EOT- Authorization-3338-0330003. pdf	98153 42426749cc777757b701a0b4ebbd6003ee0178a2	no	1
Warnings:					

Information:					
2	Application Data Sheet	2019-01-04- ADS-3338-0330003.PDF	1256217	no	8
			f181d92de9abbf6f80b5b249db5cc10520a02d50		
Warnings:					
Information:					
3	Power of Attorney	2019-01-04- POA-82A-3338-0330003.PDF	966560	no	2
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Warnings:					
Information:					
4	Oath or Declaration filed	2019-01-04- Declaration-3338-0330003.PDF	293105	no	1
			09145a4030b2ea909c101f28a1b1ce33d6641130		
Warnings:					
Information:					
5		2019-01-04- Specification-3338-0330003. pdf	436720	yes	64
			a024765ba953b3dcd79fa21cda99a7d26cf5dc94		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	56	
	Claims		57	63	
	Abstract		64	64	
Warnings:					
Information:					
6	Drawings-only black and white line drawings	2019-01-04- Drawings-3338-0330003.pdf	1030979	no	6
			e5486bc2f323200f230680d7b03616f386bcd902e		
Warnings:					
Information:					
7	Sequence Listing (Text File)	3338_0330003_SeqListing_ST2 5.TXT	3770	no	-

Warnings:					
Information:					
8	Transmittal of New Application	2019-01-04-Utility-Transmittal-3338-0330003.PDF	321266 6a331b1b21c2e2346f0f96860253bf17b07ec092	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			4406770		
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

Inventor: Arvin YANG

Applicant: Bristol-Myers Squibb Company

Application No.: *To Be Assigned*

(Continuation of Appl. No. 15/141,769; Filed:
April 28, 2016)

Filed: *Herewith*

Confirmation No.: *To Be Assigned*

Art Unit: *To Be Assigned*

Examiner: *To Be Assigned*

Atty. Docket: 3338.0330003/ELE/C-K/BMD

Title: **TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1
ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY**

**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.

/Brian M. Dudley/
Brian M. Dudley, Reg. No. 777,546, for

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

Date: January 4, 2019

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

10370165_1

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	3338.0330003/ELE/C-K/BMD
		Application Number	
Title of Invention	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY		
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
	Arvin		YANG	
Residence Information (Select One) • US Residency Non US Residency Active US Military Service				
City	Princeton	State/Province	NJ	Country of Residence US
Mailing Address of Inventor:				
Address 1	Rt. 206 & Province Line Road			
Address 2				
City	Princeton	State/Province	NJ	
Postal Code	08543	Country	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	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY		
Attorney Docket Number	3338.0330003/ELE/C-K/BMD	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	6	Suggested Figure for Publication (if any)	

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	3338.0330003/ELE/C-K/BMD
		Application Number	
Title of Invention	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY		

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.

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	15/141769	2016-04-28

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	3338.0330003/ELE/C-K/BMD	
		Application Number		
Title of Invention	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY			
Prior Application Status	Expired			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)	
15/141769	Claims benefit of provisional	62/153973	2015-04-28	
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.				Add

Foreign Priority Information:

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 ^j (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the Add button.			Add

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	3338.0330003/ELE/C-K/BMD
		Application Number	
Title of Invention	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY		

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.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	3338.0330003/ELE/C-K/BMD
		Application Number	
Title of Invention	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY		

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	Remove	
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. Add			

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.

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	3338.0330003/ELE/C-K/BMD
		Application Number	
Title of Invention	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY		

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.			
Remove			
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. Add			

Signature: [Remove](#)

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	/Brian M. Dudley/ Brian M. Dudley, Reg. No. 777,546, for		Date (YYYY-MM-DD)	2019-01-04
First Name	Ji Eun	Last Name	Kim	Registration Number
				68504
Additional Signature may be generated within this form by selecting the Add button.				Add

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	3338.0330003/ELE/C-K/BMD
		Application Number	
Title of Invention	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY		

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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 inspections or an issued patent.
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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/AIA/82B 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	Arvin YANG
Title	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY
Art Unit	To Be Assigned
Examiner Name	To Be Assigned
Attorney Docket Number	3338.0330003/ELE/C-K/BMD

SIGNATURE of Applicant or Patent Practitioner

Signature	/Brian M. Dudley/ Brian M. Dudley, Reg. No. 777,546, for	Date (Optional)	January 4, 2019
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.



*Total of 1 forms are submitted.

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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.)

☒ 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:

☒ 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		

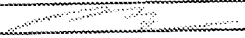
I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

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)
- ☒ 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 3, 2015
Name	Paul D. Golan		
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.

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12549-US-NP

Atty. Dkt. No. 3338.0330001

PTO/AIA/01 (06-12)

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

Title of Invention

TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY

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 15/141,769

filed on April 28, 2016

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 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.

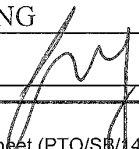
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LEGAL NAME OF INVENTOR

Inventor: Arvin YANG

Date ~~(Optional)~~: August 3rd 2016

Signature: 

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

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TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application is a continuation of U.S. Application No. 15/141,769 filed April 28, 2016, which claims benefit to U.S. Provisional Application No. 62/153,973 filed April 28, 2015, each of which is incorporated herein by reference in its entirety.

REFERENCE TO A SEQUENCE LISTING SUBMITTED ELECTRONICALLY VIA EFS-WEB

[0002] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web, and is hereby incorporated by reference in its entirety. Said ASCII copy, created on January 4, 2019, is named 3338_0330003_SeqListing_ST25.txt and is 3,770 bytes in size.

[0003] Throughout this application, various publications are referenced in parentheses by author name and date, or by Patent No. or Patent Publication No. 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

[0004] This invention relates to a method of treating PD-L1-negative melanoma comprising administering a combination of an anti-PD-1 antibody and an anti-CTLA-4 antibody.

BACKGROUND OF THE INVENTION

[0005] Human cancers harbor numerous genetic and epigenetic alterations, generating neoantigens potentially recognizable by the immune system (Sjoblom *et al.* (2006) *Science* 314:268-74). The adaptive immune system, comprised of T and B lymphocytes, has powerful anti-cancer potential, with a broad capacity and exquisite specificity to respond to diverse tumor antigens. Further, the immune system demonstrates considerable plasticity and a memory component. The successful harnessing of all these attributes of the adaptive immune system would make immunotherapy unique among all cancer treatment modalities.

[0006] Recently, several immune checkpoint pathway inhibitors have begun to provide new immunotherapeutic approaches for treating cancer, including the development of an antibody (Ab), ipilimumab (YERVOY®), that binds to and inhibits Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) for the treatment of patients with advanced melanoma and the development of antibodies such as nivolumab and pembrolizumab (formerly lambrolizumab; USAN Council Statement, (2013) Pembrolizumab: Statement on a nonproprietary name adopted by the USAN Council (ZZ-165), November 27, 2013) that bind specifically to the Programmed Death-1 (PD-1) receptor and block the inhibitory PD-1/PD-1 ligand pathway.

[0007] The promise of the emerging field of personalized medicine is that advances in pharmacogenomics will increasingly 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.

SUMMARY OF THE INVENTION

[0008] The present disclosure provides a method for treating a melanoma comprising (i) identifying a patient having a PD-L1-negative melanoma tumor; and (ii) administering to the patient (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4. The present disclosure also provides a method for treating a melanoma comprising administering to a patient afflicted with a melanoma tumor (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4, wherein the patient is identified as having a PD-L1-negative melanoma tumor prior to the administration.

[0009] The present disclosure further provides a method for extending a progression-free survival period for over 8 months in a patient afflicted with a melanoma tumor comprising administering to the patient (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4, wherein the patient is identified as having a PD-L1-negative melanoma tumor prior to the administration and wherein the patient demonstrates progression-free survival for over 8 months. In certain embodiments, the progression-free survival of the patient is extended after the administration for over about 11 months, about 12 months, about 13 months, about 14 months, about 15 months, about 16 months, about 17 months, about 18 months, about 2 years, about 3 years, about 4 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, or about 10 years. In one particular embodiment, the progression-free survival of the patient is extended for over 11 months.

[0010] The present disclosure also provides a method for reducing a tumor size at least by 10% in a patient afflicted with a melanoma tumor comprising administering to the patient (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding

portion thereof that binds specifically to a human CTLA-4, wherein the patient is identified as having a PD-L1-negative melanoma tumor prior to the administration and wherein the administration reduces the tumor size at least about 10%, about 20%, about 30%, about 40%, or about 50% compared to the tumor size prior to the administration.

[0011] The present disclosure also provides a method for increasing an objective response rate to be higher than 40% in a patient population, each of whom is afflicted with a melanoma tumor, in a cancer treatment comprising administering to the patient (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4, wherein each patient is identified as having a PD-L1-negative melanoma tumor prior to the administration and wherein the objective response rate is higher than 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75%.

[0012] The present disclosure also provides a method for selecting a patient suitable for an anti-PD-1 antibody and anti-CTLA-4 antibody combination therapy comprising (i) identifying a patient having a PD-L1-negative melanoma tumor; and (ii) instructing a healthcare provider to administer to the patient (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4.

[0013] In certain embodiments, the methods disclosed herein further comprise identifying the patient as having a melanoma tumor that does not express PD-L1 prior to the administration. In some embodiments, the patient is characterized by (i) extended progression-free survival for over 8 months, (ii) tumor size reduction at least about 10%, about 20%, about 30%, about 40%, or about 50% compared to the tumor size prior to the administration, or (iii) both.

[0014] In some embodiments, the methods disclosed herein further comprise measuring a PD-L1 expression on the melanoma tumor. In certain embodiments, the measuring further comprises assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface. In one particular embodiment, the presence of PD-L1 is determined using an automated IHC assay.

[0015] The present disclosure further provides a kit for treating a patient afflicted with a melanoma tumor, the kit comprising (a) a dosage ranging from 0.1 to 10 mg/kg body weight of an anti-PD-1 antibody or an antigen-binding portion thereof; (b) a dosage ranging from 0.1 to 10 mg/kg body weight of an anti-CTLA-4 antibody or an antigen-binding portion thereof; and (c) instructions for using the anti-PD-1 antibody or the antigen-binding portion thereof and the anti-CTLA-4 antibody or the antigen-binding portion thereof in any of the methods disclosed herein.

BRIEF DESCRIPTION OF THE FIGURES

[0016] Fig. 1 shows a patient flow diagram of the randomized, double-blind, multicenter, phase 3 trial.

[0017] Figs. 2A-C show progression-free survival data in the intention-to-treat population (Fig. 2A), in patients with positive PD-L1 status (Fig. 2B), and Negative PD-L1 Status (Fig. 2C). Each graph shows the progression free survival for patients treated with nivolumab alone (solid line), ipilimumab alone (dashed line), or the combination of nivolumab and ipilimumab (dotted line) in months (Figs. 2A-C). The number at risk in months for each of nivolumab, nivolumab plus ipilimumab, and ipilimumab is shown below each x-axis (Figs. 2A-C). PD-L1 expression status is based on verified PD-L1 assay data (Figs. 2B-C).

[0018] Figs. 3A and 3B show subgroup analyses of progression-free survival among patients treated with nivolumab alone compared to ipilimumab alone (Fig. 3A) and patients treated with nivolumab plus ipilimumab compared to ipilimumab alone (Fig. 3B).

[0019] Figs. 4A-4C show the tumor burden change in target lesions in patients treated with nivolumab alone (Fig. 4A), nivolumab plus ipilimumab (Fig. 4B), and ipilimumab alone (Fig. 4C). In each graph, the y-axis shows the best reduction from baseline in target lesions (%) and the x-axis represents each patient (Figs. 4A-C).

DETAILED DESCRIPTION OF THE INVENTION

[0020] The present invention relates to identifying an optimal strategy to treat a patient having a PD-L1-negative melanoma. The present invention shows that in a patient having a PD-L1-negative melanoma tumor, a combination therapy of an anti-PD-1 antibody and an anti-CTLA-4 antibody provides a better response (e.g., progression-free survival) than a monotherapy of either an anti-PD-1 antibody or an anti-CTLA-4 antibody. Furthermore, the combination therapy when given to a population of patients can increase the objective response rate compared to the monotherapy.

Definitions

[0021] 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.

[0022] The term "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0023] It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0024] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[0025] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. The headings provided herein are not limitations of the various aspects of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety.

[0026] "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. Routes of administration for the formulations disclosed herein 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. In some embodiments, the formulation is administered via a non-parenteral route, in some embodiments, orally. Other non-parenteral routes include a topical, epidermal or mucosal route of administration, for example, intranasally, 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.

[0027] 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.

[0028] 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 antibodies 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.

[0029] 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 antibody 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 antibodies; monoclonal and polyclonal antibodies; chimeric and humanized antibodies; human or nonhuman antibodies; wholly synthetic antibodies; and single chain antibodies. A nonhuman antibody 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 antibody.

[0030] The term "monoclonal antibody" ("mAb") refers to a non-naturally occurring preparation of antibody molecules of single molecular composition, *i.e.*, antibody 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 antibody. MAbs may be produced by hybridoma, recombinant, transgenic or other techniques known to those skilled in the art.

[0031] A "human" antibody (HuMAb) refers to an antibody having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region is also derived from human germline immunoglobulin sequences. The human antibodies 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 antibodies 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" antibodies and "fully human" antibodies are used synonymously.

[0032] A "humanized antibody" refers to an antibody in which some, most or all of the amino acids outside the CDR domains of a non-human antibody are replaced with corresponding amino acids derived from human immunoglobulins. In one embodiment of a humanized form of an antibody, 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 antibody to bind to a particular antigen. A "humanized" antibody retains an antigenic specificity similar to that of the original antibody.

[0033] A "chimeric antibody" refers to an antibody in which the variable regions are derived from one species and the constant regions are derived from another species, such as an antibody in which the variable regions are derived from a mouse antibody and the constant regions are derived from a human antibody.

- [0034] An "anti-antigen" antibody refers to an antibody that binds specifically to the antigen. For example, an anti-PD-1 antibody binds specifically to PD-1 and an anti-CTLA-4 antibody binds specifically to CTLA-4.
- [0035] An "antigen-binding portion" of an antibody (also called an "antigen-binding fragment") refers to one or more fragments of an antibody that retain the ability to bind specifically to the antigen bound by the whole antibody.
- [0036] 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 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. A "cancer" or "cancer tissue" can include a tumor.
- [0037] "Cytotoxic T-Lymphocyte Antigen-4" (CTLA-4) refers to an immunoinhibitory receptor belonging to the CD28 family. CTLA-4 is expressed exclusively on T cells *in vivo*, and binds to two ligands, CD80 and CD86 (also called B7-1 and B7-2, respectively). The term "CTLA-4" as used herein includes human CTLA-4 (hCTLA-4), variants, isoforms, and species homologs of hCTLA-4, and analogs having at least one common epitope with hCTLA-4. The complete hCTLA-4 sequence can be found under GenBank Accession No. AAB59385.
- [0038] The term "progression-free survival," which can be abbreviated as PFS, as used herein refers to the length of time during and after the treatment of a solid tumor (*i.e.*, melanoma) that a patient lives with the disease but it does not get worse.
- [0039] "Dosing interval," as used herein, means the amount of time that elapses between multiple doses of a formulation disclosed herein being administered to a subject. Dosing interval can thus be indicated as ranges.
- [0040] The term "dosing frequency" as used herein refers to the frequency of administering doses of a formulation disclosed herein in a given time. Dosing frequency can be indicated as the number of doses per a given time, *e.g.*, once a week or once in two weeks.
- [0041] The use of the term "fixed dose" with regard to a composition of the invention means that two or more different antibodies in a single composition are present in the composition in particular (fixed) ratios with each other. In some embodiments, the fixed

dose is based on the weight (*e.g.*, mg) of the antibodies. In certain embodiments, the fixed dose is based on the concentration (*e.g.*, mg/ml) of the antibodies. In some embodiments, the ratio is at least about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:6, about 1:7, about 1:8, about 1:9, about 1:10, about 1:15, about 1:20, about 1:30, about 1:40, about 1:50, about 1:60, about 1:70, about 1:80, about 1:90, about 1:100, about 1:120, about 1:140, about 1:160, about 1:180, about 1:200, about 200:1, about 180:1, about 160:1, about 140:1, about 120:1, about 100:1, about 90:1, about 80:1, about 70:1, about 60:1, about 50:1, about 40:1, about 30:1, about 20:1, about 15:1, about 10:1, about 9:1, about 8:1, about 7:1, about 6:1, about 5:1, about 4:1, about 3:1, or about 2:1 mg first antibody to mg second antibody. For example, the 3:1 ratio of a first antibody and a second antibody can mean that a vial can contain about 240 mg of the first antibody and 80 mg of the second antibody or about 3 mg/ml of the first antibody and 1 mg/ml of the second antibody.

[0042] The use of the term "flat dose" with regard to the composition of the invention means a dose that is administered to a patient without regard for the weight or body surface area (BSA) of the patient. The flat dose is therefore not provided as a mg/kg dose, but rather as an absolute amount of the agent (*e.g.*, the anti-CTLA-4 antibody and/or anti-PD-1 antibody). For example, a 60 kg person and a 100 kg person would receive the same dose of the composition (*e.g.*, 240 mg of an anti-PD-1 antibody and 80 mg of an anti-CTLA-4 antibody in a single fixed dosing formulation vial containing both 240 mg of an anti-PD-1 antibody and 80 mg of an anti-CTLA-4 antibody (or two fixed dosing formulation vials containing 120 mg of an anti-PD-1 antibody and 40 mg of an anti-CTLA-4 antibody, etc.)).

[0043] The term "weight based dose" as referred to herein means that a dose that is administered to a patient is calculated based on the weight of the patient. For example, when a patient with 60 kg body weight requires 3 mg/kg of an anti-PD-1 antibody in combination with 1 mg/kg of an anti-CTLA-4 antibody, one can draw the appropriate amounts of the anti-PD-1 antibody (*i.e.*, 180 mg) and the anti-CTLA-4 antibody (*i.e.*, 60 mg) at once from a 3:1 ratio fixed dosing formulation of an anti-PD1 antibody and an anti-CTLA-4 antibody.

[0044] The term "anti-PD-1 antibody monotherapy" as used herein includes a therapy of an anti-PD-1 antibody without an anti-CTLA-4 antibody therapy. The anti-PD-1 antibody monotherapy comprises, consists essentially of, or consists of administering one or more doses of an anti-PD-1 antibody to a patient in need thereof, but does not include administering an anti-CTLA-4 antibody. In one embodiment, the anti-PD-1 antibody monotherapy comprises administering one or more doses of an anti-PD-1 antibody to a patient in need thereof, but does not include administering an anti-CTLA-4 antibody. In another embodiment, the anti-PD-1 antibody monotherapy comprises administering one or more doses of an anti-PD-1 antibody to a patient in need thereof, but does not include administering an antibody specifically targeting a protein other than PD-1. In other embodiments, the anti-PD-1 antibody monotherapy comprises administering one or more doses of an anti-PD-1 antibody to a patient in need thereof, but does not include administering another anti-cancer agent.

[0045] 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 antibodies, 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.

[0046] "PD-L1 negative" or "PD-L1 expression negative," relating to cell surface PD-L1 expression, refers to the lack of a detectable amount of cell surface PD-L1. For cell surface expression assayed by IHC, e.g., with the mAb 28-8, a PD-L1 negative tumor or PD-L1 expression negative tumor means that less than 0.01% of cells express a detectable level of PD-L1. In some embodiments, a PD-L1 negative tumor or PD-L1 expression negative tumor means that zero (0) cells express a detectable level of PD-L1. In some embodiments, a PD-L1 negative or a PD-L1 expression negative tumor is any tumor other than a PD-L1 positive or a PD-L1 expression positive tumor.

[0047] The term "PD-L1 positive" or "PD-L1 expression positive," 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 expressing cell surface PD-L1. For cell surface expression assayed by immunohistochemistry (IHC), e.g., with the mAb 28- 8, the PD-L1 positive tumor or PD-L1 expression positive tumor means that at least about 0.01%, at least about 0.5%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, or at least about 30% of the total number of cells express PD-L1. PD-L1 positive tumor or PD-L1 expression positive tumor can also be expressed herein as tumor expressing PD-L1. In other embodiments, the PD-L1 positive tumor or PD-L1 expression positive tumor means that at least about 0.1% to at least about 20% of the total number of cells express PD-L1. In certain embodiments, the PD-L1 positive tumor or PD-L1 expression positive tumor means that at least about 0.1% to at least about 10% of the total number of cells express PD-L1. In some embodiments, the PD-L1 positive or PD-L1 expression positive tumor means that at least about 1% of the total number of cells express PD-L1 on the cell surface. In other embodiments, the PD-L1 positive or PD-L1 expression positive tumor means that at least about 5% of the total number of cells express PD-L1 on the cell surface. In one particular embodiment, PD-L1 positive or PD-L1 expression positive tumor means that at least about 1%, or in the range of 1- 5% of the total number of cells express PD-L1 on the cell surface.

[0048] "Programmed Death-1 (PD-1)" 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.

[0049] "Programmed Death Ligand-1 (PD-L1)" is one of two cell surface glycoprotein ligands for PD-1 (the other being PD-L2) that down-regulate 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.

- [0050]** A "patient" as used herein includes any patient who is afflicted with a cancer (*e.g.*, melanoma). The terms "subject" and "patient" are used interchangeably herein.
- [0051]** A "therapeutically effective amount" or "therapeutically effective dosage" of a drug or therapeutic agent 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.
- [0052]** "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 or condition, or biochemical indicia associated with a disease.
- [0053]** 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.
- [0054]** 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.
- [0055]** 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 10% or 20% (*i.e.*, $\pm 10\%$ or $\pm 20\%$). For example, about 3mg can include any number between 2.7 mg and 3.3 mg (for 10%) or between 2.4 mg and 3.6 mg (for 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.

[0056] The terms "about once a week," "once about every week," "once about every two weeks," or any other similar dosing interval terms as used herein means approximate number, and "about once a week" or "once about every week" can include every seven days $\pm$ two days, *i.e.*, every five days to every nine days. The dosing frequency of "once a week" thus can be every five days, every six days, every seven days, every eight days, or every nine days. "Once about every two weeks" can include every fourteen days $\pm$ three days, *i.e.*, every eleven days to every seventeen days. Similar approximations apply, for example, to once about every three weeks, once about every four weeks, once about every five weeks, once about every six weeks and once about every twelve weeks. In some embodiments, a dosing interval of once about every six weeks or once about every twelve weeks means that the first dose can be administered any day in the first week, and then the next dose can be administered any day in the sixth or twelfth week, respectively. In other embodiments, a dosing interval of once about every six weeks or once about every twelve weeks means that the first dose is administered on a particular day of the first week (*e.g.*, Monday) and then the next dose is administered on the same day of the sixth or twelfth weeks (*i.e.*, Monday), respectively.

[0057] 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.

[0058] Various aspects of the invention are described in further detail in the following subsections.

Methods of the Invention

[0059] The present invention is directed to a method for treating a PD-L1-negative melanoma in a subject in need thereof. The present invention shows that for PD-L1 negative tumors, a combination therapy of an anti-PD-1 antibody and an anti-CTLA-4 antibody is more suitable than a monotherapy of either an anti-PD-1 antibody or an anti-CTLA-4 antibody.

[0060] Not bound to any theory, the present invention identifies that in patients having a PD-L1-negative tumor progression-free survival and overall response rate are higher following treatment with a combination therapy with an anti-PD-1 antibody and an anti-CTLA-4 antibody than following treatment with either an anti-PD-1 antibody or an anti-CTLA-4 antibody alone. Therefore, in order to increase the response of a patient having a PD-L1-negative tumor, the present invention provides identifying a patient suitable for the combination therapy of an anti-PD-1 antibody and an anti-CTLA-4 antibody.

[0061] In one embodiment, the invention includes a method of treating a PD-L1 negative melanoma comprising administering to a patient: (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4, wherein the patient is identified as having a PD-L1-negative melanoma tumor prior to the administration. In another embodiment, the invention includes a method for treating a melanoma in a patient in need thereof comprising: (i) identifying a patient having a PD-L1-negative melanoma tumor; and (ii) administering to the patient: (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4.

[0062] In certain embodiments, the invention includes a method for extending a progression-free survival period for over 9 months in a patient afflicted with a PD-L1 negative melanoma tumor comprising administering to the patient: (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1;

and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4, wherein the patient is identified as having a PD-L1-negative melanoma tumor prior to the administration and wherein the patient demonstrates progression-free survival for over 9 months. In other embodiments, the invention provides a method for extending a progression-free survival period for over 9 months in a patient afflicted with a melanoma tumor comprising: (i) identifying a patient having a PD-L1-negative melanoma tumor; and (ii) administering to the patient (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4, wherein the patient demonstrates progression-free survival for over 9 months. According to the invention, the progression-free survival of the patient can be extended, after the administration, over about 10 months, over about 11 months, over about 12 months, over about 13 months, about 14 months, about 15 months, about 16 months, about 17 months, about 18 months, about 2 years, about 3 years, about 4 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, or about 10 years. In a particular embodiment, the progression-free survival of the patient is extended for over 10 months.

[0063] In still other embodiments, the invention is directed to a method for reducing a tumor size at least by 10% in a patient afflicted with a PD-L1 negative melanoma tumor comprising administering to the patient: (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4, wherein the patient is identified as having a PD-L1-negative melanoma tumor prior to the administration and wherein the administration reduces the tumor size at least about 10%, about 20%, about 30%, about 40%, or about 50% compared to the tumor size prior to the administration. In yet other embodiments, the method comprises (i) identifying a patient having a PD-L1-negative melanoma tumor; and (ii) administering to the patient (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4, wherein the administration reduces the tumor size at least about 10%, about 20%, about 30%, about 40%, or about 50% compared to the

tumor size prior to the administration. The tumor size, after the administration, can be reduced at least about 60%, 70%, 80%, 90% or 100%. The tumor can be completely eliminated from the patient's body after the administration.

[0064] The invention can also include a method of preventing a relapse and/or induce a remission to a patient having a PD-L1 negative melanoma tumor comprising administering to the patient: (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4, wherein the patient is identified as having a PD-L1-negative melanoma tumor prior to the administration. In some embodiments, the method of the invention comprises (i) identifying a patient having a PD-L1-negative melanoma tumor; and (ii) administering to the patient (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4.

[0065] In certain embodiments, the invention includes a method for increasing an objective response rate to be higher than 40% in a patient population, wherein each patient of the patient population is afflicted with a melanoma tumor, in a cancer treatment comprising administering to the patient: (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4, wherein each patient is identified as having a PD-L1-negative melanoma tumor prior to the administration and wherein the objective response rate is higher than 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75%. The methods can further comprise identifying each patient as having a PD-L1-negative melanoma tumor prior to the administration. In other embodiments, each patient in the methods can further be characterized by (i) extended progression-free survival for over 11 months, (ii) tumor size reduction at least about 10%, about 20%, about 30%, about 40%, or about 50% compared to the tumor size prior to the administration, or (iii) both. In some embodiments, the patient population can be at least 100 patients having a PD-L1-negative melanoma tumor. In some embodiments, the patient population can be at least 200, 300, 400, 500, 600, 700, 800, 900, or 1000 patients having a PD-L1-negative melanoma tumor.

[0066] In further embodiments, the invention provides a method for selecting a suitable cancer therapy course in a patient having a PD-L1 negative melanoma tumor comprising: (i) identifying a patient having a PD-L1-negative melanoma tumor; and (ii) instructing a healthcare provider to administer to the patient: (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4. The method further comprises administering the antibodies to the patient.

[0067] The methods of the invention as a result of the combination therapy can treat the melanoma tumor, reduce the tumor size, prevent growth of the tumor, eliminate the tumor from the patient, prevent a relapse of a tumor, induce a remission in a patient, or any combination thereof. In certain embodiments, the combination therapy induces a complete response. In other embodiments, the combination therapy induces a partial response.

Melanoma

[0068] Melanoma (MEL) is a malignant tumor of melanocytes, the melanin-producing cells found predominantly in skin. Though less common than other skin cancers, it is the most dangerous of skin cancers if not diagnosed early and causes the majority (75%) of skin cancer deaths. The incidence of MEL is increasing worldwide in Caucasian populations, especially where peoples with low amounts of skin pigmentation receive excessive ultraviolet light exposure from the sun. In Europe, the incidence rate is < 10-20 per 100,000 population; in the USA 20-30 per 100,000; and in Australia, where the highest incidence is observed, 50-60 per 100,000 (Garbe *et al.*, *Eur. J. Cancer*. 48(15):2375-90 (2012)). MEL accounts for about 5% of all new cases of cancer in the United States (U.S.), and the incidence continues to rise by almost 3% per year. This translates to an estimated 76,690 new cases in the U.S. in 2013 with 9,480 associated deaths (Siegel *et al.*, *CA Cancer J. Clin.* 63(1):11-30 (2013)).

[0069] For in situ (stage 0) or early-stage MEL (Stages I-II), surgical excision is the primary treatment. In general, the prognosis is excellent for patients with localized disease and tumors 1.0 mm or less in thickness, with 5-year survival rates of more than 90% (NCCN GUIDELINES®, 2013- Melanoma). Where surgical excision is not feasible for in situ melanoma due to comorbidity or cosmetically sensitive tumor location, topical

imiquimod (INN) and radiotherapy are emerging as treatments, especially for *lentigo maligna*. Chemotherapeutic agents for treating MEL include dacarbazine, temozolomide and imatinib for melanoma with a 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.

[0070] For patients with localized melanomas more than 1.0 mm in thickness, survival rates range from 50-90%. The likelihood of regional nodal involvement increases with increasing tumor thickness. With Stage III MEL (clinically positive nodes and/or in-transit disease), 5-year survival rates range from 20-70%. By far the most lethal is Stage IV MEL where long-term survival in patients with distant metastatic melanoma is less than 10% (NCCN GUIDELINES®, 2013 - melanoma).

[0071] The types of melanoma that can be treated with the present methods include, but are not limited to, lentigo maligna, lentigo maligna melanoma, superficial spreading melanoma, acral lentiginous melanoma, mucosal melanoma, nodular melanoma, polypoid melanoma, desmoplastic melanoma, amelanotic melanoma, soft-tissue melanoma, melanoma with small nevus-like cells, melanoma with features of a Spitz nevus, or uveal melanoma. The stages of melanoma that can be treated with the present methods include, but are not limited to, (i) Stage I / II (invasive melanoma): T1a characterized by less than 1.0 mm primary tumor thickness, without ulceration, and mitosis $< 1/\text{mm}^2$; T1b characterized by less than 1.0 mm primary tumor thickness, with ulceration or mitoses $\geq 1/\text{mm}^2$; T2a characterized by 1.01–2.0 mm primary tumor thickness, without ulceration; (ii) Stage II (high risk melanoma): T2b characterized by 1.01–2.0 mm primary tumor thickness, with ulceration; T3a characterized by 2.01–4.0 mm primary tumor thickness, without ulceration; T3b characterized by 2.01–4.0 mm primary tumor thickness, with ulceration; T4a characterized by greater than 4.0 mm primary tumor thickness, without ulceration; or T4b characterized by greater than 4.0 mm primary tumor thickness, with ulceration; (iii) Stage III (regional metastasis): N1 characterized by single positive lymph node; N2 characterized by two to three positive lymph nodes or regional skin/in-transit metastasis; or N3 characterized by four positive lymph nodes or one lymph node and regional skin/in-transit metastases; and (iv) Stage IV (distant metastasis): M1a characterized by distant skin metastasis, normal LDH; M1b characterized by Lung

metastasis, normal LDH; or M1c characterized by other distant metastasis or any distant metastasis with elevated LDH. PD-L1-negative tumors that are treatable by the present methods can lack PD-L1 expression on the surface of tumor cells and/or tumor infiltrating inflammatory cells.

Measurement of PD-L1 expression

[0072] In certain embodiments, identifying a patient suitable for a combination therapy for the present methods includes measuring or assessing a PD-L1 expression on the surface of the melanoma tumor cells or tumor infiltrating inflammatory cells. The phrases "tumors expressing PD-L1," "PD-L1 expressing tumor," "PD-L1 positive tumor," and "PD-L1 expression positive tumor" are used interchangeably herein. The meaning of the phrases is provided elsewhere herein. The methods of measuring or assessing the PD-L1 expression can be achieved by any methods applicable.

[0073] In order to assess the PD-L1 expression, in one embodiment, a test tissue sample is obtained from the patient who is in need of the therapy. In another embodiment, the assessment of PD-L1 expression can be achieved without obtaining a test tissue sample. In some embodiments, selecting a suitable patient includes (i) optionally providing a test tissue sample obtained from a patient with cancer of the tissue, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells; and (ii) assessing the proportion of cells in the test tissue sample that express PD-L1 on the surface of the cells based on an assessment that the proportion of cells in the test tissue sample that express PD-L1 on the cell surface is lower than a predetermined threshold level. A test tissue sample can be considered to be PD-L1-negative if less than about 5% of the cells in the test tissue express PD-L1 on the cell surface. In other embodiments, a test tissue sample is considered to be PD-L1-negative if less than about 4%, less than about 3%, less than about 2%, less than about 1%, less than about 0.5%, less than about 0.1%, less than about 0.01% or 0% of the cells in the test tissue express PD-L1 on the cell surface. In one particular example, the test tissue sample can be considered to be PD-L1-negative if less than about 5% of the cells in the test tissue express PD-L1 on the cell surface.

[0074] In any of the methods comprising the measurement of PD-L1 expression in a test tissue sample, however, 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 embodiments the "measuring" or "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 healthcare provider for use in selecting a suitable candidate for the combination therapy of an anti-PD-1 antibody and an anti-CTLA-4 antibody. In certain embodiments, the steps that provide the intermediate result is performed by a medical practitioner or someone acting under the direction of a medical practitioner. In other embodiments, these steps are performed by an independent laboratory or by an independent person such as a laboratory technician.

[0075] 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 some embodiments, PD-L1 expression is assayed by IHC. In other embodiments of all of these methods, cell surface expression of PD-L1 is assayed using, *e.g.*, IHC or *in vivo* imaging.

[0076] 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 and Weissleder, *Cold Spring Harb. Perspect. Biol.* 2(12):a003848 (2010)). Antibody 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 and Wu, *Cancer Biother. Radiopharm.* 25(3):253-61 (2010); Olafsen *et al.*, *Protein Eng. Des. Sel.* 23(4):243-9 (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 other 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 some embodiments, the IHC assay is performed using an anti-PD-L1 mAb to bind to the PD-L1 polypeptide, if present.

Assaying Cell-Surface PD-L1 Expression by Automated IHC

[0077] In one embodiment of the present methods, an automated IHC method is used to assay the expression of PD-L1 on the surface of cells in FFPE tissue specimens. This 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 antibody or portion thereof and human PD-L1. In certain embodiments, the test and control tissue samples are FFPE samples. The formation of a complex can then be 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.

[0078] 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 110°C 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 postprimary blocking agent; incubating with NovoLink Polymer; adding a chromogen substrate and developing; and counterstaining with hematoxylin.

[0079] 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%.

[0080] 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 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.

[0081] 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.

[0082] A histoscore is used as a more quantitative measure of the IHC data. The histoscore is calculated as follows:

$$\text{Histoscore} = [(\% \text{ tumor} \times 1 (\text{low intensity})) + (\% \text{ tumor} \times 2 (\text{medium intensity})) + (\% \text{ tumor} \times 3 (\text{high intensity}))]$$

[0083] 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). A test sample can be designated as PD-L1-negative even though some level of PD-L1 expression is detected. For example, a designation of PD-L1-negative can be assigned to a specimen having a final histoscore of about 15 or less, of about 10 or less, about 9 or less, about 8 or less, about 7 or less, about 6 or less, about 5 or less, about 4 or less, about 3 or less, about 2 or less, about 1 or less, or of 0.

[0084] 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.*, *Sci. Transl. Med.* 4(127):127ra37 (2012)).

Anti-PD-1 antibodies

[0085] 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-presenting cells as well as many human cancers and have been shown to down regulate T cell activation and

cytokine secretion upon binding to PD-1. Inhibition of the PD-1/PD-L1 interaction mediates potent antitumor activity in preclinical models.

[0086] HuMAbs that bind specifically to PD-1 with high affinity have been disclosed in U.S. Patent Nos. 8,008,449 and 8,779,105. Other anti-PD-1 mAbs have been described in, for example, U.S. Patent Nos. 6,808,710, 7,488,802, 8,168,757 and 8,354,509, and PCT Publication No. WO 2012/145493. 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 1×10^{-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 antibody responses; and (j) inhibits tumor cell growth *in vivo*. Anti-PD-1 antibodies useful for the present invention include mAbs that bind specifically to human PD-1 and exhibit at least one, at least two, at least three, at least four, or at least five, of the preceding characteristics.

[0087] In one embodiment, the anti-PD-1 antibody is nivolumab. Nivolumab (also known as "OPDIVO[®]"; formerly designated 5C4, BMS-936558, MDX-1106, or ONO-4538) is a fully human IgG4 (S228P) PD-1 immune checkpoint inhibitor antibody that selectively prevents interaction with PD-1 ligands (PD-L1 and PD-L2), thereby blocking the down-regulation of antitumor T-cell functions (U.S. Patent No. 8,008,449; Wang *et al.*, *Cancer Immunol Res.* 2(9):846-56 (2014)). In another embodiment, the anti-PD-1 antibody or fragment thereof cross-competes with nivolumab. In other embodiments, the anti-PD-1 antibody or fragment thereof binds to the same epitope as nivolumab. In certain embodiments, the anti-PD-1 antibody has the same CDRs as nivolumab.

[0088] In another embodiment, the anti-PD-1 antibody or fragment thereof cross-competes with pembrolizumab. In some embodiments, the anti-PD-1 antibody or fragment thereof binds to the same epitope as pembrolizumab. In certain embodiments, the anti-PD-1 antibody has the same CDRs as pembrolizumab. In another embodiment, the anti-PD-1 antibody is pembrolizumab. Pembrolizumab (also known as

"KEYTRUDA[®]", lambrolizumab, and MK-3475) is a humanized monoclonal IgG4 antibody directed against human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1). Pembrolizumab is described, for example, in U.S. Patent Nos. 8,354,509 and 8,900,587; *see also* <http://www.cancer.gov/drugdictionary?cdrid=695789> (last accessed: December 14, 2014). Pembrolizumab has been approved by the FDA for the treatment of relapsed or refractory melanoma.

[0089] In other embodiments, the anti-PD-1 antibody or fragment thereof cross-competes with MEDI0608. In still other embodiments, the anti-PD-1 antibody or fragment thereof binds to the same epitope as MEDI0608. In certain embodiments, the anti-PD-1 antibody has the same CDRs as MEDI0608. In other embodiments, the anti-PD-1 antibody is MEDI0608 (formerly AMP-514), which is a monoclonal antibody. MEDI0608 is described, for example, in US Pat. No. 8,609,089B2 or in <http://www.cancer.gov/drugdictionary?cdrid=756047> (last accessed December 14, 2014).

[0090] In certain embodiments, the first antibody is an anti-PD-1 antagonist. One example of the anti-PD-1 antagonist is AMP-224, which is a B7-DC Fc fusion protein. AMP-224 is discussed in U.S. Publ. No. 2013/0017199 or in <http://www.cancer.gov/publications/dictionaries/cancer-drug?cdrid=700595> (last accessed July 8, 2015).

[0091] In other embodiments, the anti-PD-1 antibody or fragment thereof cross-competes with BGB-A317. In some embodiments, the anti-PD-1 antibody or fragment thereof binds the same epitope as BGB-A317. In certain embodiments, the anti-PD-1 antibody has the same CDRs as BGB-A317. In certain embodiments, the anti-PD-1 antibody is BGB-A317, which is a humanized monoclonal antibody. BGB-A317 is described in U.S. Publ. No. 2015/0079109.

[0092] In some embodiments, the antibody is Pidilizumab (CT-011), which is an antibody previously reported to bind to PD-1 but which is believed to bind to a different target. Pidilizumab is described in US Pat. No. 8,686,119 B2 or WO 2013/014668 A1.

[0093] Anti-PD-1 antibodies useful for the disclosed compositions also include isolated antibodies that bind specifically to human PD-1 and cross-compete for binding to human PD-1 with nivolumab (*see, e.g.*, U.S. Patent Nos. 8,008,449 and 8,779,105; WO 2013/173223). The ability of antibodies to cross-compete for binding to an antigen

indicates that these antibodies bind to the same epitope region of the antigen and sterically hinder the binding of other cross-competing antibodies to that particular epitope region. These cross-competing antibodies are expected to have functional properties very similar to those of nivolumab by virtue of their binding to the same epitope region of PD-1. Cross-competing antibodies can be readily identified based on their ability to cross-compete with nivolumab in standard PD-1 binding assays such as Biacore analysis, ELISA assays or flow cytometry (*see, e.g.*, WO 2013/173223).

[0094] In certain embodiments, the antibodies that cross-compete for binding to human PD-1 with, or bind to the same epitope region of human PD-1 as, nivolumab are mAbs. For administration to human subjects, these cross-competing antibodies can be chimeric antibodies, or humanized or human antibodies. Such chimeric, humanized or human mAbs can be prepared and isolated by methods well known in the art.

[0095] Anti-PD-1 antibodies useful for the compositions of the disclosed invention also include antigen-binding portions of the above antibodies. It has been amply demonstrated that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody 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 antibody.

[0096] Anti-PD-1 antibodies suitable for use in the disclosed compositions are antibodies that bind to PD-1 with high specificity and affinity, block the binding of PD-L1 and or PD-L2, and inhibit the immunosuppressive effect of the PD-1 signaling pathway. In any of the compositions or methods disclosed herein, an anti-PD-1 "antibody" includes an antigen-binding portion or fragment that binds to the PD-1 receptor and exhibits the functional properties similar to those of whole antibodies in inhibiting ligand binding and upregulating the immune system. In certain embodiments, the anti-PD-1 antibody or antigen-binding portion thereof cross-competes with nivolumab for binding to human PD-1. In other embodiments, the anti-PD-1 antibody or antigen-binding portion thereof is a chimeric, humanized or human monoclonal antibody or a portion thereof. In certain

embodiments, the antibody is a humanized antibody. In other embodiments, the antibody is a human antibody. Antibodies of an IgG1, IgG2, IgG3 or IgG4 isotype can be used.

[0097] In certain embodiments, the anti-PD-1 antibody or antigen-binding portion thereof comprises a heavy chain constant region which is of a human IgG1 or IgG4 isotype. In certain other embodiments, the sequence of the IgG4 heavy chain constant region of the anti-PD-1 antibody or antigen-binding portion thereof contains an S228P mutation which replaces a serine residue in the hinge region with the proline residue normally found at the corresponding position in IgG1 isotype antibodies. This mutation, which is present in nivolumab, prevents Fab arm exchange with endogenous IgG4 antibodies, while retaining the low affinity for activating Fc receptors associated with wild-type IgG4 antibodies (Wang *et al.*, *Cancer Immunol Res.* 2(9):846-56 (2014)). In yet other embodiments, the antibody comprises a light chain constant region which is a human kappa or lambda constant region. In other embodiments, the anti-PD-1 antibody or antigen-binding portion thereof is a mAb or an antigen-binding portion thereof. In certain embodiments of any of the therapeutic methods described herein comprising administration of an anti-PD-1 antibody, the anti-PD-1 antibody is nivolumab. In other embodiments, the anti-PD-1 antibody is pembrolizumab. In other embodiments, the anti-PD-1 antibody is chosen from the human antibodies 17D8, 2D3, 4H1, 4A11, 7D3 and 5F4 described in U.S. Patent No. 8,008,449. In still other embodiments, the anti-PD-1 antibody is MEDI0608 (formerly AMP-514), AMP-224, or BGB-A317.

[0098] Because anti-PD-1 and anti-PD-L1 target the same signaling pathway and have been shown in clinical trials to exhibit similar levels of efficacy in a variety of cancers, including RCC (*see* Brahmer *et al.* (2012) *N Engl J Med* 366:2455-65; Topalian *et al.* (2012a) *N Engl J Med* 366:2443-54; WO 2013/173223), an anti-PD-L1 antibody may be substituted for the anti-PD-1 Ab in any of the therapeutic methods disclosed herein. In certain embodiments, the anti-PD-L1 antibody is BMS-936559 (formerly 12A4 or MDX-1105) (*see, e.g.*, U.S. Patent No. 7,943,743; WO 2013/173223). In other embodiments, the anti-PD-L1 antibody is MPDL3280A (also known as RG7446) (*see, e.g.*, Herbst *et al.* (2013) *J Clin Oncol* 31(suppl):3000. Abstract; U.S. Patent No. 8,217,149) or MEDI4736 (Khleif (2013) In: Proceedings from the European Cancer Congress 2013; September 27-October 1, 2013; Amsterdam, The Netherlands. Abstract 802). In certain embodiments,

the antibodies that cross-compete for binding to human PD-L1 with, or bind to the same epitope region of human PD-L1 as the above-references PD-L1 antibodies are mAbs. For administration to human subjects, these cross-competing antibodies can be chimeric antibodies, or can be humanized or human antibodies. Such chimeric, humanized or human mAbs can be prepared and isolated by methods well known in the art.

Anti-PD-L1 Antibodies

[0099] In certain embodiments, the present application encompasses use of an anti-PD-L1 antibody in lieu of anti-PD-1 antibody. In one embodiment, the anti-PD-L1 antibody inhibits the binding of PD-L1 receptor, i.e., PD-1, with its ligand PD-L1.

[0100] Anti-PD-L1 antibodies useful for the invention include antibodies engineered starting from antibodies having one or more of the V_H and/or V_L sequences disclosed herein, which engineered antibodies can have altered properties from the starting antibodies. An anti-PD-L1 antibody can be engineered by a variety of modifications as described above for the engineering of modified anti-PD-1 antibodies of the invention.

[0101] Anti-PD-L1 antibodies of the invention also include isolated antibodies 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. The use of different antibodies to stain PD-L1 in frozen versus FFPE tissues, and the ability of certain antibodies 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.*, *Proc. Natl. Acad. Sci. USA* 104(9):3360-3365 (2007); Gadiot *et al.*, *Cancer* 117(10):2192-2201 (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.

[0102] In some embodiments, an anti-PD-L1 antibody useful for the present methods includes mAb 28-8 set forth in SEQ ID NOs. 1 and 2, respectively. The sequences of the heavy and light chain CDR domains of mAb 28-8, as delineated using the Kabat system, are set forth in SEQ ID NOs. 3-8. In other embodiments, an anti-PD-L1 antibody useful for the invention comprises mAbs 28-1, 28-12, 29-8 and 20-12 or an antigen-binding

portion thereof, for example, including Fab, F(ab')₂ Fd, Fv, and scFv, di-scFv or bi-scFv, and scFv-Fc fragments, diabodies, triabodies, tetrabodies, and isolated CDRs.

Anti-CTLA-4 antibodies

[0103] Anti-CTLA-4 antibodies of the instant invention bind to human CTLA-4 so as to disrupt the interaction of CTLA-4 with a human B7 receptor. Because the interaction of CTLA-4 with B7 transduces a signal leading to inactivation of T-cells bearing the CTLA-4 receptor, disruption of the interaction effectively induces, enhances or prolongs the activation of such T cells, thereby inducing, enhancing or prolonging an immune response.

[0104] HuMAbs that bind specifically to CTLA-4 with high affinity have been disclosed in U.S. Patent Nos. 6,984,720 and 7,605,238. Other anti-PD-1 mAbs have been described in, for example, U.S. Patent Nos. 5,977,318, 6,051,227, 6,682,736, and 7,034,121. The anti-PD-1 HuMAbs disclosed in U.S. Patent No. Nos. 6,984,720 and 7,605,238 have been demonstrated to exhibit one or more of the following characteristics: (a) binds specifically to human CTLA-4 with a binding affinity reflected by an equilibrium association constant (K_a) of at least about 10^7 M^{-1} , or about 10^9 M^{-1} , or about 10^{10} M^{-1} to 10^{11} M^{-1} or higher, as determined by Biacore analysis; (b) a kinetic association constant (k_a) of at least about 10^3 , about 10^4 , or about $10^5 \text{ m}^{-1} \text{ s}^{-1}$; (c) a kinetic disassociation constant (k_d) of at least about 10^3 , about 10^4 , or about $10^5 \text{ m}^{-1} \text{ s}^{-1}$; and (d) inhibits the binding of CTLA-4 to B7-1 (CD80) and B7-2 (CD86). Anti-CTLA-4 antibodies useful for the present invention include mAbs that bind specifically to human CTLA-4 and exhibit at least one, at least two, or at least three of the preceding characteristics.

[0105] An exemplary clinical anti-CTLA-4 antibody is the human mAb 10D1 (now known as ipilimumab and marketed as YERVOY[®]) as disclosed in U.S. Patent No. 6,984,720. Ipilimumab is an anti-CTLA-4 antibody for use in the methods disclosed herein. Ipilimumab is a fully human, IgG1 monoclonal antibody that blocks the binding of CTLA-4 to its B7 ligands, thereby stimulating T cell activation and improving overall survival (OS) in patients with advanced melanoma.

[0106] Another anti-CTLA-4 antibody useful for the present methods is tremelimumab (also known as CP-675,206). Tremelimumab is human IgG2 monoclonal anti-CTLA-4

antibody. Tremelimumab is described in WO/2012/122444, U.S. Publ. No. 2012/263677, or WO Publ. No. 2007/113648 A2.

[0107] Anti-CTLA-4 antibodies useful for the disclosed composition also include isolated antibodies that bind specifically to human CTLA-4 and cross-compete for binding to human CTLA-4 with ipilimumab or tremelimumab or bind to the same epitope region of human CTLA-4 as ipilimumab or tremelimumab. In certain embodiments, the antibodies that cross-compete for binding to human CTLA-4 with, or bind to the same epitope region of human CTLA-4 as does ipilimumab or tremelimumab, are antibodies comprising a heavy chain of the human IgG1 isotype. For administration to human subjects, these cross-competing antibodies are chimeric antibodies, or humanized or human antibodies. Useful anti-CTLA-4 antibodies also include antigen-binding portions of the above antibodies such as Fab, F(ab')₂, Fd or Fv fragments.

Dosages

[0108] The combination of an anti-PD-1 antibody and an anti-CTLA-4 antibody can be administered to a suitable patient in therapeutically effective amounts. For example, each antibody can be administered at a dosage ranging from at least about 0.1 to at least about 20.0 mg/kg body weight. In certain embodiments, each of the anti-PD-1 and anti-CTLA-4 antibodies is individually administered at a dosage of at least about 0.1, at least about 0.3, at least about 0.5, at least about 1, at least about 3, at least about 5, at least about 10 or at least about 20 mg/kg, *e.g.*, at least about 1 to at least about 10 mg/kg, *e.g.*, at least about 1 to at least about 3 mg/kg, *e.g.*, at least about 3 mg/kg, *e.g.*, at least about 1 mg/kg. Each of the anti-PD-1 antibody and anti-CTLA-4 antibody can be administered at a dosing frequency of at least about once every week, at least about once every 2 weeks, at least about once every 3 weeks, or at least about once every 4 weeks, or at least about once a month, for up to 6 to up to 72 doses, or for as long as clinical benefit is observed, or until unmanageable toxicity or disease progression occurs. In some embodiments, the anti-PD-1 antibody is administered at a dosage of about 1 or about 3 mg/kg. In certain embodiments, the sequenced regimen comprises administering the anti-PD-1 antibody to the subject at a dosing frequency of once about every week, once about every 2 weeks, once about every 3 weeks, or once about every 4 weeks, or once a month for 6 to 72

doses, or for as long as clinical benefit is observed, or until unmanageable toxicity or disease progression occurs. In other embodiments, the anti-PD-1 is administered at a dosage of about 1 mg/kg at a dosing frequency of once about every 3 weeks for up to 48 doses. In some embodiments, the anti-CTLA-4 antibody is administered at a dosage of about 1 or about 3 mg/kg. In certain embodiments, the sequenced regimen comprises administering the anti-CTLA-4 antibody to the subject at a dosing frequency of once about every week, at least about once every 2 weeks, at least about once every 3 weeks, or at least about once every 4 weeks, or about once a month for 6 to 72 doses, or for as long as clinical benefit is observed, or until unmanageable toxicity or disease progression occurs. In other embodiments, the anti-CTLA-4 antibody is administered at a dosage of about 3 mg/kg at a dosing frequency of once about every 3 weeks for up to 48 doses.

[0109] In other embodiments, the anti-PD-1 and anti-CTLA-4 antibodies are administered at the following dosages: (a) 0.1 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody; (b) 0.3 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody; (c) 1 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody; (d) 3 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody; (e) 5 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody; (f) 10 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody; (g) 0.1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody; (h) 0.3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody; (i) 1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody; (j) 3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody; (k) 5 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody; or (l) 10 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody. In a particular embodiment, the methods include administration of 1 mg/kg of an anti-PD-1 antibody and 3 mg/kg of an anti-CTLA-4 antibody.

[0110] In some embodiments, the dosage of each of the anti-PD-1 and anti-CTLA-4 antibodies is kept constant during the induction dosing schedule and the maintenance dosing schedule. In certain embodiments, a regimen comprises: (i) an induction dosing schedule comprising combined administration of the anti-PD-1 and anti-CTLA-4 antibodies at a dosing frequency of at least once about every 2 weeks, at least once about every 3 weeks, or at least once about every 4 weeks, or at least about once a month, for at

least 2, 4, 6, 8 or 10 doses, followed by administration of the anti-PD-1 antibody alone at a dosing frequency of at least once every 2, 3 or 4 weeks, or at least once a month, for at least 2, 4, 6, 8 or 12 doses; followed by (ii) a maintenance dosing schedule comprising combined administration of the anti-PD-1 and anti-CTLA-4 antibodies at a dosing frequency of at least about once every 8 weeks, once about every 12 weeks, or once about every 16 weeks, or at least once a quarter, for at least 4, 6, 8, 10, 12 or 16 doses, or for as long as clinical benefit is observed, or until unmanageable toxicity or disease progression occurs. In another embodiment, the dosing schedule comprises administering about 3 mg/kg of an anti-PD-1 antibody every 2 weeks, or about 1 mg/kg of an anti-PD-1 antibody every 3 weeks plus about 3 mg/kg of an anti-CTLA-4 antibody every 3 weeks for 4 doses, followed by about 3 mg/kg of an anti-PD-1 antibody every 2 weeks for cycle 3 and beyond, or 3 mg/kg of an anti-CTLA-4 antibody every 3 weeks for 4 doses. In one particular embodiment, the dosing schedule comprises administering about 1 mg/kg of an anti-PD-1 antibody followed by an anti-CTLA-4 antibody (*e.g.*, about 3 mg/kg anti-CTLA-4 antibody) on the same day every 3 weeks for 4 doses, followed by about 3 mg/kg of an anti-PD-1 antibody every 2 weeks.

[0111] In certain embodiments of this method, the maintenance dosing schedule comprises combined administration of up to 4, 6, 8, 10, 12 or 16 doses of the anti-PD-1 and anti-CTLA-4 antibodies. In other embodiments, the concurrent regimen comprises: (i) an induction dosing schedule comprising combined administration of the anti-PD-1 and anti-CTLA-4 antibodies at a dosing frequency of once about every 2 weeks, at least once about every 3 weeks, or at least once about every 4 weeks, or about once a month, for 2, 4, 6 or 8 doses, followed by administration of the anti-PD-1 antibody alone at a dosing frequency of once about every 2 weeks, at least once about every 3 weeks, or at least once about every 4 weeks, or about once a month, for 2, 4, 6, 8 or 12 doses; followed by (ii) a maintenance dosing schedule comprising combined administration of the anti-PD-1 and anti-CTLA-4 antibodies at a dosing frequency of once every once about every 8, once about every 12 or once about every 16 weeks, or once a quarter, for 4, 6, 8, 10, 12 or 16 doses, or for as long as clinical benefit is observed, or until unmanageable toxicity or disease progression occurs.

[0112] In a particular embodiment, the anti-PD-1 and anti-CTLA-4 antibodies are administered at dosages of about 1 mg/kg anti-PD-1 antibody every three weeks and about 3 mg/kg of anti-CTLA-4 antibody every three weeks. In another embodiment, the patient is administered at a dose of about 1 mg/kg of an anti-PD-1 antibody, followed by an anti-CTLA-4 antibody on the same day, every 3 weeks for 4 doses, then 3 mg/kg of an anti-PD-1 antibody every 2 weeks.

[0113] In certain embodiments of the present methods, the anti-PD-1 and anti-CTLA-4 antibodies are formulated for parenteral administration, *e.g.*, intravenous administration. In certain other embodiments, when the anti-PD-1 and anti-CTLA-4 antibodies are administered in combination, they are administered within about 30 minutes of each other. Either antibody may be administered first, that is, in certain embodiments, the anti-PD-1 antibody is administered before the anti-CTLA-4 antibody, whereas in other embodiments, the anti-CTLA-4 antibody is administered before the anti-PD-1 antibody. Typically, each antibody is administered intravenously over a period of about 60 minutes. In further embodiments, the anti-PD-1 and anti-CTLA-4 antibodies are administered concurrently, either admixed as a single composition in a pharmaceutically acceptable formulation for concurrent administration, or concurrently as separate compositions with each antibody in a pharmaceutically acceptable formulation.

[0114] In some embodiments, the anti-PD-1 antibody and the anti-CTLA-4 antibody are formulated in a single composition. The ratio of the amount of the anti-PD-1 antibody and the amount of the anti-CTLA-4 antibody in the single composition can be 10:1 to 1:10. In other embodiments, the ratio of the amount of the anti-PD-1 antibody and the amount of the anti-CTLA-4 antibody in the single composition is 5:1, 4:1, 3:1, 2:1, 1:1, 1:2, 1:3, 1:4, or 1:5. In a particular embodiment, the ratio of the amount of the anti-PD-1 antibody and the amount of the anti-CTLA-4 antibody in the single composition is 1:3.

[0115] In some embodiments, the composition is administered at a flat dose regardless of the weight of the patient. For example, each of the anti-PD-1 antibody with the anti-CTLA-4 antibody may be administered at a flat dose of 20, 50, 75, 80, 160, 200, 240, 300, 360, 400, 480, 500, 750 or 1500 mg, without regard to the patient's weight. In some embodiments the composition is administered at a weight-based dose at any dose disclosed herein. In some embodiments, the amount of the anti-PD-1 antibody and the

amount of the anti-CTLA-4 antibody administered to the patient at a single dose are identical.

[0116] In certain embodiments of the present methods, the therapeutically effective dosage of the anti-PD-1 antibody or antigen-binding portion thereof is a flat dosing (not a bodyweight based dosing) and comprises about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 140 mg, about 160 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about 260 mg, about 280 mg, or about 300 mg. In other embodiments, the therapeutically effective dosage of the anti-PD-1 antibody or antigen-binding portion thereof comprises about 320 mg, 360mg, 400 mg, 420mg, 480 mg, 500mg, 540 mg, 550mg, 600mg, 620 mg, 650mg, 680mg, 700 mg, 720mg, 780 mg, 800mg, 840mg, or 900mg.. In some embodiments, the dose of the anti-PD-1 antibody in the composition is between about 60 mg and about 300 mg, between about 60 mg and about 100 mg, between about 100 mg and about 200 mg, or between about 200 mg and about 300 mg. In some embodiments, the amount of the anti-PD-1 antibody in the composition is at least about 80 mg, about 160 mg, or about 240mg. In some embodiments, the dose of the anti-PD-1 antibody in the composition is at least about 240 mg or at least about 80 mg.

[0117] In other embodiments, the dosages are given every week, every two weeks, every three weeks, every four weeks, every five weeks, every six weeks, every seven weeks, every eight weeks, every nine weeks, or every 10 weeks.

[0118] In some embodiments, the anti-PD-1 antibody or antigen-binding portion thereof is administered at a dose of about 240 mg. In embodiments, the anti-PD-1 antibody or antigen-binding portion thereof is administered at a dose of about 360 mg. In embodiments, the anti-PD-1 antibody or antigen-binding portion thereof is administered at a dose of about 480 mg. In one embodiment, 360mg of the anti-PD-1 antibody or antigen binding fragment is administered once every 3 weeks. In another embodiment, 480mg of the anti-PD-1 antibody or antigen binding fragment is administered once every 4 weeks.

[0119] In other embodiments, the therapeutically effective dosage of the anti-CTLA-4 antibody or antigen-binding portion thereof is a flat dosing (not a bodyweight based dosing) and comprises about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 140 mg, about 160 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about

260 mg, about 280 mg, or about 300 mg. In other embodiments, the therapeutically effective dosage of the anti-CTLA-4 antibody or antigen-binding portion thereof comprises about 320 mg, 360mg, 400 mg, 420mg, 480 mg, 500mg, 540 mg, 550mg, 600mg, 620 mg, 650mg, 680mg, 700 mg, 720mg, 780 mg, 800mg, 840mg, or 900mg. In some embodiments, the dose of the anti-CTLA-4 antibody in the composition is between about 60 mg and about 300 mg, between about 60 mg and about 100 mg, between about 100 mg and about 200 mg, or between about 200 mg and about 300 mg. In some embodiments, the amount of the anti-CTLA-4 antibody in the composition is at least about 80 mg, about 160 mg, or about 240 mg. In some embodiments, the dose of the anti-CTLA-4 antibody in the composition is at least about 240 mg or at least about 80 mg.

[0120] In some embodiments, a flat dose of an anti-PD-1 antibody is 80 mg, and a flat dose of an anti-CTLA-4 antibody is 240 mg.

[0121] In some embodiments, the anti-PD-1 antibody is administered at a subtherapeutic dose, *i.e.*, a dose of the therapeutic agent that is significantly lower than the usual or FDA-approved dose when administered as monotherapy for the treatment of the cancer. The quantity of the second antibody in the composition is calculated based on the desired ratio.

[0122] In some embodiments, the composition is administered by intravenous infusion about once per week, about once every 2 weeks, about once every 3 weeks, or about once a month. In certain embodiments, the composition is administered once every 3 weeks. In some embodiments, the infusion occurs over at least about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 60 minutes, about 90 minutes, about 2 hours, about 3 hours, about 4 hours or about 5 hours.

[0123] Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention can be flat or 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.

Kits

[0124] Also within the scope of the present invention are kits, including pharmaceutical kits, comprising a combination of an anti-PD-1 antibody and an anti-CTLA-4 antibody, for therapeutic uses, and diagnostic kits comprising an anti-PD-L1 antibody for assaying membranous PD-L1 expression as a biomarker for screening patients for the combination therapy or for predicting the efficacy of the combination therapy. 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 antibody is co-packaged with an anti-CTLA-4 antibody in unit dosage form. In certain embodiments of a diagnostic kit, the anti-PD-L1 antibody is co-packaged with an anti-PD-1 antibody and an anti-CTLA-4 antibody for performing an assay to detect and/or quantify PD-L1 expression.

[0125] In certain embodiments, the pharmaceutical kit comprises the anti-human PD-1 HuMAb, nivolumab. In other embodiments, the pharmaceutical kit comprises the anti-human PD-L1 HuMAb, BMS-936559. In yet other embodiments, the pharmaceutical kit comprises the anti-human CTLA-4 HuMAb, ipilimumab. In certain embodiments, the diagnostic kit comprises the rabbit anti-human PD-L1 mAb, 28-8, comprising the V_H and V_L regions whose amino acid sequences are set forth in SEQ ID NOs. 1 and 2, respectively. In other embodiments, the diagnostic kit comprises the murine anti-human PD-L1 mAb, 5H1 (Dong *et al.*, *Nature Med.* 8(8):793-800 (2002)).

[0126] In some embodiments, the invention provides a kit for treating a patient afflicted with a melanoma tumor, the kit comprising:

- (a) a dosage ranging from at least about 0.1 to at least about 10 mg/kg body weight of an anti-PD-1 antibody or an antigen-binding portion thereof;
- (b) a dosage ranging from at least about 0.1 to at least about 10 mg/kg body weight of an anti-CTLA-4 antibody or an antigen-binding portion thereof; and
- (c) instructions for using the anti-PD-1 antibody or the antigen-binding portion thereof and the anti-CTLA-4 antibody or the antigen-binding portion thereof in the methods disclosed herein.

[0127] The present invention is further illustrated by the following examples which should not be construed as further limiting. The contents of all references cited throughout this application are expressly incorporated herein by reference.

EXAMPLES

EXAMPLE 1

[0128] A randomized, double-blind, multicenter, phase 3 trial was conducted to evaluate the safety and efficacy of nivolumab alone or nivolumab combined with ipilimumab in comparison with ipilimumab alone in previously untreated metastatic melanoma.

Patients

[0129] Eligible patients had histologically confirmed stage III (unresectable) or stage IV melanoma, and no prior systemic treatment for unresectable or metastatic melanoma. Other eligibility criteria included an age of at least 18 years, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 (indicating no symptoms) or 1 (indicating mild symptoms), measurable disease by computed tomography or magnetic resonance imaging per RECIST v1.1, availability of tissue collected from metastatic or unresectable tumors for the assessment of PD-L1 status, and known BRAF V600 mutation status (or consent to BRAF V600 mutation testing per local standards). Key exclusion criteria were presence of active brain metastases, ocular melanoma, or autoimmune disease, and any prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody. Patients who required systemic corticosteroid treatment or other immunosuppressive medications within 14 days of study drug administration were excluded.

Study Design and Treatment

- [0130]** In the double-blind, phase 3 study, enrolled patients were randomly assigned in a 1:1:1 ratio to receive 3 mg of nivolumab per kilogram of body weight every 2 weeks (plus ipilimumab-matched placebo), or 1 mg of nivolumab per kilogram every 3 weeks plus 3 mg of ipilimumab per kilogram every 3 weeks for 4 doses (plus nivolumab-matched placebo), followed by 3 mg of nivolumab per kilogram every 2 weeks for cycle 3 and beyond, or 3 mg of ipilimumab per kilogram every 3 weeks for 4 doses (plus nivolumab-matched placebo).
- [0131]** Both nivolumab and ipilimumab were administered by intravenous infusion. Randomization was stratified according to tumor PD-L1 status (positive vs. negative or indeterminate), BRAF mutation status (V600 mutation positive vs. wild-type), and American Joint Committee on Cancer metastasis stage (M0, M1a, or M1b vs. M1c). Treatment continued until RECIST v1.1-defined disease progression, unacceptable toxicity, or withdrawal of consent. Patients could be treated beyond progression provided they had a clinical benefit without clinical deterioration, and did not have substantial adverse effects, as assessed by the investigator.
- [0132]** Progression-free survival and overall survival were co-primary end points. Secondary end points included objective response rate, tumor PD-L1 expression as a predictive biomarker for progression-free and overall survival, and health-related quality of life. Exploratory end points include duration of objective response and safety/tolerability of study drug therapy.

Assessments

- [0133]** Patients were assessed for tumor response, according to RECIST v1.1 at 12 weeks after randomization and continuing every 6 weeks for 49 weeks, and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Progression-free survival was defined as the time between the date of randomization and the first date of documented progression or death, whichever occurred first. Patients treated beyond progression were considered to have progressive disease at the time of the initial progression event, as assessed by the investigator, regardless of subsequent tumor responses. Expression of PD-L1 on the surface of the tumor cells was assessed in a central laboratory by immunohistochemistry in formalin-fixed, paraffin-embedded tumor

specimens using a rabbit monoclonal anti-human PD-L1 antibody (clone 28-8) and an analytically validated automated assay developed by Dako (Carpinteria, CA). PD-L1 positivity was defined as at least 5% of tumor cells showing cell surface PD-L1 staining of any intensity in a section containing at least 100 tumor cells that could be evaluated. Indeterminate status was attributed to samples for which tumor cell–surface expression could not be discerned because of melanin content or strong cytoplasmic staining.

[0134] Any patient who received at least one dose of study drug in each of the 3 treatment groups was included in the assessment of safety. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.18. Safety assessments were made continuously during the treatment phase, and up to 100 days after the last dose of study drug.

Statistical Analysis

[0135] A study sample size of approximately 915 patients, randomized to the 3 treatment arms in a 1:1:1 ratio, was planned. For the comparison of progression-free survival, the number of events projected to be observed at a follow-up of at least 9 months provided approximately 83% power to detect an average hazard ratio of 0.71 with a type I error of 0.005 (two-sided). Progression-free survival was compared between nivolumab plus ipilimumab and ipilimumab alone, and between nivolumab alone and ipilimumab alone with the use of a two-sided log-rank test stratified according to PD-L1 status, BRAF mutation status, and metastasis stage (as described above). The study was not designed for a formal statistical comparison between the nivolumab alone and nivolumab plus ipilimumab groups. Hazard ratios and corresponding two-sided 99.5% confidence intervals (CIs) were estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. Progression-free survival curves, medians with 95% CIs, and progression-free survival rates at 6, 12, and 18 months with 95% CIs were estimated using Kaplan-Meier methodology. Overall survival will be analyzed when all patients have a minimum follow-up of 22 months.

Results

Patients and Treatment

[0136] From July 2013 through March 2014, a total of 1296 patients were enrolled at 137 centers in Australia, Europe, Israel, New Zealand, and North America. A total of 945 patients underwent randomization: 316 patients were assigned to the nivolumab group, 314 to the nivolumab plus ipilimumab group, and 315 to the ipilimumab group (~~Figure~~ Fig. 1). Baseline characteristics were balanced across the three groups. A total of 58.0% had stage M1c disease, 36.1% had an elevated lactate dehydrogenase level, 31.5% had a BRAF mutation, and 73.5% had negative PD-L1 status (Table 1).

[0137] All randomized patients had been followed for a minimum of 9 months at the time of database lock (February 17, 2015); 117 of 313 patients (37.4%) in the nivolumab group, 93 of 313 patients (29.7%) in the nivolumab plus ipilimumab group, and 50 of 311 patients (16.1%) in the ipilimumab group were continuing study treatment (Table 2). The most frequent reason for discontinuation was disease progression in the nivolumab and ipilimumab monotherapy groups (154 of 313 patients [49.2%] and 202 of 311 patients [65.0%], respectively), versus study drug toxicity in the nivolumab plus ipilimumab group (120 of 313 patients [38.3%]). The number of patients who had died was 85 (27.2%) in the nivolumab group, 86 (27.5%) in the nivolumab plus ipilimumab group, and 114 (36.7%) in the ipilimumab group.

[0138] The median number of doses in patients who received nivolumab alone or ipilimumab alone was 15 (range 1-38) and 4 (1-4), respectively. In the combination group, the median number of doses was 4 (range 1-39) for nivolumab and 4 (range 1-4) for ipilimumab; 147 of 313 patients (47%) received four or more doses of nivolumab monotherapy after combination treatment.

Table 1. Baseline Characteristics of the Patients.

Characteristic	Nivolumab alone (N=316)	Nivolumab plus Ipilimumab (N=314)	Ipilimumab alone (N=315)	Total (N=945)
Age — yr				
Mean	58.7	59.3	60.8	59.6
Range	25–90	18–88	18–89	18–90
Age groups — no. (%)				
<65 yr	198 (62.7)	185 (58.9)	182 (57.8)	565 (59.8)
≥ 65, < 75 yr	79 (25.0)	94 (29.9)	89 (28.3)	262 (27.7)
≥ 75 yr	39 (12.3)	35 (11.1)	44 (14.0)	118 (12.5)
Sex — no. (%)				
Male	202 (63.9)	206 (65.6)	202 (64.1)	610 (64.6)
Female	114 (36.1)	108 (34.4)	113 (35.9)	335 (35.4)
ECOG performance status — no. (%)				
0	238 (75.3)	230 (73.2)	224 (71.1)	692 (73.2)
1	77 (24.4)	83 (26.4)	91 (28.9)	251 (26.6)
2	1 (0.3)	0	0	1 (0.1)
Not reported	0	1 (0.3)	0	1 (0.1)
M stage — no. (%)				
M1c	184 (58.2)	181 (57.6)	183 (58.1)	548 (58.0)
M0, M1a, or M1b	132 (41.8)	133 (42.4)	132 (41.9)	397 (42.0)
Lactate dehydrogenase — no. (%)*				
≤ ULN	196 (62.0)	199 (63.4)	194 (61.6)	589 (62.3)
>ULN	112 (35.4)	114 (36.3)	115 (36.5)	341 (36.1)
≤2x ULN	271 (85.8)	276 (87.9)	279 (88.6)	826 (87.4)

>2x ULN	37 (11.7)	37 (11.8)	30 (9.5)	104 (11.0)
Unknown	8 (2.5)	1 (0.3)	6 (1.9)	15 (1.6)
Brain metastases at baseline — no. (%)				
Yes	8 (2.5)	11 (3.5)	15 (4.8)	34 (3.6)
No	308 (37.5)	303 (96.5)	300 (95.2)	911 (96.4)
PD-L1 status — no. (%)				
Positive	80 (27.8)	68 (24.5)	75 (27.1)	223(26.4)
Negative	208 (72.2)	210 (75.5)	202 (72.9)	620 (73.5)
BRAF status — no. (%)				
Mutation	100 (31.6)	101 (32.2)	97 (30.8)	298 (31.5)
No mutation	216 (68.4)	213 (67.8)	218 (69.2)	647 (68.5)

* ULN denotes upper limit of normal.

Efficacy

- [0139]** The median progression-free survival was 6.5 months (95% confidence interval [CI], 4.3 to 9.5) in the nivolumab group, 11.5 months (95% CI, 8.9 to 16.5) in the nivolumab plus ipilimumab group, and 2.9 months (95% CI, 2.8 to 3.4) in the ipilimumab group (Fig. 2A). A significant improvement in progression-free survival was observed in the nivolumab plus ipilimumab group as compared with the ipilimumab group (hazard ratio, 0.42; 95% CI, 0.31 to 0.57; $P < 0.0001$) (Fig. 2A). A significant improvement in progression-free survival was also observed in the nivolumab group as compared with the ipilimumab group (hazard ratio, 0.57; 95% CI, 0.43 to 0.76; $P < 0.00001$) (Fig. 2A). The hazard ratio for the comparison between nivolumab plus ipilimumab and nivolumab groups was 0.74 (95% CI, 0.60 to 0.92).
- [0140]** Analyses of progression-free survival among prespecified patient subgroups showed a consistent improvement with nivolumab or nivolumab plus ipilimumab as compared with ipilimumab, including subgroups defined by PD-L1 status, BRAF mutation status, and metastasis stage (Figs. 3A and 3B). In the combination group, median PFS was 11.7 months (95% CI, 8.0 to not reached) among patients with a BRAF mutation and was 11.2 months (95% CI, 8.3 to not reached) in patients with wild-type BRAF (Fig. 3B). For patients with a positive PD-L1 tumor status, median progression-free survival in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups was 14.0 months (95% CI, 9.1 to not reached), 14.0 months (95% CI, 9.7 to not reached), and 3.9 months (95% CI, 2.8 to 4.2), respectively (Fig. 2B). For patients with a negative PD-L1 tumor status, median progression-free survival in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups was 5.3 months (95% CI, 2.8 to 7.1 months), 11.2 months (95% CI, 8.0 to not reached) and 2.8 months (95% CI, 2.8 to 3.1), respectively (Fig. 2C).
- [0141]** Investigator-assessed objective response rates were 43.7% (95% CI, 38.1 to 49.3%), 57.6% (95% CI, 52.0 to 63.2), and 19.0% (95% CI, 14.9 to 23.8) in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups, respectively (Table 3). The percentage of patients with a complete response was higher in the nivolumab plus ipilimumab group than in either the nivolumab or ipilimumab alone groups (11.5% vs.

8.9% and 2.2%) (Table 3). Time to objective response was similar in each group (Table 3), and the median duration of response was not reached in any of the groups.

[0142] Median reduction in the sum of the longest diameters of tumor target lesions was -34.5% (interquartile range: -75.4 to 15.4), -51.1% (-75.8 to -10.2), and 5.8% (-28.0 to 33.3) in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups, respectively (Figs. 4A-4C). Among patients with PD-L1-positive tumors, the objective response rates were 57.5% (95% CI, 45.9 to 68.5), 72.1% (95% CI, 59.9 to 82.3), and 21.3% (95% CI, 12.7 to 32.3) for the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups, respectively; in patients with PD-L1-negative tumors, the objective response rates were 41.3% (95% CI, 34.6 to 48.4), 54.8% (95% CI, 47.8 to 61.6), and 17.8% (95% CI, 12.8 to 23.8) (Table 4).

Adverse Events

[0143] Treatment-related adverse events of any grade occurred in 82.1%, 95.5%, and 86.2% of patients in the nivolumab, nivolumab plus ipilimumab groups, and ipilimumab groups, respectively (Table 5). The most common adverse events in the nivolumab group were fatigue (in 34.2% of patients), rash (in 21.7%), and diarrhea (in 19.2%). In the nivolumab plus ipilimumab and ipilimumab groups, diarrhea (in 44.1% and 33.1% of patients, respectively), fatigue (in 35.1% and 28.0%), and pruritus (in 33.2% and 35.4%) were most common (Table 5). The incidence of treatment-related adverse events of grade 3 or 4 was also higher in the nivolumab plus ipilimumab group than in either the nivolumab or ipilimumab groups (55.0% vs. 16.3% and 27.3%), with diarrhea being the most common (2.2%, 9.3%, and 6.1% in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups, respectively) (Table 5). Treatment-related adverse events of any grade leading to discontinuation occurred in 7.7%, 36.4%, and 14.8% of patients in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups, respectively, with the most common being diarrhea (in 1.9%, 8.3%, and 4.5%, respectively) and colitis (in 0.6%, 8.3%, and 7.7%, respectively) (Table 5). One death due to study-drug toxicity was reported in the nivolumab group (neutropenia) and one in the ipilimumab group (cardiac arrest), although such adverse events have not been associated with these drugs in prior studies. No treatment-related deaths were reported in the combination group.

Table 2. Patient Disposition.*

	Nivolumab alone (N=313)	Nivolumab plus Ipilimumab (N=313)	Ipilimumab alone (N=311)
Patients in the treatment period — no. (%)			
Continuing	117 (37.4)	93 (29.7)	50 (16.1)
Not continuing	196 (62.6)	220 (70.3)	261 (83.9)
Reason for not continuing the treatment — no. (%)			
Disease progression	154 (49.2)	69 (22.0)	202 (65.0)
Study drug toxicity	27 (8.6)	120 (38.3)	47 (15.1)
Adverse event unrelated to study drug	5 (1.6)	12 (3.8)	4 (1.3)
Patient request to discontinue treatment	5 (1.6)	5 (1.6)	4 (1.3)
Death	5 (1.6)	5 (1.6)	4 (1.3)
Maximum clinical benefit	2 (0.6)	2 (0.6)	0
Poor/non-compliance	1 (0.3)	1 (0.3)	1 (0.3)
Patient withdrew consent	0	3 (1.0)	0
Lost to follow-up	1 (0.3)	0	0
Patient no longer meets study criteria	0	1 (0.3)	0
Other	0	3 (1.0)	2 (0.6)
Patients in the study — no. (%)			
Continuing	223 (71.2)	221 (70.6)	189 (60.8)
Died	85 (27.2)	86 (27.5)	114 (36.7)
Not continuing	5 (1.6)	6 (1.9)	8 (2.6)

*At the time of database lock on February 17, 2015.

Table 3. Response to Treatment.

Response	Nivolumab alone (N=316)	Nivolumab plus Ipilimumab (N=314)	Ipilimumab alone (N=315)
Best overall response — no. (%)[†]			
Complete response	28 (8.9)	36 (11.5)	7 (2.2)
Partial response	110 (34.8)	145 (46.2)	53 (16.8)
Stable disease	34 (10.8)	41 (13.1)	69 (21.9)
Progressive disease	119 (37.7)	71 (22.6)	154 (48.9)
Could not be determined	25 (7.9)	21 (6.7)	32 (10.2)
Objective response[†]			
No. of patients (%) [95% CI]	138 (43.7 [38.1–49.3])	181 (57.6 [52.0–63.2])	60 (19.0 [14.9–23.8])
Estimated odds ratio (95% CI) [§]	3.40 (2.02–5.72)	6.11 (3.59–10.38)	---
Two-sided P value	<0.00001	<0.00001	---
Time to objective response — mo			
No. of responders	138	181	60
Median	2.78	2.76	2.79
Range	2.3–12.5	1.1–11.6	2.5–12.4

[†] Best overall response were assessed by the investigators with the use of RECIST v1.1.

[‡] Data include patients with a complete response and those with a partial response.

[§] Relative to ipilimumab alone.

Table 4. Objective Response Rate by PD-L1 Status.

PD-L1 Positive			
	Nivolumab alone (N=80)	Nivolumab plus Ipilimumab (N=68)	Ipilimumab alone (N=75)
Objective response[†]			
No. of patients (% [95% CI])	46 (57.5 [45.9–68.5])	49 (72.1 [59.9–82.3])	16 (21.3 [12.7–32.3])
Estimated odds ratio (95% CI) [§]	5.03 (2.44–10.37)	10.41 (4.63–23.40)	---
PD-L1 Negative			
	Nivolumab alone (N=208)	Nivolumab plus Ipilimumab (N=210)	Ipilimumab alone (N=202)
Objective response[†]			
No. of patients (% [95% CI])	86 (41.3 [34.6–48.4])	115 (54.8 [47.8–61.6])	36 (17.8 [12.8–23.8])
Estimated odds ratio (95% CI) [§]	3.25 (2.05–5.13)	5.90 (3.71–9.38)	---

[†] **Best overall response was assessed by the investigators with the use of RECIST v1.1.**

[§] Relative to ipilimumab alone.

[0144] The most frequent grade 3 or 4 treatment-related select adverse events were diarrhea (2.2%, 9.3%, and 6.1% of patients in the nivolumab, nivolumab plus ipilimumab, and ipilimumab groups, respectively), colitis (in 0.6%, 7.7%, and 8.7%, respectively), increased alanine aminotransferase (in 1.3%, 8.3%, and 1.6%, respectively), and increased aspartate aminotransferase (in 1.0%, 6.1%, and 0.6%, respectively) (Table 6). With the use of immune modulatory agents, resolution rates for grade 3 or 4 select adverse events were generally similar across treatment groups, and were between 85-100% across organ categories in the nivolumab plus ipilimumab group. As observed in prior studies, most endocrine events in all treatment groups did not resolve (Table 7).

Discussion

[0145] In this randomized, double-blind, phase 3 study, both nivolumab alone and the combination of nivolumab and ipilimumab significantly increased progression-free survival and objective response rates, as compared with ipilimumab alone, in previously untreated advanced melanoma. These results were observed independently of PD-L1 tumor status, BRAF mutation status, or metastasis stage. Baseline characteristics of study participants were typical of patients with advanced melanoma, although the BRAF mutation rate (31.5%) was lower than the 40-50% generally reported for advanced disease. While not a primary end point of the study, the combination of nivolumab and ipilimumab resulted in numerically longer progression-free survival and a higher response rate as compared with nivolumab alone in the overall study population. While time to response was similar between groups, the first tumor assessment was done at week 12 and thus the possibility that responses may have occurred earlier with the combination remains unknown.

Table 5. Adverse Events (Safety Population).*

Event	Nivolumab alone (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab alone (N=311)	
	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4
	<i>no. of patients with event (%)</i>					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event [†]	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine aminotransferase	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate aminotransferase	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

* The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

† The treatment-related adverse events listed here were reported in at least 10% of the patients in any of the three study groups.

Table 6. Treatment-related Select Adverse Events (Safety Population).*

Event	Nivolumab alone (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab alone (N=311)	
	Total	Grade 3 or 4	Total	Grade 3 or 4	Total	Grade 3 or 4
<i>no. of patients with event (%)</i>						
Any select adverse event	194 (62.0)	24 (7.7)	275 (87.9)	124 (39.6)	229 (73.6)	58 (18.6)
Treatment-related select adverse event†						
Skin	131 (41.9)	5 (1.6)	185 (59.1)	18 (5.8)	168 (54.0)	9 (2.9)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	68 (21.7)	1 (0.3)	89 (28.4)	9 (2.9)	65 (20.9)	5 (1.6)
Rash maculo-papular	13 (4.2)	1 (0.3)	37 (11.8)	6 (1.9)	37 (11.9)	1 (0.3)
Vitiligo	23 (7.3)	1 (0.3)	21 (6.7)	0	12 (3.9)	0
Gastrointestinal	61 (19.5)	7 (2.2)	145 (46.3)	46 (14.7)	114 (36.7)	36 (11.6)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Hepatic	20 (6.4)	8 (2.6)	94 (30.0)	59 (18.8)	22 (7.1)	5 (1.6)
Increase in alanine aminotransferase	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Increase in aspartate aminotransferase	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Endocrine	45 (14.4)	2 (0.6)	94 (30.0)	15 (4.8)	34 (10.9)	7 (2.3)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Hyperthyroidism	13 (4.2)	0	31 (9.9)	3 (1.0)	3 (1.0)	0
Hypophysitis	2 (0.6)	1 (0.3)	24 (7.7)	5 (1.6)	12 (3.9)	6 (1.9)
Pulmonary	5 (1.6)	1 (0.3)	22 (7.0)	3 (1.0)	6 (1.9)	1 (0.3)
Pneumonitis	4 (1.3)	1 (0.3)	20 (6.4)	3 (1.0)	5 (1.6)	1 (0.3)

* The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

† The treatment-related select adverse events listed here were reported in at least 5% of the patients in any of the three study groups.

Table 7. Management of Treatment-related Select Adverse Events With Immune Modulatory Medication (IMM).

Select Adverse Event Organ Category	Nivolumab			Nivolumab plus Ipilimumab			Ipilimumab		
	Patients managed with IMM, n (%)	Patients with resolution of AE after treatment with IMM, n (%)	Median time to resolution, weeks (95% CI)	Patients managed with IMM, n (%)	Patients with resolution of AE after treatment with IMM, n (%)	Median time to resolution, weeks (95% CI)	Patients managed with IMM, n (%)	Patients with resolution of AE after treatment with IMM, n (%)	Median time to resolution, weeks (95% CI)
Skin Grade 3-4	33/131 (25.2) 3/5 (60.0)	17 (54.8) 3 (75.0)	34.9 (18.0, NE) 2.1 (0.9, NE)	80/185 (43.2) 12/18 (66.7)	55 (75.3) 12 (85.7)	8.6 (7.0, 12.6) 3.4 (1.1, 12.4)	58/168 (34.5) 5/9 (55.6)	41 (74.5) 5 (83.3)	12.4 (8.9, 19.1) 6.1 (4.4, NE)
Gastrointestinal Grade 3-4	9/61 (14.8) 5/7 (71.4)	5 (71.4) 3 (50.0)	4.0 (0.8, NE) NE (0.8, NE)	71/145 (49.0) 41/46 (89.1)	62 (93.9) 41 (97.6)	4.5 (3.5, 5.7) 3.0 (1.9, 4.3)	54/114 (47.4) 33/36 (91.7)	44 (88.0) 31 (88.6)	4.9 (2.9, 7.6) 4.7 (1.9, 6.1)
Endocrine Grade 3-4	5/45 (11.1) 2/2 (100)	2 (40.0) 0	24.3 (7.1, NE) NE (NE, NE)	36/94 (38.3) 10/15 (66.7)	14 (41.2) 5 (45.5)	NE (10.4, NE) NE (4.5, NE)	15/34 (44.1) 7/7 (100.0)	4 (28.6) 3 (42.9)	NE (0.71, NE) NE (0.43, NE)
Hepatic Grade 3-4	8/22 (36.4) 7/8 (87.5)	6 (100.0) 6 (100.0)	7.0 (2.0, 27.1) 7.0 (2.0, 27.1)	46/95 (48.4) 37/60 (61.7)	43 (95.6) 38 (100.0)	5.9 (3.3, 6.6) 4.1 (3.0, 6.1)	3/22 (13.6) 2/5 (40.0)	3 (100.0) 2 (100.0)	4.1 (4.0, 7.7) 5.9 (4.0, 7.7)
Pulmonary Grade 3-4	4/5 (80.0) 1/1 (100)	4 (100.0) 1 (100.0)	3.3 (2.3, 9.1) 2.3 (NE, NE)	17/22 (77.3) 2/3 (66.7)	16 (94.1) 2 (100.0)	6.1 (1.1, 8.3) 4.2 (1.1, 7.3)	3/6 (50.0) 1/1 (100)	2 (66.7) 1 (100.0)	6.1 (6.0, 6.3) 4.7 (NE, NE)
Renal Grade 3-4	1/3 (33.3) 0/1	1 (100.0) 0	0.3 (NE, NE) -	4/17 (23.5) 3/6 (50.0)	3 (100.0) 3 (100.0)	1.7 (0.4, 3.7) 1.7 (0.4, 3.6)	3/8 (37.5) 1/1 (100)	3 (100.0) 1 (100.0)	4.6 (0.6, 16.1) 4.6 (NE, NE)

[0146] The median progression-free survival reported for the combination of nivolumab and ipilimumab in this study (11.7 months in BRAF-mutant patients) is similar to that recently reported for the combination of BRAF and MEK inhibition in BRAF-mutant metastatic melanoma (9.9 months for vemurafenib and cobimetinib; 9.3 to 11.4 months for dabrafenib and trametinib). Resistance to such targeted therapies is almost inevitable when used as monotherapy and in many cases is very rapid. The confirmed rate of objective response for combined nivolumab and ipilimumab (57.6%) is numerically higher than observed with PD-1 blockade alone in advanced melanoma (nivolumab [40%] in treatment-naïve patients with wild-type BRAF or pembrolizumab [37%] in ipilimumab-naïve patients).

[0147] The results of subgroup analyses suggest that the greatest benefit for the combination of nivolumab and ipilimumab versus nivolumab alone may occur in the setting of negative PD-L1 tumor expression. In the PD-L1-positive group, both nivolumab alone and nivolumab plus ipilimumab resulted in a similar prolongation of progression-free survival as compared with ipilimumab alone, although objective response rates were numerically higher in the combination group versus either nivolumab or ipilimumab alone. Thus, the use of PD-L1 as a biomarker may allow clinicians to make more informed decisions about the risk-benefit of combination therapy versus monotherapy. Nonetheless, the observation of at least additive activity of the combination of ipilimumab and nivolumab in the setting of negative PD-L1 expression is of interest in melanoma as well as in other tumor types in which PD-1 checkpoint inhibitors are under evaluation.

[0148] The incidence of adverse events in this study was, in general, lowest in the nivolumab group and highest in the combination group. The overall incidence of grade 3 or 4 drug-related adverse events was higher in the combination group as compared with ipilimumab alone (39.6% versus 18.6%), as a result of a slightly higher incidence in most adverse events, particularly hepatic toxicity, where the rates of grade 3 or 4 ALT/AST elevations were 6-8% for the combination and approximately 1% for ipilimumab alone. One drug-related death was reported in each of the nivolumab and ipilimumab groups but none in the combination group. Overall, the safety profile of the combination of nivolumab and ipilimumab was consistent with previous experience with nivolumab or ipilimumab alone. No new safety signals were identified, and adverse events were manageable with established treatment guidelines as most

select adverse events resolved with immune modulatory agents. These data suggest that the combination of nivolumab and ipilimumab can be used safely in a broad range of clinical settings.

[0149] In summary, the report shows increased progression-free survival and objective response rates for nivolumab alone and the combination of nivolumab and ipilimumab, as compared with ipilimumab alone, in previously untreated advanced melanoma. Adverse events with the combination were managed with established algorithms, with no study drug-related deaths. The combination of nivolumab and ipilimumab may represent a means to improve outcomes with either agent as monotherapy, particularly for patients having PD-L1-negative tumors. Overall, nivolumab alone and the combination of nivolumab and ipilimumab are promising treatment options for previously untreated advanced melanoma.

SEQUENCES

V_H amino acid sequence of 28-8 (*Oryctolagus cuniculus*) (SEQ ID NO:1)

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly Val Gln Cys Leu Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Thr Ile Thr Asn Tyr His Met Phe Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile Thr Ser Ser Gly Ile Gly Ser Ser Ser Thr Thr Tyr Tyr Ala Thr Trp Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asn Leu Arg Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Asp Tyr Phe Thr Asn Thr Tyr Tyr Ala Leu Asp Ile Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser

V_L amino acid sequence of 28-8 (*Oryctolagus cuniculus*) (SEQ ID NO:2)

Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp Leu Pro Gly Ala Arg Cys Ala Leu Val Met Thr Gln Thr Pro Ser Ser Thr Ser Thr Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser Gln Ser Ile Ser Val Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ser Ala Ser Thr Leu Ala Ser Gly Val Pro Ser Arg Phe Lys Gly Ser Arg Ser Gly Thr Glu Tyr Thr Leu Thr Ile Ser Gly Val Gln Arg Glu Asp Ala Ala Thr Tyr Tyr Cys Leu Gly Ser Ala Gly Ser

Heavy Chain CDR1 sequence of 28-8 (*Oryctolagus cuniculus*) (SEQ ID NO:3)

Asn Tyr His Met Phe

Heavy Chain CDR2 sequence of 28-8 (*Oryctolagus cuniculus*) (SEQ ID NO:4)

Val Ile Thr Ser Ser Gly Ile Gly Ser Ser Ser Thr Thr Tyr Tyr Ala Thr Trp Ala Lys Gly

Heavy Chain CDR3 sequence of 28-8 (*Oryctolagus cuniculus*) (SEQ ID NO:5)

Asp Tyr Phe Thr Asn Thr Tyr Tyr Ala Leu Asp Ile

Light Chain CDR1 sequence of 28-8 (*Oryctolagus cuniculus*) (SEQ ID NO:6)

Gln Ala Ser Gln Ser Ile Ser Val Tyr Leu Ala

Light Chain CDR2 sequence of 28-8 (*Oryctolagus cuniculus*) (SEQ ID NO:7)

Ser Ala Ser Thr Leu Ala Ser

Light Chain CDR3 sequence of 28-8 (*Oryctolagus cuniculus*) (SEQ ID NO:8)

Leu Gly Ser Ala Gly Ser Asp Asp Ala Ala

What is claimed is:

1. A method for treating a melanoma comprising:
 - (i) identifying a patient having a PD-L1-negative melanoma tumor; and
 - (ii) administering to the patient:
 - (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and
 - (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4.
2. A method for treating a melanoma comprising administering to a patient afflicted with a melanoma tumor:
 - (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and
 - (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4,

wherein the patient is identified as having a PD-L1-negative melanoma tumor prior to the administration.

3. A method for extending a progression-free survival period for over 8 months in a patient afflicted with a melanoma tumor comprising administering to the patient:
 - (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and
 - (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4,

wherein the patient is identified as having a PD-L1-negative melanoma tumor prior to the administration and wherein the patient demonstrates progression-free survival for over 8 months.

4. The method of claim 3, wherein the progression-free survival of the patient is extended after the administration for over about 11 months, about 12 months, about 13 months, about 14

months, about 15 months, about 16 months, about 17 months, about 18 months, about 2 years, about 3 years, about 4 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, or about 10 years.

5. The method of claim 4, wherein the progression-free survival of the patient is extended for over 11 months.
6. A method for reducing a tumor size at least by 10% in a patient afflicted with a melanoma tumor comprising administering to the patient:
 - (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and
 - (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4,

wherein the patient is identified as having a PD-L1-negative melanoma tumor prior to the administration and wherein the administration reduces the tumor size at least about 10%, about 20%, about 30%, about 40%, or about 50% compared to the tumor size prior to the administration.

7. The method of any one of claims 2 to 6, further comprising identifying the patient as having a melanoma tumor that does not express PD-L1 prior to the administration.
8. The method of any one of claims 1 to 7, wherein the patient is characterized by (i) extended progression-free survival for over 8 months, (ii) tumor size reduction at least about 10%, about 20%, about 30%, about 40%, or about 50% compared to the tumor size prior to the administration, or (iii) both.
9. A method for increasing an objective response rate to be higher than 40% in a patient population, each of whom is afflicted with a melanoma tumor, in a cancer treatment comprising administering to the patient:
 - (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and

(b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4,

wherein each patient is identified as having a PD-L1-negative melanoma tumor prior to the administration and wherein the objective response rate is higher than 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75%.

10. The method of claim 9, further comprising identifying each patient of the patient population as having a PD-L1-negative melanoma tumor prior to the administration.
11. The method of claim 9 or 10, wherein each patient of the patient population is further characterized by (i) extended progression-free survival for over 8 months, (ii) tumor size reduction at least about 10%, about 20%, about 30%, about 40%, or about 50% compared to the tumor size prior to the administration, or (iii) both.
12. The method of any one of claims 9 to 11, wherein the patient population comprises at least about 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 patients having a PD-L1-negative melanoma tumor.
13. A method for selecting a patient suitable for an anti-PD-1 antibody and anti-CTLA-4 antibody combination therapy comprising:
 - (i) identifying a patient having a PD-L1-negative melanoma tumor; and
 - (ii) instructing a healthcare provider to administer to the patient:
 - (a) an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and
 - (b) an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4.
14. The method of any one of claims 1, 7, 10, and 13, wherein the identifying comprises measuring a PD-L1 expression on the melanoma tumor.
15. The method of any one of claims 1 to 14, wherein the administration treats the melanoma tumor.

16. The method of claim 14 or 15, wherein the measuring comprises providing a test tissue sample obtained from the patient, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells.
17. The method of claim 16, wherein the measuring further comprises assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface.
18. The method of claim 17, wherein the test tissue sample is a formalin-fixed paraffin-embedded (FFPE) tissue sample.
19. The method of claim 18, wherein the presence of PD-L1 is determined using an automated IHC assay.
20. The method of claim 19, wherein the IHC assay is performed using an anti-PD-L1 monoclonal antibody that specifically binds to the PD-L1 and wherein the anti-PD-L1 monoclonal antibody is selected from the group consisting of 28-8, 28-1, 28-12, 29-8, 5H1, and any combination thereof.
21. The method of any one of claims 1 to 20, wherein the PD-L1-negative melanoma tumor is characterized by having less than about 5%, about 4%, about 3%, about 2%, about 1%, or about 0% of tumor cells showing binding to the anti-PD-L1 antibody or an antigen-binding portion thereof.
22. The method of any one of claims 1 to 21, wherein the anti-PD-1 antibody or antigen-binding portion thereof cross-competes with nivolumab for binding to human PD-1.
23. The method of any one of claims 1 to 22, wherein the anti-PD-1 antibody or antigen-binding portion thereof is a chimeric, humanized or human monoclonal antibody or a portion thereof.
24. The method of any one of claims 1 to 23, wherein the anti-PD-1 antibody or antigen-binding portion thereof comprises a heavy chain constant region which is of a human IgG1 or IgG4 isotype.
25. The method of any one of claims 1 to 24, wherein the anti-PD-1 antibody is nivolumab.

26. The method of any one of claims 1 to 24, wherein the anti-PD-1 antibody is pembrolizumab.
27. The method of any one of claims 1 to 26, wherein the anti-PD-1 antibody or antigen-binding portion thereof is administered at a dose ranging from 0.1 to 10.0 mg/kg body weight once every 2, 3 or 4 weeks.
28. The method of claim 27, wherein the anti-PD-1 antibody or antigen-binding portion thereof is administered at a dose of 1 or 3 mg/kg body weight once every 3 weeks.
29. The method of any one of claims 1 to 28, wherein the anti-CTLA-4 antibody or antigen-binding portion thereof cross-competes with ipilimumab for binding to human CTLA-4.
30. The method of any one of claims 1 to 29, wherein the anti-CTLA-4 antibody or antigen-binding portion thereof is a chimeric, humanized or human monoclonal antibody or a portion thereof.
31. The method of any one of claims 1 to 30, wherein the anti-CTLA-4 antibody or antigen-binding portion thereof comprises a heavy chain constant region which is of a human IgG1 isotype.
32. The method of any one of claims 1 to 31, wherein the anti-CTLA-4 antibody is ipilimumab.
33. The method of any one of claims 1 to 31, wherein the anti-CTLA-4 antibody is tremelimumab.
34. The method of any one of claims 1 to 33, wherein the anti-CTLA-4 antibody or antigen-binding portion thereof is administered at a dose ranging from 0.1 to 10.0 mg/kg body weight once every 2, 3 or 4 weeks.
35. The method of claim 34, wherein the anti-CTLA-4 antibody or antigen-binding portion thereof is administered at a dose of 1 or 3 mg/kg body weight once every 3 weeks.
36. The method of claim 35, wherein the anti-PD-1 antibody or an antigen-binding portion thereof is administered at a dose of 1 mg/kg body weight once every 3 weeks and the anti-

CTLA-4 antibody or an antigen-binding portion thereof is administered at a dose of 3 mg/kg body weight once every 3 weeks.

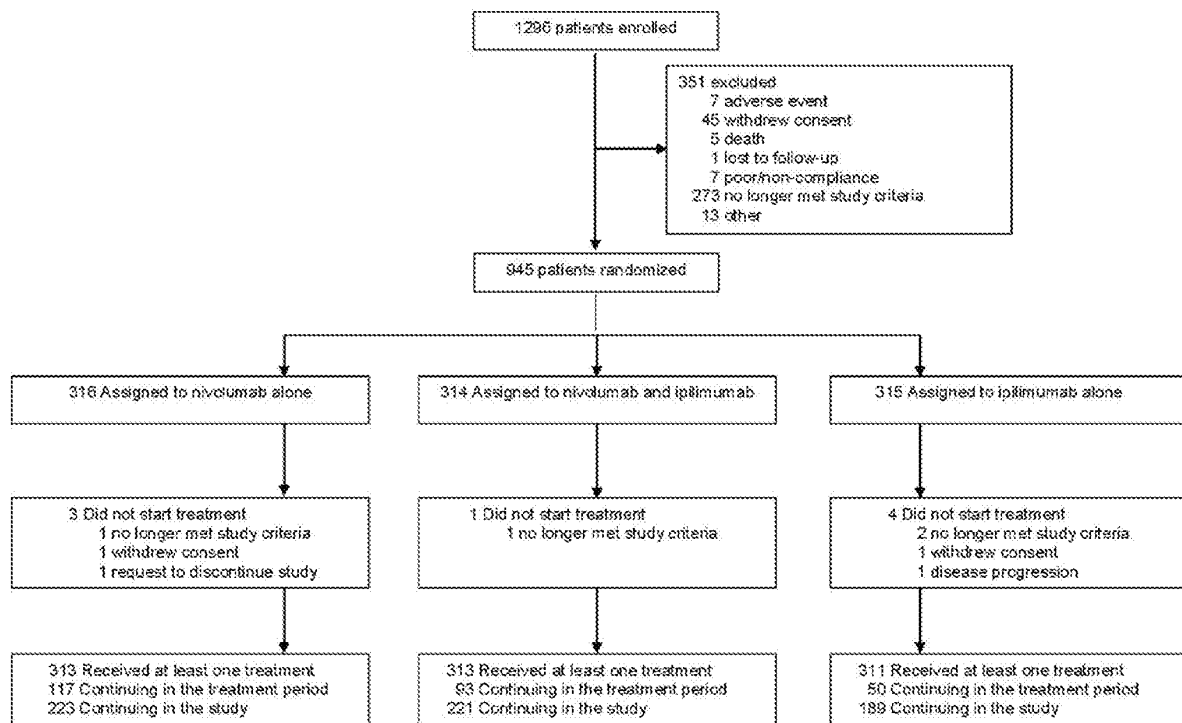
37. The method of any of claims 1 to 36, wherein the anti-PD-1 antibody or an antigen-binding portion thereof is administered concurrently with the anti-CTLA-4 antibody or an antigen-binding portion thereof.
38. The method of any of claims 1 to 36, wherein the anti-PD-1 antibody or an antigen-binding portion thereof is administered prior to or after the anti-CTLA-4 antibody or an antigen-binding portion thereof.
39. The method of any of claims 1 to 36, wherein the anti-PD-1 antibody or an antigen-binding portion thereof and the anti-CTLA-4 antibody or an antigen-binding portion thereof are in a single pharmaceutical composition.
40. The method of claim 39, wherein the pharmaceutical composition comprises the anti-PD-1 antibody and the anti-CTLA-4 antibody at a ratio of 50:1 to 1:50.
41. The method of claim 39, wherein the pharmaceutical composition comprises the anti-PD-1 antibody and the anti-CTLA-4 antibody at a ratio of 10:1 to 1:10.
42. The method of claim 39, wherein the pharmaceutical composition comprises the anti-PD-1 antibody and the anti-CTLA-4 antibody at a ratio of 3:1 to 1:3.
43. The method of claim 39, wherein the pharmaceutical composition comprises the anti-PD-1 antibody and the anti-CTLA-4 antibody at a ratio of 1:3.
44. The method of claim 39, wherein the pharmaceutical composition comprises 80 mg of the anti-PD-1 antibody and 240 mg of the anti-CTLA-4 antibody.
45. The method of claim any of claims 1 to 38, wherein the anti-PD-1 and anti-CTLA-4 antibodies are administered within 30 minutes of each other.

46. The method of any one of claims 1 to 45, further comprising administering an anti-cancer agent.
47. A kit for treating a patient afflicted with a melanoma tumor, the kit comprising:
- (a) a dosage ranging from 0.1 to 10 mg/kg body weight of an anti-PD-1 antibody or an antigen-binding portion thereof;
 - (b) a dosage ranging from 0.1 to 10 mg/kg body weight of an anti-CTLA-4 antibody or an antigen-binding portion thereof; and
 - (c) instructions for using the anti-PD-1 antibody or the antigen-binding portion thereof and the anti-CTLA-4 antibody or the antigen-binding portion thereof in the method of any one of claims 1 to 46.

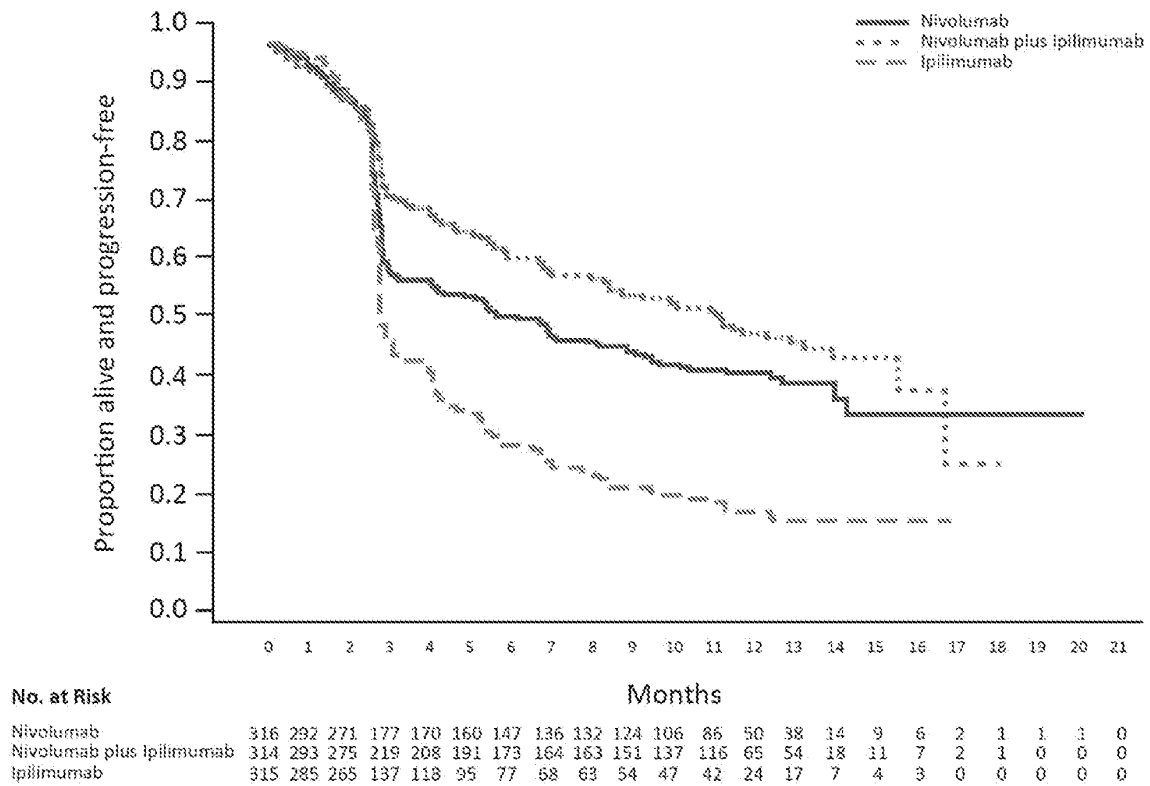
ABSTRACT

The invention provides a method of treating a melanoma comprising (i) identifying a patient having a PD-L1-negative melanoma and (ii) administering to the patient a combination of an anti-PD-1 antibody or an antigen-binding portion thereof and an anti-CTLA-4 antibody or an antigen-binding portion thereof. The methods of the invention can extend progression-free survival for over 8 months and/or reduces the tumor size at least about 10%, about 20%, about 30%, about 40%, or about 50% compared to the tumor size prior to the administration.

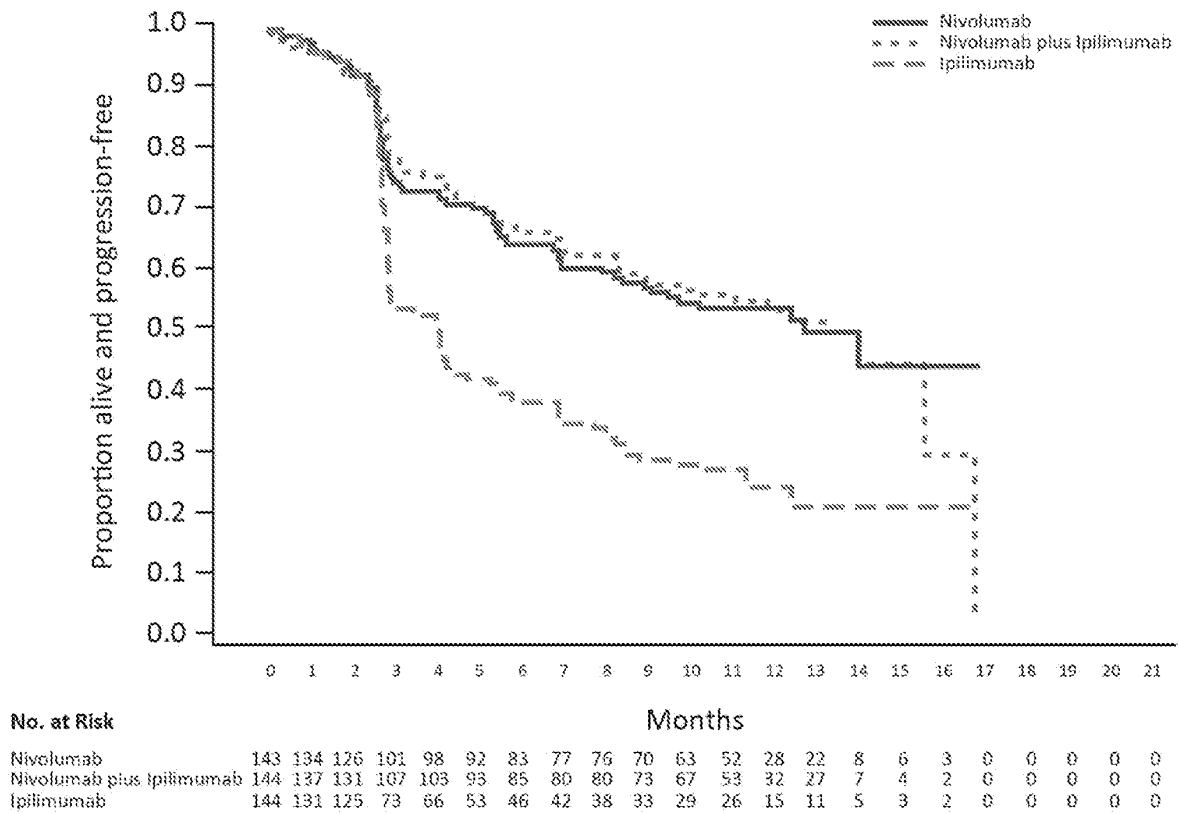
Fig. 1 – Patient Flow Diagram: Enrollment, Randomization, and Follow-up of Patients in the Study



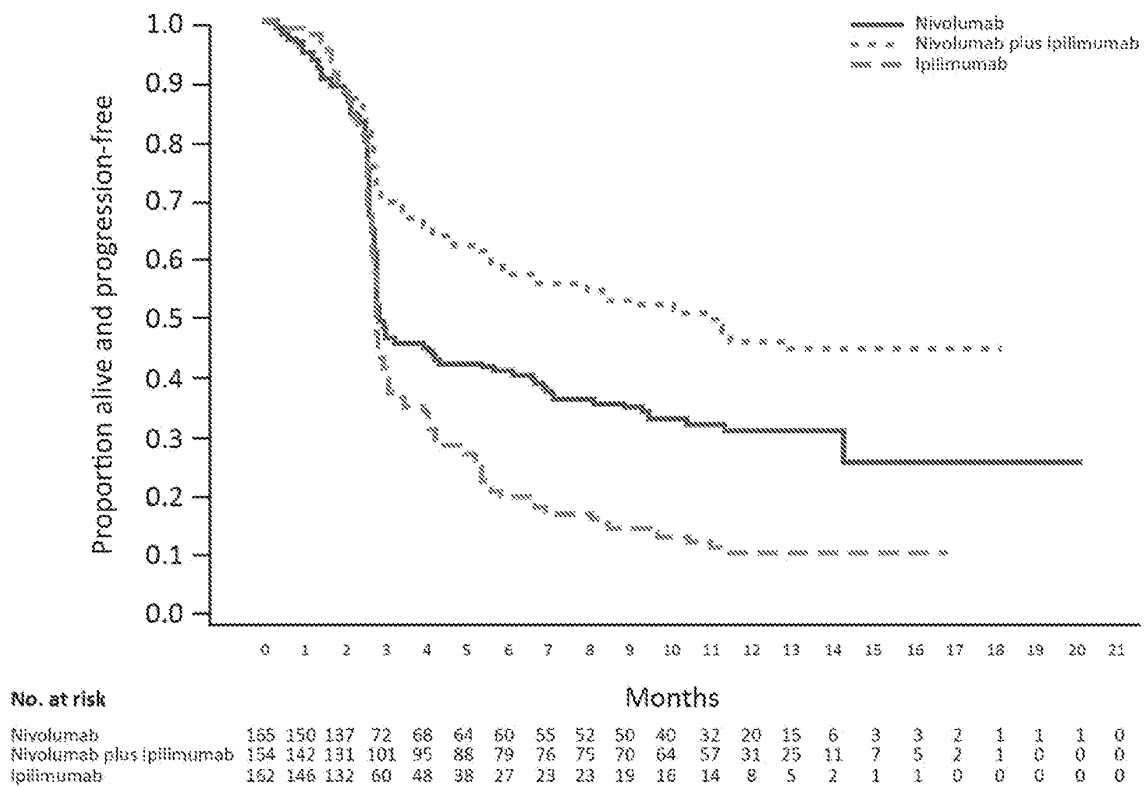
Atty Dkt No 3338.0330003

Fig. 2A – Progression-free Survival (Intention-to-Treat Population)

Atty Dkt No 3338.0330003

Fig. 2B – Progression-free Survival in Patients with Positive PD-L1 Status

Atty Dkt No 3338.0330003

Fig. 2C – Progression-free Survival in Patients with Negative PD-L1 Status

Atty Dkt No 3338.0330003

Fig. 3 – Subgroup Analyses of Progression-free Survival

Fig. 3A Nivolumab versus ipilimumab

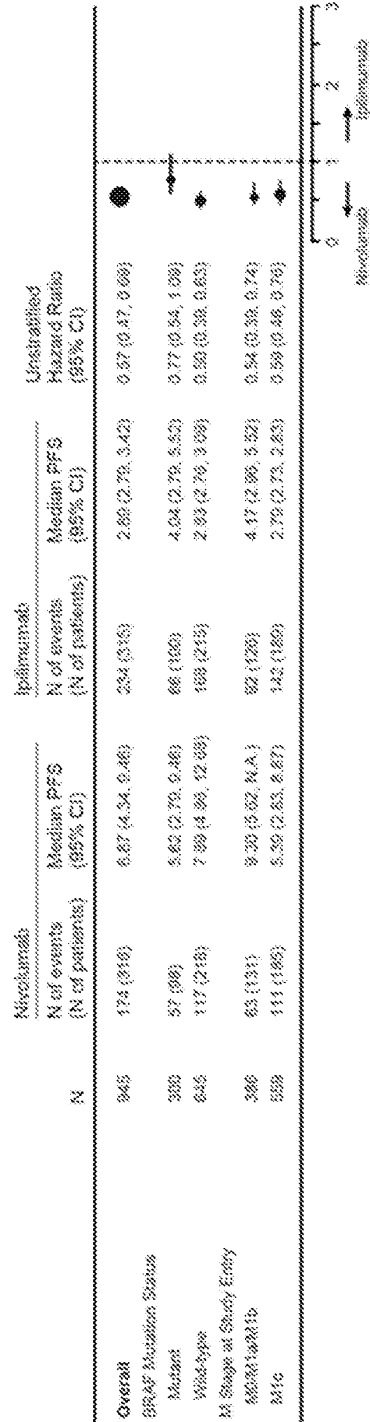
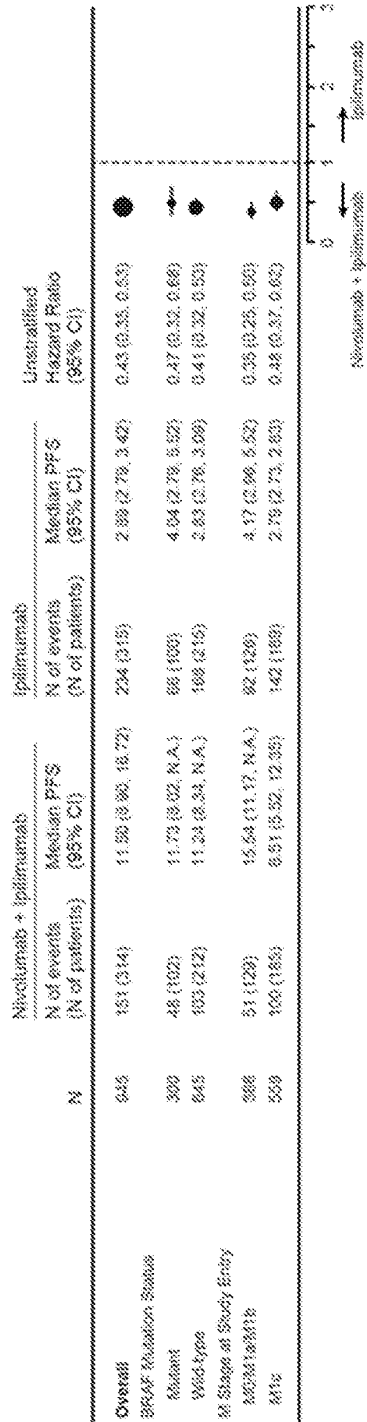
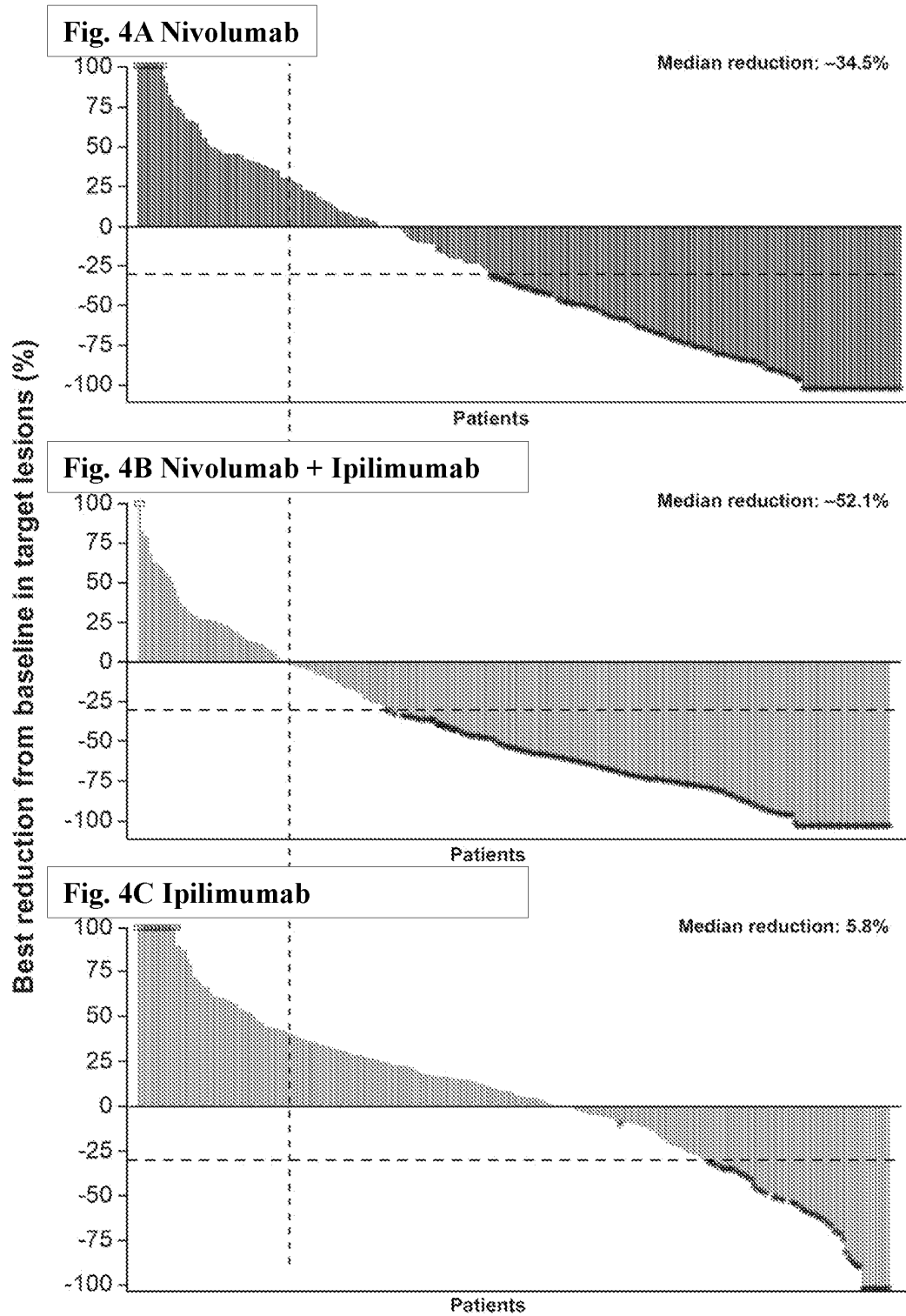


Fig. 3B Nivolumab plus ipilimumab versus ipilimumab





Atty Dkt No 3338.0330003

SCORE Placeholder Sheet for IFW Content

Application Number: 16240316

Document Date: 01/04/2019

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Sequence Listing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
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SCORE Placeholder Sheet for IFW Content

Application Number: 16240316

Document Date: 01/04/2019

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Drawing

At the time of document entry (noted above):

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- External customers may access SCORE content via PAIR using the Supplemental Content tab.

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Sequence Listing was accepted.
See attached Validation Report.
If you need help call the Patent Electronic Business Center at (866)
217-9197 (toll free).
Reviewer: Wheat Jr, Scott (ASRC)
Timestamp: [year=2019; month=1; day=8; hr=9; min=26; sec=56; ms=504;]
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Validated By CRFValidator v 1.0.5

Application No: 16240316 Version No: 1.0

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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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
16/240,316	01/04/2019	Arvin YANG	3338.0330003/ELE/C- K/BMD

CONFIRMATION NO. 4170

115018

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

FORMALITIES LETTER



OC000000105183129

Date Mailed: 01/18/2019

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
- The application search fee must be submitted.
- The application examination fee must be submitted.
- Additional claim fees of \$ **5400** as an undiscounted entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.
The surcharge is due for any one of:
 - late submission of the basic filing fee, search fee, or examination fee,
 - late submission of inventor's oath or declaration,
 - filing an application that does not contain at least one claim on filing, or
 - submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. No entity status discount is in effect. If applicant is qualified for small entity status, a written assertion of small entity status must be submitted to establish small entity status. (See 37 CFR 1.27). If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- \$ **300** basic filing fee.
- \$ **160** surcharge.
- \$ **660** search fee.
- \$ **760** examination fee.
- \$ **1380** for **3** independent claims over 3.
- \$ **3200** for **32** total claims over 20.

- \$ **820** for multiple dependent claim surcharge.
- \$(**0**) previous unapplied payment amount.
- \$ **7280** TOTAL FEE BALANCE DUE.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice".
<https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html>

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at <http://www.uspto.gov/ebc>.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/fstefhanos/

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET Substitute for Form PTO-1360 (For use with Form PTO/SB/06)							Application Number 16240316		Filing Date				
							Applicant(s) Arvin YANG						
							* May be used for additional claims or amendments						
CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT			*		*		*	
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Alexandria, Virginia 22313-1450
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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
16/240,316	01/04/2019		0.00	3338.0330003/ELE/C-K/BMD	47	6

CONFIRMATION NO. 4170

115018

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

FILING RECEIPT



0000000103183128

Date Mailed: 01/18/2019

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)

Arvin YANG, Princeton, NJ;

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 15/141,769 04/28/2016 PAT 10174113
which claims benefit of 62/153,973 04/28/2015

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: 01/17/2019

page 1 of 3

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/240,316**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No
Title

TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY

Preliminary Class

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 16/240,316				
APPLICATION AS FILED - PART I										
(Column 1)		(Column 2)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY				
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	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), (j), 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))	52	minus 20 = *	32			x 100 =	3200			
INDEPENDENT CLAIMS (37 CFR 1.16(h))	6	minus 3 = *	3			x 460 =	1380			
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))							820			
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL		TOTAL	7120			
APPLICATION AS AMENDED - PART II										
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY		
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=		x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=		x	=
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE			TOTAL ADD'L FEE	
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=		x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=		x	=
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE			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.										

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Arvin YANG

Applicant: Bristol-Myers Squibb Co.

Application No.: 16/240,316

Filing Date: January 4, 2019

Title: **TREATMENT OF PD-L1
NEGATIVE MELANOMA USING
AN ANTI-PD-1 ANTIBODY AND
AN ANTI-CTLA-4 ANTIBODY**

Confirmation No.: 4170

Art Unit: *To Be Assigned*

Examiner: *To Be Assigned*

Atty. Docket: 3338.0330003/ELE/C-K

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 begin on page 2 of this paper.

Remarks begin on page 6 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.

Electronic Patent Application Fee Transmittal				
Application Number:		16240316		
Filing Date:		04-Jan-2019		
Title of Invention:		TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY		
First Named Inventor/Applicant Name:		Arvin YANG		
Filer:		Brian Mason Dudley/Nikiya Alexander		
Attorney Docket Number:		3338.0330003/ELE/C-K/BMD		
Filed as Large Entity				
Filing Fees for Utility 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
Pages:				
Claims:				
Miscellaneous-Filing:				
LATE FILING FEE FOR OATH OR DECLARATION	1051	1	160	160
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1880

Electronic Acknowledgement Receipt	
EFS ID:	35449774
Application Number:	16240316
International Application Number:	
Confirmation Number:	4170
Title of Invention:	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY
First Named Inventor/Applicant Name:	Arvin YANG
Customer Number:	115018
Filer:	Brian Mason Dudley/Nikiya Alexander
Filer Authorized By:	Brian Mason Dudley
Attorney Docket Number:	3338.0330003/ELE/C-K/BMD
Receipt Date:	18-MAR-2019
Filing Date:	04-JAN-2019
Time Stamp:	17:11:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$1880
RAM confirmation Number	031919INTEFSW17114200
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	2019-03-18- Transmittal-3338-0330003.pdf	203447	no	2
			3f003cd6d42e500f1b8bab028c041ef03585932c		
Warnings:					
Information:					
2		2019-03-18- PAM-3338-0330003.pdf	119171	yes	7
			bfd9f7a14f6c7a663648b6e6a3264cc61a1f05b5		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Applicant Arguments/Remarks Made in an Amendment		6	7	
	Claims		2	5	
	Preliminary Amendment		1	1	
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	37225	no	2
			5aab2c71abaaee8fd836da0d3cbc8bd1a1584a1		
Warnings:					
Information:					
Total Files Size (in bytes):			359843		

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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.

TRANSMITTAL FORM <i>(to be used for all correspondence after initial filing)</i>	Application Number	16/240,316
	Filing Date	January 4, 2019
	First Named Inventor	Arvin Yang
	Art Unit	To Be Assigned
	Examiner Name	To Be Assigned
Total Number of Pages in This Submission	Attorney Docket Number	3338.0330003/ELE/C-K

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): \$1720.00 payment of Patent Application fee (including basic filing, search and examination fees); and \$160.00 payment of Surcharge for late filing fee
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	/Brian M. Dudley/	
Printed name	Brian M. Dudley	
Date	March 18, 2019	Reg. No. 77,546

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 and 1.14. 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.

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

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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.

Remarks

Upon entry of the foregoing amendment, claims 2, 3, 8, 14, 16-18, 20, 21, 25, 32, 34-38, 46, and 48-50 are pending in the application, with claims 1 and 50 being the independent claims. Claims 1, 4-7, 9-13, 15, 19, 22-24, 26-31, 33, 39-45, and 47 are sought to be canceled without prejudice to or disclaimer of the subject matter therein. Applicant reserves the right to pursue the cancelled subject matter in one or more continuing applications. Claims 2, 3, 8, 14, 16, 18, 20, 21, 25, 32, 34-38, and 46 are sought to be amended. New claims 48-49 are sought to be added.

Support for the amendments to the claims can be found throughout the specification as filed. Specifically, support for amended claims 2 and 36 and new claims 48-50 can be found, *inter alia*, at paragraphs [0115]-[0119], [0130], and [0131]. Support for amended claim 18 can be found, *inter alia*, at original claim 19. Support for amended claim 20 can be found, *inter alia*, at paragraphs [0102] and [0125]. Support for amended claim 21 can be found, *inter alia*, at paragraph [0047]. Support for amended claim 25 can be found, *inter alia*, at original claim 26. In addition, claims 3, 8, 14, 16, 18, 20, 21, 25, 32, 34-38, and 46 are amended for clarity, to update claim dependency, and/or for antecedent basis.

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

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.

/Brian M. Dudley/

Brian M. Dudley
Attorney for Applicant
Registration No. 77,546

Date: March 18, 2019

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

12850178

Amendments to the Claims

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

1. (Cancelled)
2. (Currently Amended) A method for treating a melanoma comprising administering to a patient afflicted with a melanoma tumor[[:]]
[[(a)]] an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1 ("anti-PD-1 antibody") at a flat dose of 240 mg once every two weeks or 480 mg once every four weeks; ~~and~~
~~— (b) — an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4;~~

~~wherein the patient is identified as having a PD-L1 negative melanoma tumor prior to the administration.~~
3. (Currently Amended) ~~The~~[[A]] method of claim 2 ~~for extending a progression free survival period for over 8 months in a patient afflicted with a melanoma tumor~~ further comprising administering to the patient:
~~— (a) — an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1; and~~
~~— (b) — an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4~~[[,]]("anti-CTLA-4 antibody")

~~wherein the patient is identified as having a PD-L1 negative melanoma tumor prior to the administration and wherein the patient demonstrates progression free survival for over 8 months.~~
- 4-7. (Cancelled)
8. (Currently Amended) The method of claim 2 ~~any one of claims 1 to 7~~, wherein the patient is characterized by (i) extended progression-free survival for over 8 months, (ii) tumor size

Atty. Dkt. No. 3338.0330003/ELE/C-K

reduction at least about 10%, about 20%, about 30%, about 40%, or about 50% compared to the tumor size prior to the administration, or (iii) both.

9-13. (Cancelled)

14. (Currently Amended) The method of claim 2 ~~any one of claims 1, 7, 10, and 13~~, further comprising wherein the identifying comprises measuring a PD-L1 expression on the melanoma tumor prior to the administration.

15. (Cancelled)

16. (Currently Amended) The method of claim 14 ~~or 15~~, wherein the measuring comprises providing a test tissue sample obtained from the patient, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells.

17. (Original) The method of claim 16, wherein the measuring further comprises assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface.

18. (Currently Amended) The method of claim 17, wherein the test tissue sample is a formalin-fixed paraffin- embedded (FFPE) tissue sample, and wherein the presence of PD-L1 is determined using an automated IHC assay.

19. (Cancelled)

20. (Currently Amended) The method of claim 18[[19]], wherein the IHC assay is performed using an anti-PD-L1 monoclonal antibody that specifically binds to the PD-L1 and wherein the anti-PD-L1 monoclonal antibody comprises a variable heavy chain region comprising the amino acid sequence set forth in SEQ ID NO: 1 and a variable light region comprising the amino acid sequence set forth in SEQ ID NO: 2 ~~is selected from the group consisting of 28-8, 28-1, 28-12, 29-8, 5H1, and any combination thereof~~.

21. (Currently Amended) The method of claim 2 ~~any one of claims 1 to 20~~, wherein the PD-L1-positive ~~negative~~ melanoma tumor is characterized by having less than at least about 5%;

Atty. Dkt. No. 3338.0330003/ELE/C-K

~~about 4%, about 3%, about 2%, about 1%, or about 0%~~ of tumor cells showing binding to the anti-PD-L1 antibody or an antigen-binding portion thereof.

22-24. (Cancelled)

25. (Currently Amended) The method of claim 2 ~~any one of claims 1 to 24~~, wherein the anti-PD-1 antibody is nivolumab or pembrolizumab.

26-31. (Cancelled)

32. (Currently Amended) The method of claim 3 ~~any one of claims 1 to 31~~, wherein the anti-CTLA-4 antibody is ipilimumab.

33. (Cancelled)

34. (Currently Amended) The method of claim 3 ~~any one of claims 1 to 33~~, wherein the anti-CTLA-4 antibody ~~or antigen-binding portion thereof~~ is administered at a dose ranging from 0.1 to 10.0 mg/kg body weight once every 2, 3 or 4 weeks.

35. (Currently Amended) The method of claim 34, wherein the anti-CTLA-4 antibody ~~or antigen-binding portion thereof~~ is administered at a dose of 1 or 3 mg/kg body weight once every 3 weeks.

36. (Currently Amended) The method of claim 34[[35]], wherein ~~the anti-PD-1 antibody or an antigen-binding portion thereof~~ is administered at a dose of 1 mg/kg body weight ~~once every 3 weeks~~ and the anti-CTLA-4 antibody ~~or an antigen-binding portion thereof~~ is administered at a flat dose of about 80 mg, about 160 mg, or about 240 mg ~~3 mg/kg body weight once every 3 weeks~~.

37. (Currently Amended) The method of claim 3 ~~any of claims 1 to 36~~, wherein the anti-PD-1 antibody ~~or an antigen-binding portion thereof~~ is administered concurrently with the anti-CTLA-4 antibody ~~or an antigen-binding portion thereof~~.

38. (Currently Amended) The method of claim 3 ~~any of claims 1 to 36~~, wherein the anti-PD-1 antibody ~~or an antigen-binding portion thereof~~ is administered prior to or after the anti-CTLA-4 antibody ~~or an antigen-binding portion thereof~~.
- 39-45. (Cancelled)
46. (Currently Amended) The method of claim 3 ~~any one of claims 1 to 45~~, further comprising administering an anti-cancer agent.
47. (Cancelled)
48. (New) The method of claim 3, wherein the anti-PD-1 antibody is administered at a flat dose of 240 mg once every two weeks.
49. (New) The method of claim 3, wherein the anti-PD-1 antibody is administered at a flat dose of 480 mg once every four weeks.
50. (New) A method for treating a melanoma in a patient afflicted with a melanoma tumor, comprising administering to the patient nivolumab as a monotherapy at a flat dose of 240 mg once every two weeks or 480 mg once every four weeks, wherein the patient is identified as having a PD-L1-positive melanoma tumor prior to the administration.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 16/240,316				
APPLICATION AS FILED - PART I										
(Column 1)		(Column 2)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY				
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	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), (j), 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))	20	minus 20 = *				x 100 =	0.00			
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	1720			
APPLICATION AS AMENDED - PART II										
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY		
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=		x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=		x	=
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
TOTAL ADD'L FEE									TOTAL ADD'L FEE	
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=		x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=		x	=
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
TOTAL ADD'L FEE									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
16/240,316	01/04/2019		1880	3338.0330003/ELE/C-K/BMD	20	2

CONFIRMATION NO. 4170

UPDATED FILING RECEIPT

115018

Sterne, Kessler, Goldstein & Fox P.L.L.C.

1100 New York Avenue NW

Washington, DC 20005



0000000108718643

Date Mailed: 03/22/2019

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)

Arvin YANG, Princeton, NJ;

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 15/141,769 04/28/2016 PAT 10174113
which claims benefit of 62/153,973 04/28/2015

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: 01/17/2019

page 1 of 3

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/240,316**

Projected Publication Date: 06/27/2019

Non-Publication Request: No

Early Publication Request: No
Title

TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY

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.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/240,316	01/04/2019	Arvin YANG	3338.0330003/ELE/C- K/BMD

CONFIRMATION NO. 4170

115018

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

PUBLICATION NOTICE



OC000000109229564

Title:TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY

Publication No.US-2019-0194328-A1

Publication Date:06/27/2019

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/>.

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			Art Unit	1644	
			Examiner Name	OUSPENSKI, Ilia I.	
			Attorney Docket Number	3338.0330003/ELE/C-K/BMD	
Sheet	1	of	12		

U. S. PATENT DOCUMENTS					
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		Number-Kind Code ² (if known)			
	US1	US-5977318-A	11-02-1999	LINSLEY; Peter S. et al.	
	US2	US-6051227-A	04-18-2000	ALLISON; James Patrick et al.	
	US3	US-6682736-B1	01-27-2004	HANSON; Douglas Charles et al.	
	US4	US-6808710-B1	10-26-2004	WOOD; Clive et al.	
	US5	US-6984720-B1	01-10-2006	KORMAN; Alan J. et al.	
	US6	US-7034121-B2	04-25-2006	CARRENO; Beatriz M. et al.	
	US7	US-7488802-B2	02-10-2009	COLLINS; Mary et al.	
	US8	US-7595048-B2	09-29-2009	HONJO; Tasuku et al.	
	US9	US-7605238-B2	10-20-2009	KORMAN; Alan J. et al.	
	US10	US-7943743-B2	05-17-2011	KORMAN; Alan J. et al.	
	US11	US-8008449-B2	08-30-2011	KORMAN; Alan J. et al.	
	US12	US-8168757-B2	05-01-2012	FINNEFROCK; Adam C. et al.	
	US13	US-8217149-B2	07-10-2012	IRVING; Bryan et al.	
	US14	US-8354509-B2	01-15-2013	CARVEN; Gregory John et al.	
	US15	US-8383796-B2	02-26-2013	KORMAN; Alan J. et al.	
	US16	US-8609089-B2	12-17-2013	LANGERMANN; Solomon et al.	
	US17	US-8686119-B2	04-01-2014	ROTEM-YEHUDAR RINAT et al.	
	US18	US-8779105-B2	07-15-2014	KORMAN; Alan J. et al.	
	US19	US-8900587-B2	12-02-2014	CARVEN; Gregory John et al.	
	US20	US-9084776-B2	07-21-2015	KORMAN; Alan J. et al.	
	US21	US-9102725-B2	08-11-2015	KORMAN; Alan J. et al.	
	US22	US-9273135-B2	03-01-2016	KORMAN; Alan J. et al.	

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			Art Unit	1644	
			Examiner Name	OUSPENSKI, Ilia I.	
			Attorney Docket Number	3338.0330003/ELE/C-K/BMD	
Sheet	2	of	12		

U. S. PATENT DOCUMENTS					
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		Number-Kind Code ² (if known)			
	US23	US-9358289-B2	06-07-2016	KORMAN; Alan J. et al.	
	US24	US-9387247-B2	07-12-2016	KORMAN; Alan J. et al.	
	US25	US-9492539-B2	11-15-2016	KORMAN; Alan J. et al.	
	US26	US-9492540-B2	11-15-2016	KORMAN; Alan J. et al.	
	US27	US-20060110383-A1	05-25-2006	HONJO; Tasuku et al.	
	US28	US-20120263677-A1	10-18-2012	EAGLE; Craig J. et al.	
	US29	US-20130017199-A1	01-17-2013	LANGERMANN; Solomon	
	US30	US-20130309250-A1	11-21-2013	COGSWELL; John et al.	
	US31	US-20150079109-A1	03-19-2015	LI; Kang et al.	
	US32	US-20160075782-A1	03-17-2016	KORMAN; Alan J. et al.	
	US33	US-20160362495-A1	12-15-2016	KORMAN; Alan J. et al.	
	US34	US-8168179-B2	05-01-2012	HONJO; Tasuku et al.	
	US35	US-8728474-B2	05-20-2014	HONJO; Tasuku et al.	
	US36	US-9067999-B1	06-30-2015	HONJO; Tasuku et al.	
	US37	US-9073994-B2	07-07-2015	HONJO; Tasuku et al.	
	US38	US-9212224-B2	12-15-2015	COGSWELL; John et al.	
	US39	US-9393301-B2	07-19-2016	HONJO; Tasuku et al.	
	US40	US-9402899-B2	08-02-2016	HONJO; Tasuku et al.	
	US41	US-9439962-B2	09-13-2016	HONJO; Tasuku et al.	
	US42	US-20150125463-A1	05-07-2015	COGSWELL; John P. et al.	
	US43	US-20160090417-A1	03-31-2016	COGSWELL; John P. et al.	
	US44	US-20160362489-A1	12-15-2016	YANG; Arvin et al.	

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			Art Unit	1644	
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		Number-Kind Code ² (if known)			
	US45	US-20170051060-A1	02-23-2017	HONJO; Tasuku et al.	
	US46	US-20170088615-A1	03-30-2017	ALAN; J. Korman	
	US47	US-20160022814-A1	01-28-2016	PETIT; R et al.	
	US48	US-20150290316-A1	10-15-2015	GRAZIANO; R.F. et al.	
	US49	US-20090217401-A1	08-27-2009	KORMAN; A.J. et al.	
	US50	US-9856320-B2	01-02-2018	COGSWELL; John P. et al.	
	US51	US-10174113-B2	01-08-2019	YANG; Arvin	
	US52	US-10441655-B2	10-15-2019	KORMAN; A.J. et al.	
	US53	US-20200138945-A1	05-07-2020	KORMAN; A.J. et al.	
	US54	US-20200062846-A1	02-27-2020	HONJO; Tasuku et al.	
	US55	US-10577423-B2	03-03-2020	COGSWELL; John P. et al.	
	US56	US-10604575-B2	03-31-2020	COGSWELL; John P. et al.	
	US57	US-10323093-B2	06-18-2019	COGSWELL; John P. et al.	
	US58	US-10266596-B1	04-23-2019	COGSWELL; John P. et al.	
	US59	US-10266595-B2	04-23-2019	COGSWELL; John P. et al.	
	US60	US-10266594-B2	04-23-2019	COGSWELL; John P. et al.	
	US61	US-10308714-B2	06-04-2019	COGSWELL; John P. et al.	
	US62	US-10316091-B2	06-11-2019	COGSWELL; John P. et al.	
	US63	US-10323092-B2	06-18-2019	COGSWELL; John P. et al.	
	US64	US-10138299-B2	11-27-2018	COGSWELL; John P. et al.	
	US65	US-10316090-B2	06-11-2019	COGSWELL; John P. et al.	
	US66	US-10072082-B2	09-11-2018	COGSWELL; John P. et al.	

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				Art Unit	1644
				Examiner Name	OUSPENSKI, Ilia I.
				Attorney Docket Number	3338.0330003/ELE/C-K/BMD
Sheet	4	of	12		

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	US67	US-20200308282-A1	10-01-2020	COGSWELL; John P. et al.	
	US68	US-20190135920-A1	05-09-2019	COGSWELL; John P. et al.	
	US69	US-20190153099-A1	05-23-2019	COGSWELL; John P. et al.	
	US70	US-20190112377-A1	04-18-2019	COGSWELL; John P. et al.	
	US71	US-20190112376-A1	04-18-2019	COGSWELL; John P. et al.	
	US72	US-20190100590-A1	04-04-2019	COGSWELL; John P. et al.	
	US73	US-20190092863-A1	03-28-2019	COGSWELL; John P. et al.	
	US74	US-20190100589-A1	04-04-2019	COGSWELL; John P. et al.	
	US75	US-20180319887-A1	11-08-2018	COGSWELL; John P. et al.	
	US76	US-20180312590-A1	11-01-2018	COGSWELL; John P. et al.	
	US77	US-20180282414-A1	06-18-2018	COGSWELL; John P. et al.	
	US78	US-20180282413-A1	10-04-2018	COGSWELL; John P. et al.	
	US79	US-20180273624-A1	09-27-2018	COGSWELL; John P. et al.	
	US80	US-20200010549-A1	01-09-2020	YANG; Arvin	

FOREIGN PATENT DOCUMENTS						
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		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
	FP1	WO-2006121168-A1	11-16-2006	ONO PHARMACEUTICAL CO., LTD. et al.		☐

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		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
	FP2	WO-2007005874-A2	01-11-2007	MEDAREX, INC. <i>et al.</i>		☐
	FP3	WO-2007113648-A2	10-11-2007	PFIZER PRODUCTS INC. <i>et al.</i>		☐
	FP4	WO-2012122444-A1	09-13-2012	PROVECTUS PHARMACEUTICALS, INC. <i>et al.</i>		☐
	FP5	WO-2012145493-A1	10-26-2012	AMPLIMMUNE, INC. <i>et al.</i>		☐
	FP6	WO-2013014668-A1	01-31-2013	CURETECH LTD. <i>et al.</i>		☐
	FP7	WO-2013173223-A1	11-21-2013	BRISTOL-MYERS SQUIBB COMPANY		☐
	FP8	WO-2004004771-A1	01-15-2004	ONO PHARMACEUTICAL CO [JP], <i>et al.</i>		☒
	FP9	WO-2015042246-A1	03-26-2015	SQUIBB BRISTOL MYERS CO [US]		☐
	FP10	WO-2016176503-A1	11-03-2016	BRISTOL-MYERS SQUIBB COMPANY [US]		☐
	FP11	WO-2016176504-A1	11-03-2016	BRISTOL-MYERS SQUIBB COMPANY [US]		☐

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Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)			Complete if Known		
			Application Number	16/240,316	
			Filing Date	January 4, 2019	
			First Named Inventor	YANG, Arvin	
			Art Unit	1644	
			Examiner Name	OUSPENSKI, Ilia I.	
			Attorney Docket Number	3338.0330003/ELE/C-K/BMD	
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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	ASCIERTO, P.A., <i>et al.</i> , "Biomarkers for Immunostimulatory Monoclonal Antibodies in Combination Strategies for Melanoma and Other Tumor Types," Clinical Cancer Research 19(5):1009-1020, American Association for Cancer Research, United States (2013).	☐	
	NPL2	ASCIERTO, P.A., <i>et al.</i> , "The Additional Facet of Immunoscore: Immunoprofiling as a Possible Predictive Tool for Cancer Treatment," Journal of Translational Medicine 11:54, BioMed Central Ltd., England, 4 pages (2013).	☐	
	NPL3	BRAHMER, J.R., <i>et al.</i> , "Safety and Activity of Anti-PD-L1 Antibody in Patients with Advanced Cancer," The New England Journal of Medicine 366(26):2455-2465, Massachusetts Medical Society, United States (2012).	☐	
	NPL4	CONDEELIS, J. and WEISSLEDER, R., "In Vivo Imaging in Cancer," Cold Spring Harbor Perspectives in Biology 2(12):a003848, Cold Spring Harbor Laboratory Press, United States (2010).	☐	
	NPL5	DONG, H., <i>et al.</i> , "Tumor-associated B7-H1 Promotes T-cell Apoptosis: A Potential Mechanism of Immune Evasion," Nature Medicine 8(8):793-800, Nature Publishing Company, United States (2002).	☐	
	NPL6	GADIOT, J., <i>et al.</i> , "Overall Survival and PD-L1 Expression in Metastasized Malignant Melanoma," Cancer 117(10):2192-2201, American Cancer Society, United States (2011).	☐	
	NPL7	GARBE, C., <i>et al.</i> , "Diagnosis and Treatment of Melanoma. European Consensus-based Interdisciplinary Guideline – Update 2012," European Journal of Cancer 48(15):2375-2390, Elsevier Ltd., England (2012).	☐	
	NPL8	GenBank, "cytotoxic T-lymphocyte-associated protein 4 [Homo sapiens]," Accession Number AAB59385.1, November 1, 1994, accessed at https://www.ncbi.nlm.nih.gov/protein/AAB59385 , accessed on December 6, 2016, 3 pages.	☐	

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	NPL9	GenBank, "RecName: Full=Programmed cell death 1 ligand 1; Short=PD-L1; Short=PD-CD1 ligand 1; Short=Programmed death ligand 1; AltName: Full=B7 homolog 1; Short=B7-H1; AltName: CD_antigen=CD274; Flags: Precursor," Accession Number Q9NZQ7.1, November 2, 2016, accessed at https://www.ncbi.nlm.nih.gov/protein/Q9NZQ7 , accessed on December 6, 2016, 11 pages.	☐
	NPL10	GenBank, "Human hPD-1 (hPD-1) mRNA, complete cds," Accession Number U64863.1, October 12, 2005, accessed at https://www.ncbi.nlm.nih.gov/nucleotide/U64863 , accessed on December 6, 2016, 3 pages.	☐
	NPL11	HAMANISHI, J., <i>et al.</i> , "Programmed Cell Death 1 Ligand 1 and Tumor-infiltrating CD8 ⁺ T Lymphocytes are Prognostic Factors of Human Ovarian Cancer," Proceedings of the National Academy of Sciences USA 104(9):3360-3365, National Academy of Sciences, United States (2007).	☐
	NPL12	HERBST, R.S., <i>et al.</i> , "A Study of MPDL3280A, an Engineered PD-L1 Antibody in Patients with Locally Advanced or Metastatic Tumors," Journal of Clinical Oncology 31(Suppl; Abstr 3000), American Society of Clinical Oncology, United States (2013).	☐
	NPL13	International Search Report and Written Opinion for International Application No. PCT/US2016/029877, European Patent Office, Rijswijk, mailed on July 13, 2016, 16 pages.	☐
	NPL14	KHLEIF, S., <i>et al.</i> , "MEDI4736, An Anti-PD-L1 Antibody with Modified Fc Domain: Preclinical Evaluation and Early Clinical Results from a Phase 1 Study in Patients with Advanced Solid Tumors," Abstract 802, in Proceedings from the European Cancer Congress 2013, Amsterdam, The Netherlands (September 27-October 1, 2013).	☐
	NPL15	MAHONEY, K.M., <i>et al.</i> , "The Next Immune-Checkpoint Inhibitors: PD-1/PD-L1 Blockade in Melanoma," Clinical Therapeutics 37(4):764-782, Elsevier HS Journals, Inc., United States (March 29, 2015).	☐

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	NPL16	MARZUKA, A., <i>et al.</i> , "Melanoma Treatments: Advances and Mechanisms," Journal of Cellular Physiology 230(11):2626-2633, Wiley Periodicals, Inc., United States (July 27, 2015).	☐	
	NPL17	MCCABE, K.E. and WU, A.M., "Positive Progress in ImmunoPET – Not Just a Coincidence," Cancer Biotherapy & Radiopharmaceuticals 25(3):253-261, Mary Ann Liebert, Inc., United States (2010).	☐	
	NPL18	National Comprehensive Cancer Network, "NCCN GUIDELINES," nccn.org, accessed at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site , accessed on December 8, 2016, 4 pages.	☐	
	NPL19	NCI Drug Dictionary, anti-PD-1 Fusion Protein AMP-224, accessed on December 1, 2016, retrieved from the Internet URL: https://www.cancer.gov/publications/dictionaries/cancer-drug?cdrid=700595 .	☐	
	NPL20	NCI Drug Dictionary, anti-PD-1 monoclonal antibody MEDI0680, accessed on December 1, 2016, retrieved from the Internet URL: https://www.cancer.gov/publications/dictionaries/cancer-drug?cdrid=756047 .	☐	
	NPL21	NCI Drug Dictionary, pembrolizumab, accessed on December 1, 2016, retrieved from the Internet URL: https://www.cancer.gov/drugdictionary?cancer-drug?cdrid=695789 .	☐	
	NPL22	OLAFSEN, T., <i>et al.</i> , "ImmunoPET imaging of B-Cell Lymphoma Using ¹²⁴ I-Anti-CD20 scFv Dimers (Diabodies)," Protein Engineering, Design & Selection 23(4):243-249, Oxford University Press, England (2010).	☐	
	NPL23	OTT, P.A., <i>et al.</i> , "CTLA-4 and PD-1/PD-L1 Blockade: New Immunotherapeutic Modalities with Durable Clinical Benefit in Melanoma Patients," Clinical Cancer Research 19(19):5300-5309, American Association of Cancer Research, United States (2013).	☐	

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	NPL24	PHILIPS, G.K. and ATKINS, M., "Therapeutic Uses of Anti-PD-1 and Anti-PD-L1 Antibodies," International Immunology 27(1):39-46, The Japanese Society for Immunology, Japan (October 16, 2014).	☐	
	NPL25	SIEGEL, R., <i>et al.</i> , "Cancer Statistics, 2013," CA: A Cancer Journal for Clinicians 63(1):11-30, American Cancer Society, United States (2013).	☐	
	NPL26	SJOBLOM, T., <i>et al.</i> , "The Consensus Coding Sequences of Human Breast and Colorectal Cancers," Science 314(5797):268-274, American Association for the Advancement of Science, United States (2006).	☐	
	NPL27	TAUBE, J.M., <i>et al.</i> , "Colocalization of Inflammatory Response With B7-H1 Expression in Human Melanocytic Lesions Supports an Adaptive Resistance Mechanism of Immune Escape," Science Translational Medicine 4(127):127ra37, American Association for the Advancement of Science, United States (2012).	☐	
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	NPL29	United States Adopted Name (USAN) Drug Finder, "Pembrolizumab: Statement on a nonproprietary name adopted by the USAN Council (ZZ-165)," published November 27, 2013, accessed at https://search.usan.ama-assn.org/usan/documentDownload?uri=%2Funstructured%2Fbinary%2Fusan%2Fpembrolizumab.pdf , accessed on December 8, 2016, 2 pages.	☐	
	NPL30	WANG, C., <i>et al.</i> , "In Vitro Characterization of the Anti-PD-1 Antibody Nivolumab, BMS-936558, and In Vivo Toxicology in Non-Human Primates," Cancer Immunology Research 2(9):846-856, American Association for Cancer Research, United States (May 28, 2014).	☐	

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	NPL31	WOLCHOK, J.D., <i>et al.</i> , "Nivolumab plus Ipilimumab in Advanced Melanoma," The New England Journal of Medicine 369(2):122-133, Massachusetts Medical Society, United States (2013).	☐	
	NPL32	BOWYER, S., <i>et al.</i> , "Efficacy and Toxicity of Treatment with the Anti-CTLA-4 Antibody Ipilimumab in Patients with Metastatic Melanoma after Prior Anti-PD-1 Therapy," British Journal of Cancer 114(10):1084-1089, Nature Publishing Group, England (May 2016).	☐	
	NPL33	NCCN GUIDELINES (2014), available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site , last accessed May 30, 2014.	☐	
	NPL34	Office Action mailed December 6, 2017, in United States Patent Application No. 15/141,772, Yang, A. <i>et al.</i> , filed April 28, 2016, 17 pages.	☐	
	NPL35	Office Action mailed April 12, 2018, in United States Patent Application No. 15/141,772, Yang, A. <i>et al.</i> , filed April 28, 2016, 13 pages.	☐	
	NPL36	TZARTOS, S.J., <i>et al.</i> , "Epitope Mapping by Antibody Competition. Methodology and Evaluation of the Validity of the Technique," Methods in Molecular Biology 66:55-66, Humana Press, United States (1996).	☐	
	NPL37	International Search Report and Written Opinion for International Application No. PCT/US2016/029878, European Patent Office, Rijswijk, mailed on July 13, 2016, 15 pages.	☐	
	NPL38	Kuenen, B., <i>et al.</i> "A Phase I Pharmacologic Study of Necitumumab (IMC-11 F8), a Fully Human IgG1 Monoclonal Antibody Directed Against EGFR in Patients with Advanced Solid Malignancies," <i>Clin Cancer Res.</i> , 16(6):1915-23, United States (2010).	☐	
	NPL39	Wang, D.D., <i>et al.</i> "Fixed Dosing Versus Body Size-Based Dosing of Monoclonal Antibodies in Adult Clinical Trials," <i>J Clin Pharmacol.</i> , 49(9):1012-24, United States (2009)	☐	

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	NPL40	Office Action mailed May 2, 2018, in United States Patent Application No. 15/311,409, Feltquate, D. <i>et al.</i> , filed November 15, 2016, 13 pages.	☐	
	NPL41	Office Action mailed June 13, 2018, in United States Patent Application No. 15/210,612, Manekas, D. <i>et al.</i> , filed July 14, 2016, 16 pages.	☐	
	NPL42	BAI, S., et al., "A Guide to Rational Dosing of Monoclonal Antibodies," Clin Pharmacokinetics 51(2):119-135, Springer-Business, United States (February 2012).	☐	
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	NPL44	PAN, S-D., et al., "Weight-based dosing in medication use: what should we know?," Patient Preference and Adherence 10:549-560, Dove Medical Press, United Kingdom (April 12, 2016).	☐	
	NPL45	OPDIVO (nivolumab) [package insert], 32 pages; Bristol-Myers Squibb: Approved by U.S. Food and Drug Administration, United States; (August 2018).	☐	
	NPL46	Advisory Action mailed August 3, 2018, in United States Patent Application No. 15/141,772, YANG, Arvin. <i>et al.</i> , filed April 28, 2016, 3 pages.	☐	
	NPL47	GETTINGER, S.N., et al., "Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients with Previously treated Advanced Non-Small-Cell Lung Cancer," Journal of Clinical Oncology 33(18): 2004-2012, American Society of Clinical Oncology, United States (June 2015).	☐	
	NPL48	JOHNSON, D. B., et al., "Immune Checkpoint Inhibitors in NSCLC," Current Treatment Option in Oncology 15(4):658-669, SpringerLink, United States (2014).	☐	

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	NPL49	Office Action mailed October 3, 2018 in United States Patent Application No. 15/141,772, Yang, A et al., filed April 28, 2016, 17 pages.	☐
	NPL50	ZHAO, X., et al., "Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors," Annals of Oncology: Official Journal of the European Society for Medical Oncology 28(8):2002-2008, Oxford Journals, England (2017).	☐
	NPL51	LONG, G.V., et al. "Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer," Annals of Oncology 29(11):2208-13 (November 1, 2018).	☐
	NPL52	POLLACK, M.H., et al., "Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma," Annals of Oncology 29(1):250-55 (January 1, 2018).	☐

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Examiner Signature		Date Considered	
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*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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Electronic Acknowledgement Receipt	
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Application Number:	16240316
International Application Number:	
Confirmation Number:	4170
Title of Invention:	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY
First Named Inventor/Applicant Name:	Arvin YANG
Customer Number:	115018
Filer:	Brian Mason Dudley/Jeanette Yando
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	2021-02-03-IDS-Pleading-3338-0330003.pdf	106824 13767f4e1f2d346d62fae85d3defdd888e7694fa	no	3
Warnings:					

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	2021-02-03-IDS-SB08A-B-3338-0330003.pdf	248776	no	12
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3	Non Patent Literature	NPL51_LONG-2018.PDF	130310	no	6
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Information:					
4	Non Patent Literature	NPL52_POLLACK-2018.PDF	138243	no	6
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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. <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

Inventor: Arvin YANG

Applicant: Bristol-Myers Squibb Company

Application No.: 16/240,316

Filing Date: January 4, 2019

Confirmation No.: 4170

Art Unit: 1644

Examiner: OUSPENSKI, Ilia I.

Atty. Docket: 3338.0330003/ELE/C-K/BMD

Title: **TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1
ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY**

Information Disclosure Statement

Mail Stop Amendment

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

Commissioner:

Listed on accompanying IDS Form 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 Form 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 document appears below in accordance with 37 C.F.R. § 1.98(a)(3).

Document **FP8**, WO-2004004771-A1, is in a foreign language. An English language abstract is appended to the face page of Document **FP8**. Additionally, Document **US45**, US-20170051060-A1, is believed to be an English language equivalent of Document **FP8**.

Copies of documents **NPL51-NPL52** 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-US80** on the attached IDS Form are submitted.

Copies of the **FP1-FP11** and **NPL1-NPL50** 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. 15/141,769, filed April 28, 2016 (now United States Patent No. 10,174,113 B2, issued January 8, 2019), 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. 15/141,769, filed April 28, 2016 (now United States Patent No. 10,174,113 B2, issued January 8, 2019), in accordance with MPEP 2001.06(b), and indicate in the next

Atty. Dkt. No. 3338.0330003/ELE/C-K/AHB

communication from the office that the art cited in the earlier prosecution history has been reviewed in connection with the present application.

It is respectfully requested that the Examiner initial and return a copy of the enclosed IDS Form, 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.

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Atty. Dkt. No. 3338.0330003/ELE/C-K/AHB



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/240,316	01/04/2019	Arvin YANG	3338.0330003/ ELE/C-K/BMD	4170
115018	7590	03/24/2021	EXAMINER	
Sterne, Kessler, Goldstein & Fox P.L.L.C. 1100 New York Avenue NW Washington, DC 20005			OUSPENSKI, ILIA I	
			ART UNIT	PAPER NUMBER
			1644	
			NOTIFICATION DATE	DELIVERY MODE
			03/24/2021	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

DETAILED ACTION

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

2. Applicant's preliminary amendment filed on 03/18/2019 is acknowledged. Claims 2-3, 8, 14, 16-18, 20-21, 25, 32, 34-38, 46 and 48-50 are pending.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

4. Applicant's attention is drawn to the language of claim 21, which defines PD-L1-positive tumor as having at least about 5% of tumor cells showing binding to an anti-PD-L1 antibody. Those skilled in the art often distinguish cell surface PD-L1 staining from intracellular staining when evaluating a tumor for PD-L1 expression. Applicant is invited to consider amending the claim or making a clarifying comment, if deemed appropriate.

5. The following is a quotation of **35 U.S.C. 112(b)**:

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

6. Claims 14, 16-18, 20-21 and 50 are rejected under **35 U.S.C. 112(b)** as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor regards as the invention.

(i) Claims 14, 16-18 and 20-21 are indefinite, because the recitation of a step of measuring PD-L1 expression on the tumor prior to administration of anti-PD-1 antibody appears to imply that the result of said measuring is somehow related to the step of administering, yet no indication of such relationship is provided.

(ii) Claim 21 is indefinite, because the recitations of “the PD-L1-positive melanoma tumor” and “the anti-PD-L1 antibody” lack proper antecedent basis in the base claim.

(iii) Claim 50 is indefinite in the recitation of a “PD-L1-positive melanoma tumor,” because it is unknown how PD-L1 positivity is defined.

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.

7. The following is a quotation of **35 U.S.C. 112(a)**:

(a) IN GENERAL.—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 or joint inventor of carrying out the invention.

8. Claims 2-3, 8, 14, 16-18, 20-21, 32, 34-38, 46 and 48-49 are rejected under **35 U.S.C. 112(a)** because the specification, while being enabling for a method for treating melanoma comprising administering
nivolumab or pembrolizumab at 240 mg every two weeks or 480 mg every four weeks,

with or without ipilimumab at 1 or 3 mg/kg every 3 weeks, or at about 80 mg, 160 mg, or 240 mg every 2, 3 or 4 weeks,

does not reasonably provide enablement for a method for treating melanoma comprising administering

a generically recited anti-PD-1 antibody at 240 mg every two weeks or 480 mg every four weeks,

with or without a generically recited anti-CTLA4 antibody at 1 or 3 mg/kg every 3 weeks, or at about 80 mg, 160 mg, or 240 mg every 2, 3 or 4 weeks.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in *In re Wands* (858 F.2d 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.

The claims are directed to methods of treating a disease by administering any antibody, including any type of antigen binding fragment thereof, which binds specifically to human PD-1, with or without any antibody or fragment which binds specifically to human CTLA4, according to exact dosing regimen.

A person of ordinary skill in the art is aware that optimal therapeutic dosage and administration schedule of a monoclonal antibody against a specified target protein depends on numerous antibody-intrinsic factors, including, to name a few, the target epitope, affinity and avidity to the epitope, off-target binding, penetration into the target tissue, half-life in various tissues, and binding to Fc receptors. Yet, even thorough

knowledge of these factors is insufficient to determine an appropriate dosing regimen, which requires clinical trials for each new antibody to the same target protein. Furthermore, a milligram of a full-length immunoglobulin contains fewer molecules than a milligram of an antigen-binding fragment, such as an scFv. Effective dosage also depends on any concurrent therapies.

As an example, nivolumab is approved by the FDA as a monotherapy for melanoma at the same regimen as recited in the present claims, i.e. 240 mg every 2 weeks or 480 mg every 4 weeks (Opdivo FDA Label, 2021). However, if used in combination with ipilimumab, the approved dose is 1 mg/kg every 3 weeks (1d), which corresponds to 80 mg for a typical patient. Pembrolizumab is approved for melanoma at 200 mg every 3 weeks (Keytruda FDA Label, 2020), which is a substantially lower dose compared to nivolumab. Another anti-PD-1 antibody, cemiplimab-rwlc, is approved (for metastatic cutaneous squamous cell carcinoma) at 350 mg every 3 weeks (Libtayo FDA Label, 2020).

As another example, Naing et al. (2019) report the results of a phase I clinical trial of yet another anti-PD-1 monoclonal antibody, MEDI0680. In Introduction, they review the state of the art as follows (internal references omitted):

“Nivolumab and pembrolizumab have shown different safety and efficacy profiles in varying tumor types, despite sharing the same mechanism of action. Antagonistic antibodies targeting the same protein may have the same mechanism of action, but differences in immunogenicity, binding affinity, plasma half-life, and tissue penetration could affect clinical efficacy, safety, and pharmacokinetics. Anti-PD-1 mAbs vary due to the degree of antibody humanization and sequence differences in their complementarity-determining regions (CDRs), which determine the precise epitopes bound on the target. MEDI0680 differs from nivolumab and pembrolizumab in its CDR sequence and affinity, which may impact its safety or clinical activity.”

Naing et al. tested MEDI0680 at 0.1, 0.5, 2.5, 10 and 20 mg/kg once every 2 or 3 weeks, and observed objective responses only at the highest doses, especially at 20 mg/kg every 2 weeks (the Abstract, p. 6-7, Table 4), which corresponds to 1600 mg per dose for a typical patient, i.e. 6.7-fold higher than the 240 mg dose recited in the present claims.

Accordingly, it would be clear to the skilled artisan that without at least a phase I or phase I/II clinical trial, it is unpredictable whether any anti-PD-1 antibody or anti-CTLA4 antibody or fragment other than nivolumab, pembrolizumab and ipilimumab would have clinically relevant therapeutic efficacy and acceptable toxicity if administered according to the dosing regimen recited in the claims.

Given the resource-intensive nature of clinical trials and the inherent risks to human health, the skilled artisan would reasonably conclude that experimentation required to determine whether a given antibody or fragment is sufficiently safe and effective if administered according to the recited regimen would be unnecessarily, and improperly, extensive and undue.

9. The following is a quotation of the appropriate paragraphs of **35 U.S.C. 102** that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.

(a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

10. Claims 2, 8, 14, 16-18, 21, 25 and 50 are rejected under **35 U.S.C. 102(a)(1)** as being anticipated by Opdivo FDA Label (March 2015; see entire document).

According to the Label, Opdivo (nivolumab) indicated for the treatment of patients with unresectable or metastatic melanoma, to be administered at 3 mg/kg every 2 weeks (e.g. p. 1). As average human body weight is conventionally assumed to be 80 kg, 3 mg/kg is equivalent to 240 mg.

Since the method taught by the Label is the same as recited in claim 2, the outcomes are inherently the same, including those recited in claim 3.

The Label further teaches that in clinical studies, PD-L1 expression had no clinically important effect on the clearance of nivolumab (p. 17), indicating that PD-L1 expression had been measured in those studies.

Claims 16-18 are included in the rejection, because assessing the proportion of positive cells by automated immunohistochemistry (IHC) of formalin-fixed paraffin-embedded tissue was a standard procedure for evaluating the expression of specific proteins in tumor samples, and as such would be at once envisaged by a person of ordinary skill in the art.

Claim 21 is included, because the recited definition of PD-L1-positive melanoma does not result in a manipulative difference of the claimed method from the method taught in the prior art.

Accordingly, the Label teaches all of the limitations of the claimed method, and as such anticipates the claimed invention.

11. Claims 2-3, 8, 14, 16-18, 20-21, 25, 32, 34-38, 46, 48 and 50 are rejected under **35 U.S.C. 102(a)(2)** as being anticipated by Cogswell et al. (US 20150125463; cited on IDS; see entire document).

Cogswell teaches a method of treating melanoma by administering nivolumab (BMS-936558, or 5C4) at a dose of 3 mg/kg every 2 weeks (e.g. [0266], [0268]). As average human body weight is conventionally assumed to be 80 kg, 3 mg/kg is equivalent to 240 mg. The treatment resulted in tumor size reduction and increased progression-free survival in some patients (e.g. [0285]-[0288], Tables 1-4, and Fig. 4).

Cogswell further teaches an automated IHC protocol for assessing PD-L1 expression in FFPE specimens using anti-PD-L1 antibody 28-8 (e.g. [0299]-[0300]). Antibody 28-8 has variable regions of SEQ ID NOS: 35 and 36, which are identical to instantly recited SEQ ID NOS: 1 and 2 (see SCORE). Cogswell teaches a preferable predetermined threshold value of 5 %, wherein the predetermined threshold value 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 [0053]. Accordingly, Cogswell teaches all of the limitations of claims 2, 8, 14, 16-18, 20-21, 25 and 50.

Cogswell further teaches a method of treating melanoma comprising combined administration of the anti-PD-1 and anti-CTLA-4 antibodies, such as nivolumab and ipilimumab, once every 2, 3 or 4 weeks, wherein the anti-PD-1 antibody is administered at 3 mg/kg, and the anti-CTLA4 antibody is administered at 1 mg/kg or 3 mg/kg (e.g. claims 14, 15, 22 and 23). 1 mg/kg corresponds to 80 mg, and 3 mg/kg corresponds to 240 mg. Accordingly, Cogswell explicitly teaches all dosing regimen of anti-PD-1 and anti-CTLA4 antibodies recited in claims 3, 32, 34-36 and 48.

Claims 37 and 38 are included in the rejection, because they recite all possible orders of administering the two antibodies.

Claim 46 is included, because many of Cogswell's patients received prior systemic therapy (e.g. [0329]), and also because administering an anti-cancer agent would be at once envisaged by a skilled artisan since it was routine in the art to combine cancer treatments both concurrently and sequentially.

At least in view of the above, the teachings of the reference anticipate the instantly claimed invention.

12. The nonstatutory **double patenting** rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(I)(1) - 706.02(I)(3) for applications not subject to examination under the first inventor to file

provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

13. Claims 2, 3, 8, 25, 32, 34-38, 46 and 48 are rejected on the ground of nonstatutory **double patenting** as being unpatentable over claims 1-22 of U.S. Patent No. 9856320 (cited on IDS).

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the claims of the '320 Patent.

The claims of the '320 Patent are directed to a method of treating cancer comprising administering an anti-PD-1 antibody at 3 mg/kg (equivalent to 240 mg) and an anti-CTLA-4 antibody at 1 mg/kg (equivalent to 80 mg) once every 2 or 3 weeks (claim 1), wherein the antibodies are nivolumab and ipilimumab (claims 2 and 3), wherein the cancer is melanoma (claim 8), wherein the treatment provides a reduction in tumor size (claim 7), and wherein the treatment is further combined with an additional anti-cancer agent (claim 11), thereby anticipating instant claims 2, 3, 32, 34-38, 46 and 48.

The claims of the '320 Patent are further directed to a method of treating cancer comprising administering an anti-PD-1 antibody alone at 3 mg/kg (equivalent to 240 mg)

every 2 weeks (claims 1, 5, and 13), wherein the antibody is nivolumab (claim 2), wherein the cancer is melanoma (claim 20), wherein the treatment provides a reduction in tumor size (claim 18), and wherein the treatment is further combined with an additional anti-cancer agent (claim 22), thereby anticipating instant claims 2, 8 and 25.

14. Claims 2, 8, 14, 16-18, 20, 25 and 50 are rejected on the ground of nonstatutory **double patenting** as being unpatentable over claims 2-12 and 16 of U.S. Patent No. 10174113 (cited on IDS).

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the claims of the '113 Patent.

The claims of the '320 Patent are further directed to a method of treating melanoma comprising administering an anti-PD-1 antibody at 240 mg once every 2 weeks or 480 mg once every 4 weeks (claims 2, 11 and 12), wherein the antibody is nivolumab (claim 10), wherein the treatment provides extended progression-free survival for over 8 months following the administration and/or tumor size reduction at least about 10% (claim 3), and wherein the treatment further comprises administering an anti-cancer agent (claim 16).

The method further comprises measuring a PD-L1 expression on the melanoma tumor prior to the administration (claim 4), wherein the measuring comprises providing a test tissue sample obtained from the patient, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells (claim 5), wherein the measuring further comprises assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface (claim 6), wherein the test tissue sample is a formalin-fixed paraffin-embedded (FFPE) tissue sample, and wherein the presence of PD-L1 is determined using an automated IHC assay (claim 7), and wherein the IHC assay is performed using an anti-PD-L1 monoclonal antibody that specifically binds to the PD-L1 and wherein the

anti-PD-L1 monoclonal antibody comprises a variable heavy region comprising the amino acid sequence set forth in SEQ ID NO: 1 and a variable light region comprising the amino acid sequence set forth in SEQ ID NO: 2 (claim 8).

15. Claims 2, 8, 14, 16-18, 20-21, 25 and 50 are provisionally rejected on the ground of nonstatutory **double patenting** as being unpatentable over claims 3, 9, 15, 17-22, 26, 28-29 and 49 of copending Application No. 16430106, published as US 20200010549 (cited on IDS).

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are anticipated by or obvious over the claims of the '106 application.

The claims of the '106 application are directed to a method for treating melanoma comprising

administering to the patient an anti-PD1 antibody monotherapy,

wherein the patient is identified as having a PD-L1 positive melanoma tumor prior to the administration (claim 3),

wherein the anti-PD-1 antibody is administered at a dose ranging from 0.1 to 10.0 mg/kg body weight once every 2, 3 or 4 weeks (claim 28),

wherein the anti-PD-1 antibody is administered at a dose of 1 or 3 mg/kg body weight once every 3 weeks (claim 29),

wherein the anti-PD-1 antibody is nivolumab (claim 26).

In view of the above recitations, a person of ordinary skill in the art would at once envisage a regimen of 3 mg/kg (equivalent to 240 mg) every 2 weeks. Alternatively, such regimen would be obvious in view of the combined recitations of claims 28 and 29.

The claims of the '106 application further recite that the patient is characterized by extended progression-free survival following the administration, tumor size reduction at least about 10%, or both (claim 9).

The method further comprises measuring a PD-L1 expression on the melanoma tumor (claim 15), wherein the measuring comprises providing a test tissue sample obtained from the patient, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells (claim 17), wherein the measuring further comprises assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface (claim 18), wherein the test tissue sample is a formalin-fixed paraffin-embedded (FFPE) tissue sample (claim 19), wherein the presence of PD-L1 is determined using an automated IHC assay using anti-PD-L1 antibody 28-8 (claims 20 and 21) [antibody 28-8 has variable regions of instantly recited SEQ ID NOS: 1 and 2], wherein the PD-L1 positive melanoma tumor is characterized by having at least about 5% of tumor cells showing binding to the anti-PD-L1 antibody (claim 22), and wherein the method further comprises administering an anti-cancer agent (claim 49).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

16. Conclusion: no claim is allowed.

17. The following prior art is cited of record but not presently relied upon:

Non-Comparative, Multi-Cohort, Single Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in classical Hodgkin Lymphoma (cHL) Subjects. AdisInsight: Trials (Jul 10, 2014). The reference teaches administering nivolumab at a flat dose of 240 mg every 2 weeks.

Motzer et al. (2015; Published online ahead of print at www.jco.org on December 1, 2014) J Clin Oncol; 33(13): 1430–1437. Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial. Present a population pharmacokinetic model defining the rationale for nivolumab monotherapy dosing regimen of 3 mg/kg intravenously every 2 weeks.

Brahmer et al. (2010) J Clin Oncol; 28(19): 3167–3175. Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates.

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Wolchok et al. (2013) N Engl J Med; 369: 122-133 (cited on IDS). Nivolumab plus Ipilimumab in Advanced Melanoma.

18. 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 IOUSPENSKI/
Primary Examiner, Art Unit 1644

<i>Notice of References Cited</i>	Application/Control No. 16/240,316		Applicant(s)/Patent Under Reexamination YANG, Arvin	
	Examiner ILIA I OUSPENSKI		Art Unit 1644	Page 1 of 3

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
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*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
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	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Naing et al. (2019) Journal for ImmunoTherapy of Cancer 7: 225; 15 pages.
	V	Opdivo FDA Label, 2021; 110 pages.
	W	Opdivo FDA Label, 2015, 27 pages.
	X	Keytruda FDA Label, 2020; 91 pages.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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PTO-892 (Rev. 01-2001)

Notice of References Cited

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<i>Notice of References Cited</i>	Application/Control No. 16/240,316		Applicant(s)/Patent Under Reexamination YANG, Arvin	
	Examiner ILIA I OUSPENSKI		Art Unit 1644	Page 2 of 3

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	S					
	T					

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	U	Libtayo FDA Label, 2020; 17 pages.
	V	Motzer et al. (2015; Published online ahead of print at www.jco.org on December 1, 2014) J Clin Oncol; 33(13): 1430-1437.
	W	Brahmer et al. (2010) J Clin Oncol; 28(19): 3167-3175.
	X	Hodi et al. (2010) N Engl J Med; 363: 711-723.

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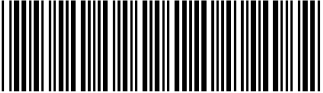
*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Non-Comparative, Multi-Cohort, Single Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in classical Hodgkin Lymphoma (cHL) Subjects. AdisInsight: Trials (Jul 10, 2014); 6 pages.
	V	
	W	
	X	

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Notice of References Cited

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<i>Search Notes</i> 	Application/Control No. 16/240,316	Applicant(s)/Patent Under Reexamination YANG, Arvin
	Examiner ILIA IOUSPENSKI	Art Unit 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	03/20/2021	io
Sequence search: in SCORE	03/20/2021	io
WEST: attached	03/20/2021	io
Dialog: attached	03/20/2021	io
Inventor search	03/20/2021	io

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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WEST Search History

DATE: Saturday, March 20, 2021

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	<i>DB=PGPB,USPT,EPAB,JPAB,DWPI,FPRS; THES=ASSIGNEE; PLUR=YES; OP=ADJ</i>		
☐	L10	L9 and L4.clm. and L7.clm. and melanoma\$.clm.	5
☐	L9	L8 and (yang-a\$.in. or Bristol\$.as.,aanm.)	10
☐	L8	((L4 near10 L7) near10 melanoma\$)	1266
☐	L7	(L5 or L6)	49054
☐	L6	(Ipilimumab or (BMS 734016) or BMS734016 or mdx010 or (mdx 010) or 10D1 or Yervoy\$)	17009
☐	L5	(CTLA4\$ or ctla-4\$ or cd152\$ or anti-ctla4\$ or anti-ctla-4\$ or anti-cd152\$ or ".alpha.ctla4\$" or ".alpha.ctla-4\$" or ".alpha.cd152\$")	42699
☐	L4	(L1 or L2 or L3)	86512
☐	L3	(pembrolizumab or Keytruda\$ or lambrolizumab or MK-3475 or MK3475 or MK03475 or (Merck 3475) or (SCH 900475) or SCH-900475 or SCH900475)	10133
☐	L2	(nivolumab or 5C4 or BMS-936558 or bms936558 or MDX-1106\$ or mdx1106 or (mdx 1106) or GTPL7335 or gtpl-7335 or ONO-4538 or ono4538 or Opdivo\$)	12442
☐	L1	(anti-pd-1\$ or anti-hpd-1\$ or anti-pd1\$ or anti-pdhd1\$ or anti-cd279\$ or ".alpha.pd-1\$" or ".alpha.hpd-1\$" or ".alpha.pd1\$" or ".alpha.pdhd1\$" or ".alpha.cd279\$" or pd-1\$ or hpd-1\$ or pd1\$ or pdhd1\$ or cd279\$)	83125

END OF SEARCH HISTORY

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)			Complete if Known		
			Application Number	16/240,316	
			Filing Date	January 4, 2019	
			First Named Inventor	YANG, Arvin	
			Art Unit	1644	
			Examiner Name	OUSPENSKI, Ilia I.	
			Attorney Docket Number	3338.0330003/ELE/C-K/BMD	
Sheet	1	of	12		

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	US1	US-5977318-A	11-02-1999	LINSLEY; Peter S. et al.	
	US2	US-6051227-A	04-18-2000	ALLISON; James Patrick et al.	
	US3	US-6682736-B1	01-27-2004	HANSON; Douglas Charles et al.	
	US4	US-6808710-B1	10-26-2004	WOOD; Clive et al.	
	US5	US-6984720-B1	01-10-2006	KORMAN; Alan J. et al.	
	US6	US-7034121-B2	04-25-2006	CARRENO; Beatriz M. et al.	
	US7	US-7488802-B2	02-10-2009	COLLINS; Mary et al.	
	US8	US-7595048-B2	09-29-2009	HONJO; Tasuku et al.	
	US9	US-7605238-B2	10-20-2009	KORMAN; Alan J. et al.	
	US10	US-7943743-B2	05-17-2011	KORMAN; Alan J. et al.	
	US11	US-8008449-B2	08-30-2011	KORMAN; Alan J. et al.	
	US12	US-8168757-B2	05-01-2012	FINNEFROCK; Adam C. et al.	
	US13	US-8217149-B2	07-10-2012	IRVING; Bryan et al.	
	US14	US-8354509-B2	01-15-2013	CARVEN; Gregory John et al.	
	US15	US-8383796-B2	02-26-2013	KORMAN; Alan J. et al.	
	US16	US-8609089-B2	12-17-2013	LANGERMANN; Solomon et al.	
	US17	US-8686119-B2	04-01-2014	ROTEM-YEHUDAR RINAT et al.	
	US18	US-8779105-B2	07-15-2014	KORMAN; Alan J. et al.	
	US19	US-8900587-B2	12-02-2014	CARVEN; Gregory John et al.	
	US20	US-9084776-B2	07-21-2015	KORMAN; Alan J. et al.	
	US21	US-9102725-B2	08-11-2015	KORMAN; Alan J. et al.	
	US22	US-9273135-B2	03-01-2016	KORMAN; Alan J. et al.	

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			First Named Inventor	YANG, Arvin	
			Art Unit	1644	
			Examiner Name	OUSPENSKI, Ilia I.	
			Attorney Docket Number	3338.0330003/ELE/C-K/BMD	
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U. S. PATENT DOCUMENTS					
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		Number-Kind Code ² (if known)			
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	US24	US-9387247-B2	07-12-2016	KORMAN; Alan J. et al.	
	US25	US-9492539-B2	11-15-2016	KORMAN; Alan J. et al.	
	US26	US-9492540-B2	11-15-2016	KORMAN; Alan J. et al.	
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	US28	US-20120263677-A1	10-18-2012	EAGLE; Craig J. et al.	
	US29	US-20130017199-A1	01-17-2013	LANGERMANN; Solomon	
	US30	US-20130309250-A1	11-21-2013	COGSWELL; John et al.	
	US31	US-20150079109-A1	03-19-2015	LI; Kang et al.	
	US32	US-20160075782-A1	03-17-2016	KORMAN; Alan J. et al.	
	US33	US-20160362495-A1	12-15-2016	KORMAN; Alan J. et al.	
	US34	US-8168179-B2	05-01-2012	HONJO; Tasuku et al.	
	US35	US-8728474-B2	05-20-2014	HONJO; Tasuku et al.	
	US36	US-9067999-B1	06-30-2015	HONJO; Tasuku et al.	
	US37	US-9073994-B2	07-07-2015	HONJO; Tasuku et al.	
	US38	US-9212224-B2	12-15-2015	COGSWELL; John et al.	
	US39	US-9393301-B2	07-19-2016	HONJO; Tasuku et al.	
	US40	US-9402899-B2	08-02-2016	HONJO; Tasuku et al.	
	US41	US-9439962-B2	09-13-2016	HONJO; Tasuku et al.	
	US42	US-20150125463-A1	05-07-2015	COGSWELL; John P. et al.	
	US43	US-20160090417-A1	03-31-2016	COGSWELL; John P. et al.	
	US44	US-20160362489-A1	12-15-2016	YANG; Arvin et al.	

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	US47	US-20160022814-A1	01-28-2016	PETIT; R et al.	
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	US51	US-10174113-B2	01-08-2019	YANG; Arvin	
	US52	US-10441655-B2	10-15-2019	KORMAN; A.J. et al.	
	US53	US-20200138945-A1	05-07-2020	KORMAN; A.J. et al.	
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	US55	US-10577423-B2	03-03-2020	COGSWELL; John P. et al.	
	US56	US-10604575-B2	03-31-2020	COGSWELL; John P. et al.	
	US57	US-10323093-B2	06-18-2019	COGSWELL; John P. et al.	
	US58	US-10266596-B1	04-23-2019	COGSWELL; John P. et al.	
	US59	US-10266595-B2	04-23-2019	COGSWELL; John P. et al.	
	US60	US-10266594-B2	04-23-2019	COGSWELL; John P. et al.	
	US61	US-10308714-B2	06-04-2019	COGSWELL; John P. et al.	
	US62	US-10316091-B2	06-11-2019	COGSWELL; John P. et al.	
	US63	US-10323092-B2	06-18-2019	COGSWELL; John P. et al.	
	US64	US-10138299-B2	11-27-2018	COGSWELL; John P. et al.	
	US65	US-10316090-B2	06-11-2019	COGSWELL; John P. et al.	
	US66	US-10072082-B2	09-11-2018	COGSWELL; John P. et al.	

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		Number-Kind Code ² (if known)			
	US67	US-20200308282-A1	10-01-2020	COGSWELL; John P. et al.	
	US68	US-20190135920-A1	05-09-2019	COGSWELL; John P. et al.	
	US69	US-20190153099-A1	05-23-2019	COGSWELL; John P. et al.	
	US70	US-20190112377-A1	04-18-2019	COGSWELL; John P. et al.	
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	US72	US-20190100590-A1	04-04-2019	COGSWELL; John P. et al.	
	US73	US-20190092863-A1	03-28-2019	COGSWELL; John P. et al.	
	US74	US-20190100589-A1	04-04-2019	COGSWELL; John P. et al.	
	US75	US-20180319887-A1	11-08-2018	COGSWELL; John P. et al.	
	US76	US-20180312590-A1	11-01-2018	COGSWELL; John P. et al.	
	US77	US-20180282414-A1	06-18-2018	COGSWELL; John P. et al.	
	US78	US-20180282413-A1	10-04-2018	COGSWELL; John P. et al.	
	US79	US-20180273624-A1	09-27-2018	COGSWELL; John P. et al.	
	US80	US-20200010549-A1	01-09-2020	YANG; Arvin	

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		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
	FP1	WO-2006121168-A1	11-16-2006	ONO PHARMACEUTICAL CO., LTD. et al.		☐

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			Application Number	16/240,316	
			Filing Date	January 4, 2019	
			First Named Inventor	YANG, Arvin	
			Art Unit	1644	
			Examiner Name	OUSPENSKI, Ilia I.	
			Attorney Docket Number	3338.0330003/ELE/C-K/BMD	
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FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	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
		Country Code ² Number ⁴ Kind Code ⁵ (if known)				
	FP2	WO-2007005874-A2	01-11-2007	MEDAREX, INC. <i>et al.</i>		☐
	FP3	WO-2007113648-A2	10-11-2007	PFIZER PRODUCTS INC. <i>et al.</i>		☐
	FP4	WO-2012122444-A1	09-13-2012	PROVECTUS PHARMACEUTICALS, INC. <i>et al.</i>		☐
	FP5	WO-2012145493-A1	10-26-2012	AMPLIMMUNE, INC. <i>et al.</i>		☐
	FP6	WO-2013014668-A1	01-31-2013	CURETECH LTD. <i>et al.</i>		☐
	FP7	WO-2013173223-A1	11-21-2013	BRISTOL-MYERS SQUIBB COMPANY		☐
	FP8	WO-2004004771-A1	01-15-2004	ONO PHARMACEUTICAL CO [JP], <i>et al.</i>		☒
	FP9	WO-2015042246-A1	03-26-2015	SQUIBB BRISTOL MYERS CO [US]		☐
	FP10	WO-2016176503-A1	11-03-2016	BRISTOL-MYERS SQUIBB COMPANY [US]		☐
	FP11	WO-2016176504-A1	11-03-2016	BRISTOL-MYERS SQUIBB COMPANY [US]		☐

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	NPL1	ASCIERTO, P.A., <i>et al.</i> , "Biomarkers for Immunostimulatory Monoclonal Antibodies in Combination Strategies for Melanoma and Other Tumor Types," Clinical Cancer Research 19(5):1009-1020, American Association for Cancer Research, United States (2013).	☐	
	NPL2	ASCIERTO, P.A., <i>et al.</i> , "The Additional Facet of Immunoscore: Immunoprofiling as a Possible Predictive Tool for Cancer Treatment," Journal of Translational Medicine 11:54, BioMed Central Ltd., England, 4 pages (2013).	☐	
	NPL3	BRAHMER, J.R., <i>et al.</i> , "Safety and Activity of Anti-PD-L1 Antibody in Patients with Advanced Cancer," The New England Journal of Medicine 366(26):2455-2465, Massachusetts Medical Society, United States (2012).	☐	
	NPL4	CONDEELIS, J. and WEISSLEDER, R., "In Vivo Imaging in Cancer," Cold Spring Harbor Perspectives in Biology 2(12):a003848, Cold Spring Harbor Laboratory Press, United States (2010).	☐	
	NPL5	DONG, H., <i>et al.</i> , "Tumor-associated B7-H1 Promotes T-cell Apoptosis: A Potential Mechanism of Immune Evasion," Nature Medicine 8(8):793-800, Nature Publishing Company, United States (2002).	☐	
	NPL6	GADIOT, J., <i>et al.</i> , "Overall Survival and PD-L1 Expression in Metastasized Malignant Melanoma," Cancer 117(10):2192-2201, American Cancer Society, United States (2011).	☐	
	NPL7	GARBE, C., <i>et al.</i> , "Diagnosis and Treatment of Melanoma. European Consensus-based Interdisciplinary Guideline – Update 2012," European Journal of Cancer 48(15):2375-2390, Elsevier Ltd., England (2012).	☐	
	NPL8	GenBank, "cytotoxic T-lymphocyte-associated protein 4 [Homo sapiens]," Accession Number AAB59385.1, November 1, 1994, accessed at https://www.ncbi.nlm.nih.gov/protein/AAB59385 , accessed on December 6, 2016, 3 pages.	☐	

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	NPL9	GenBank, "RecName: Full=Programmed cell death 1 ligand 1; Short=PD-L1; Short=PD-CD1 ligand 1; Short=Programmed death ligand 1; AltName: Full=B7 homolog 1; Short=B7-H1; AltName: CD_antigen=CD274; Flags: Precursor," Accession Number Q9NZQ7.1, November 2, 2016, accessed at https://www.ncbi.nlm.nih.gov/protein/Q9NZQ7 , accessed on December 6, 2016, 11 pages.	☐
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	NPL12	HERBST, R.S., <i>et al.</i> , "A Study of MPDL3280A, an Engineered PD-L1 Antibody in Patients with Locally Advanced or Metastatic Tumors," Journal of Clinical Oncology 31(Suppl; Abstr 3000), American Society of Clinical Oncology, United States (2013).	☐
	NPL13	International Search Report and Written Opinion for International Application No. PCT/US2016/029877, European Patent Office, Rijswijk, mailed on July 13, 2016, 16 pages.	☐
	NPL14	KHLEIF, S., <i>et al.</i> , "MEDI4736, An Anti-PD-L1 Antibody with Modified Fc Domain: Preclinical Evaluation and Early Clinical Results from a Phase 1 Study in Patients with Advanced Solid Tumors," Abstract 802, in Proceedings from the European Cancer Congress 2013, Amsterdam, The Netherlands (September 27-October 1, 2013).	☐
	NPL15	MAHONEY, K.M., <i>et al.</i> , "The Next Immune-Checkpoint Inhibitors: PD-1/PD-L1 Blockade in Melanoma," Clinical Therapeutics 37(4):764-782, Elsevier HS Journals, Inc., United States (March 29, 2015).	☐

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	NPL16	MARZUKA, A., <i>et al.</i> , "Melanoma Treatments: Advances and Mechanisms," Journal of Cellular Physiology 230(11):2626-2633, Wiley Periodicals, Inc., United States (July 27, 2015).	☐	
	NPL17	MCCABE, K.E. and WU, A.M., "Positive Progress in ImmunoPET – Not Just a Coincidence," Cancer Biotherapy & Radiopharmaceuticals 25(3):253-261, Mary Ann Liebert, Inc., United States (2010).	☐	
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	NPL19	NCI Drug Dictionary, anti-PD-1 Fusion Protein AMP-224, accessed on December 1, 2016, retrieved from the Internet URL: https://www.cancer.gov/publications/dictionaries/cancer-drug?cdrid=700595 .	☐	
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	NPL24	PHILIPS, G.K. and ATKINS, M., "Therapeutic Uses of Anti-PD-1 and Anti-PD-L1 Antibodies," International Immunology 27(1):39-46, The Japanese Society for Immunology, Japan (October 16, 2014).	☐
	NPL25	SIEGEL, R., <i>et al.</i> , "Cancer Statistics, 2013," CA: A Cancer Journal for Clinicians 63(1):11-30, American Cancer Society, United States (2013).	☐
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	NPL27	TAUBE, J.M., <i>et al.</i> , "Colocalization of Inflammatory Response With B7-H1 Expression in Human Melanocytic Lesions Supports an Adaptive Resistance Mechanism of Immune Escape," Science Translational Medicine 4(127):127ra37, American Association for the Advancement of Science, United States (2012).	☐
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	NPL29	United States Adopted Name (USAN) Drug Finder, "Pembrolizumab: Statement on a nonproprietary name adopted by the USAN Council (ZZ-165)," published November 27, 2013, accessed at https://search.usan.ama-assn.org/usan/documentDownload?uri=%2Funstructured%2Fbinary%2Fusan%2Fpembrolizumab.pdf , accessed on December 8, 2016, 2 pages.	☐
	NPL30	WANG, C., <i>et al.</i> , "In Vitro Characterization of the Anti-PD-1 Antibody Nivolumab, BMS-936558, and In Vivo Toxicology in Non-Human Primates," Cancer Immunology Research 2(9):846-856, American Association for Cancer Research, United States (May 28, 2014).	☐

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	NPL32	BOWYER, S., <i>et al.</i> , "Efficacy and Toxicity of Treatment with the Anti-CTLA-4 Antibody Ipilimumab in Patients with Metastatic Melanoma after Prior Anti-PD-1 Therapy," British Journal of Cancer 114(10):1084-1089, Nature Publishing Group, England (May 2016).	☐	
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	NPL38	Kuenen, B., <i>et al.</i> "A Phase I Pharmacologic Study of Necitumumab (IMC-11 F8), a Fully Human IgG1 Monoclonal Antibody Directed Against EGFR in Patients with Advanced Solid Malignancies," <i>Clin Cancer Res.</i> , 16(6):1915-23, United States (2010).	☐	
	NPL39	Wang, D.D., <i>et al.</i> "Fixed Dosing Versus Body Size-Based Dosing of Monoclonal Antibodies in Adult Clinical Trials," <i>J Clin Pharmacol.</i> , 49(9):1012-24, United States (2009)	☐	

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	NPL40	Office Action mailed May 2, 2018, in United States Patent Application No. 15/311,409, Feltquate, D. <i>et al.</i> , filed November 15, 2016, 13 pages.	☐
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	NPL46	Advisory Action mailed August 3, 2018, in United States Patent Application No. 15/141,772, YANG, Arvin. <i>et al.</i> , filed April 28, 2016, 3 pages.	☐
	NPL47	GETTINGER, S.N., et al., "Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients with Previously treated Advanced Non-Small-Cell Lung Cancer," Journal of Clinical Oncology 33(18): 2004-2012, American Society of Clinical Oncology, United States (June 2015).	☐
	NPL48	JOHNSON, D. B., et al., "Immune Checkpoint Inhibitors in NSCLC," Current Treatment Option in Oncology 15(4):658-669, SpringerLink, United States (2014).	☐

Examiner Signature		Date Considered	
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*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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Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)			Complete if Known		
			Application Number	16/240,316	
			Filing Date	January 4, 2019	
			First Named Inventor	YANG, Arvin	
			Art Unit	1644	
			Examiner Name	OUSPENSKI, Ilia I.	
Sheet	12	of	12	Attorney Docket Number	3338.0330003/ELE/C-K/BMD

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
	NPL49	Office Action mailed October 3, 2018 in United States Patent Application No. 15/141,772, Yang, A et al., filed April 28, 2016, 17 pages.	☐
	NPL50	ZHAO, X., et al., "Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors," Annals of Oncology: Official Journal of the European Society for Medical Oncology 28(8):2002-2008, Oxford Journals, England (2017).	☐
	NPL51	LONG, G.V., et al. "Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer," Annals of Oncology 29(11):2208-13 (November 1, 2018).	☐
	NPL52	POLLACK, M.H., et al., "Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma," Annals of Oncology 29(1):250-55 (January 1, 2018).	☐

16217601_1

Examiner Signature	/ILIA I OUSPENSKI/	Date Considered	03/18/2021
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CONFIRMATION NO. 4170

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
16/240,316	01/04/2019	424	1644 3338.0330003/ELE/C-K/B MD			
APPLICANTS Bristol-Myers Squibb Company, Princeton, NJ; INVENTORS Arvin YANG, Princeton, NJ; ** CONTINUING DATA ***** This application is a CON of 15/141,769 04/28/2016 PAT 10174113 which claims benefit of 62/153,973 04/28/2015 ** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 01/17/2019						
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and /ILIA IOUSPENSKI/ Acknowledged Examiner's Signature		☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
			NJ	6	20	2
ADDRESS Sterne, Kessler, Goldstein & Fox P.L.L.C. 1100 New York Avenue NW Washington, DC 20005 UNITED STATES						
TITLE TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY						
FILING FEE RECEIVED 1880	FEES: Authority has been given in Paper 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			

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Search Strategy

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Set#	Searched for	Results
S1	(nivolumab NEAR ipilimumab NEAR melanoma)	13339*
S7	(nivolumab NEAR "240 mg")	508°
S8	(nivolumab NEAR "480 mg")	224°
S9	((nivolumab NEAR "480 mg")) and (pd(<20150501))	0°
S10	((nivolumab NEAR ipilimumab NEAR melanoma)) and (ud(<20150501))	589°
S11	((nivolumab NEAR "240 mg")) and (pd(<20150501))	1°

* Duplicates are removed from the search, but included in the result count.

° Duplicates are removed from the search and from the result count.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 16/240,316		Filing Date 01/04/2019		☐ To be Mailed			
ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO											
APPLICATION AS FILED - PART I											
		(Column 1)	(Column 2)								
FOR		NUMBER FILED	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), (l), 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(j))		minus 20 =	*	x \$100 =							
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =	*	x \$460 =							
☐ 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											
		(Column 1)	(Column 2)	(Column 3)							
AMENDMENT	06/24/2021	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)				
	Total (37 CFR 1.16(i))	* 18	Minus ** 20	= 0	x \$100 =		0				
	Independent (37 CFR 1.16(h))	* 2	Minus *** 3	= 0	x \$480 =		0				
	☐ Application Size Fee (37 CFR 1.16(s))										
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))										
						TOTAL ADD'L FEE		0			
AMENDMENT		(Column 1)	(Column 2)	(Column 3)							
		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)				
	Total (37 CFR 1.16(i))	*	Minus **	=	x \$0 =						
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x \$0 =						
	☐ 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.						LIE					
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".						/LINDA HUMES/					
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".											
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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.**

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Electronic Petition Request	TERMINAL DISCLAIMER TO OBTAIN A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT		
Application Number	16240316		
Filing Date	04-Jan-2019		
First Named Inventor	Arvin YANG		
Attorney Docket Number	3338.0330003/ELE/C-K/BMD		
Title of Invention	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY		
☒ 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.			
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Signature	/Ji Eun Kim/
Name	Ji Eun Kim

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Electronic Patent Application Fee Transmittal				
Application Number:		16240316		
Filing Date:		04-Jan-2019		
Title of Invention:		TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY		
First Named Inventor/Applicant Name:		Arvin YANG		
Filer:		Ji Eun Kim/Jeanette Yando		
Attorney Docket Number:		3338.0330003/ELE/C-K/BMD		
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	170	170
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 (\$)				170

Doc Code: DISQ.E.FILE

Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16240316

Filing Date: 04-Jan-2019

Applicant/Patent under Reexamination: YANG

Electronic Terminal Disclaimer filed on June 24, 2021

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This patent is subject to a terminal disclaimer

☐ DISAPPROVED

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Electronic Acknowledgement Receipt	
EFS ID:	43084695
Application Number:	16240316
International Application Number:	
Confirmation Number:	4170
Title of Invention:	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY
First Named Inventor/Applicant Name:	Arvin YANG
Customer Number:	115018
Filer:	Ji Eun Kim/Jeanette Yando
Filer Authorized By:	Ji Eun Kim
Attorney Docket Number:	3338.0330003/ELE/C-K/BMD
Receipt Date:	24-JUN-2021
Filing Date:	04-JAN-2019
Time Stamp:	18:16:54
Application Type:	Utility under 35 USC 111(a)

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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	33498	no	2
			d4abeb02766a90b61764c336d4e6d40548 229907		
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30436	no	2
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Arvin YANG

Applicant: Bristol-Myers Squibb Co.

Application No.: 16/240,316

Filed: January 4, 2019

Confirmation No.: 4170

Art Unit: 1644

Examiner: OUSPENSKI, Ilia I.

Atty. Docket: 3338.0330003/ELE/C-
K/BMD

Title: **TREATMENT OF MELANOMA USING AN ANTI-PD-1 ANTIBODY (as amended)**

Amendment and Reply Under 37 C.F.R. § 1.111

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

Mail Stop Amendment

Commissioner:

In reply to the Office Action dated March 24, 2021, Applicant submits the following
Amendment and Remarks.

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

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of
this paper.

Remarks and Arguments begin on page 7 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 replace the title with the following: "Treatment of Melanoma Using an Anti-PD-1 Antibody."

Amendments to the Claims

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

1. (Cancelled)
2. (Currently Amended) A method for treating a melanoma in a human patient afflicted with a melanoma tumor comprising administering to ~~[[a]]the patient afflicted with a melanoma tumor~~

an anti-PD-1 antibody or an antigen-binding portion thereof that binds specifically to a human PD-1 ("anti-PD-1 antibody") nivolumab at a flat dose of ~~240 mg once every two weeks or~~ 480 mg once every four weeks.
3. (Currently Amended) The method of claim 2, further comprising administering to the patient an anti-CTLA-4 antibody or an antigen-binding portion thereof that binds specifically to a human CTLA-4 ("anti-CTLA-4 antibody").
- 4-7. (Cancelled)
8. (Previously Presented) The method of claim 2, wherein the patient is characterized by (i) extended progression-free survival for over 8 months, (ii) tumor size reduction at least about 10%, about 20%, about 30%, about 40%, or about 50% compared to the tumor size prior to the administration, or (iii) both.
- 9-13. (Cancelled)
14. (Currently Amended) The method of claim 2, wherein the melanoma tumor is characterized by having at least about 1% of tumor cells showing cell-surface binding to an anti-PD-L1

Atty. Dkt. No. 3338.0330003/ELE/C-K/BMD

- antibody or an antigen-binding portion thereof, further comprising measuring a wherein PD-L1 expression on the melanoma tumor is measured prior to the administration.
15. (Cancelled)
16. (Previously Presented) The method of claim 14, wherein the measuring comprises providing a test tissue sample obtained from the patient, the test tissue sample comprising tumor cells and/or tumor-infiltrating inflammatory cells.
17. (Original) The method of claim 16, wherein the measuring further comprises assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface.
18. (Currently Amended) The method of claim 17, wherein the test tissue sample [[is]]comprises a formalin-fixed paraffin-[[]]embedded (FFPE) tissue sample, and wherein the presence of PD-L1 is determined using an automated IHC assay.
19. (Cancelled)
20. (Currently Amended) The method of claim 18, wherein the IHC assay is performed using an anti-PD-L1 monoclonal antibody that specifically binds to the PD-L1 and wherein the anti-PD-L1 monoclonal antibody comprises a ~~variable~~ heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 1 and a ~~variable~~ light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 2.
- 21-31. (Cancelled)
32. (Previously Presented) The method of claim 3, wherein the anti-CTLA-4 antibody is ipilimumab.
33. (Cancelled)

34. (Previously Presented) The method of claim 3, wherein the anti-CTLA-4 antibody is administered once every 2, 3 or 4 weeks.
35. (Previously Presented) The method of claim 34, wherein the anti-CTLA-4 antibody is administered at a dose of 1 or 3 mg/kg body weight once every 3 weeks.
36. (Previously Presented) The method of claim 34, wherein the anti-CTLA-4 antibody is administered at a flat dose of about 80 mg, about 160 mg, or about 240 mg.
37. (Previously Presented) The method of claim 3, wherein the anti-PD-1 antibody is administered concurrently with the anti-CTLA-4 antibody.
38. (Previously Presented) The method of claim 3, wherein the anti-PD-1 antibody is administered prior to or after the anti-CTLA-4 antibody.
- 39-45. (Cancelled)
46. (Previously Presented) The method of claim 3, further comprising administering an anti-cancer agent.
- 47-49. (Cancelled)
50. (Currently Amended) A method for treating a melanoma in a human patient afflicted with a melanoma tumor, comprising administering to the patient nivolumab as a monotherapy at a flat dose of ~~240 mg once every two weeks~~ or 480 mg once every four weeks, wherein the patient is identified as having a PD-L1-positive melanoma tumor prior to the administration, wherein the PD-L1-positive melanoma tumor is characterized by having at least about 1% of tumor cells showing cell-surface binding to an anti-PD-L1 antibody or an antigen-binding portion thereof.

51. (New) The method of claim 14, wherein the PD-L1-positive melanoma tumor is characterized by having at least about 5% of tumor cells showing cell-surface binding to an anti-PD-L1 antibody or an antigen-binding portion thereof.
52. (New) The method of claim 50, wherein the PD-L1-positive melanoma tumor is characterized by having at least about 5% of tumor cells showing cell-surface binding to an anti-PD-L1 antibody or an antigen-binding portion thereof.

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 2, 3, 8, 14, 16-18, 20, 32, 34-38, 46, and 50-52 are pending in the application, with claims 2 and 50 being the independent claims. Claims 2, 14, 18, 20, and 50 are sought to be amended; and new claims 51 and 52 are 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 claim 2 can be found, *inter alia*, at original claim 25 and paragraphs [0085] and [0116]. Support for the amendments to claim 14 and new claims 51 and 52 can be found, *inter alia*, at paragraph [0045]. Support for the amendments to claim 50 can be found, *inter alia*, at paragraph [0045]. In addition, claims 18 and 20 are amended for clarity. Claims 21, 25, 48, and 49 are sought to be canceled without prejudice to or disclaimer of the subject matter therein. 1, 4-7, 9-13, 15, 19, 22-24, 26-31, 33, 39-45, and 47 were previously cancelled.

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 objections and rejections and that they be withdrawn.

Objection to the Title

The Examiner objected to the title for allegedly not being descriptive. Office Action, page 2. Solely to advance prosecution, the title is amended to recite "Treatment of Melanoma Using an Anti-PD-1 Antibody." The amended title is consistent with the amended claims, submitted herewith, and

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thus the title is descriptive of the invention to which the claims are directed. Accordingly, Application respectfully requests the Examiner reconsider and withdraw this objection.

Objection to Claim 21

The Examiner directed Applicant's attention to claim 21, noting that "[t]hose skilled in the art often distinguish cell surface PD-L1 staining from intracellular staining when evaluating a tumor for PD-L1 expression." Office Action, page 2. Solely to advance prosecution, claim 21 is cancelled, rendering any objection to claim 21 moot. Accordingly, Applicant respectfully requests that the Examiner withdraw any objections to claim 21.

Applicant has incorporated element of cancelled claim 21 into amended claim 14. Amended claim 14 recites the method of claim 2, wherein the melanoma tumor is characterized by having at least about 1% of tumor cells showing cell-surface binding to an anti-PD-L1 antibody or an antigen-binding portion thereof, wherein PD-L1 expression on the melanoma tumor is measured prior to the administration. As such, amended claim 14 incorporated the Examiner's proposed clarification regarding cell-surface PD-L1 expression.

Rejections under 35 U.S.C. § 112(b)

Claims 14, 16-18, and 20-21

The Examiner rejected claims 14, 16-18, and 20-21 under 35 U.S.C. § 112(b) for allegedly being indefinite "because the recitation of a step of measuring PD-L1 expression on the tumor prior to administration of anti-PD-1 antibody [in claim 14] appears to imply that the result of said

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measuring is related to the step of administering, yet no indication of such a relationship is provided." Office Action, pages 2-3. Applicant respectfully disagrees.

However, solely to advance prosecution, and without acquiescing to the Examiner's arguments, claim 21 is cancelled, rendering the Examiner's rejection of this claim moot. In addition, claim 14 is amended to recite "wherein the PD-L1-positive melanoma tumor is characterized by having at least about 1% of tumor cells showing cell-surface binding to an anti-PD-L1 antibody or an antigen-binding portion thereof, wherein PD-L1 expression on the melanoma tumor is measured prior to the administration." As such, amended claim 14 recites that the melanoma tumor is PD-L1 positive, and that the measuring occurs prior to administration. A person of ordinary skill in the art would have been able to readily identify the metes and bounds of amended claim 14. Therefore, amended claim 14 is definite.

Insofar as the Examiner's objection to claims 16-18 and 20 is due to their dependency on claim 14, these claims depend directly or indirectly from amended claim 14 and thus include every element of amended claim 14. Therefore, claims 16-18 and 20 are also definite. Accordingly, Applicant respectfully requests the Examiner reconsider and withdraw these rejections of claims 14, 16-18, and 20-21.

Claim 21

The Examiner rejected claim 21 under 35 U.S.C. § 112(b) for allegedly being indefinite. Office Action, page 3. Applicant respectfully disagrees. However, solely to advance prosecution, and

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without acquiescing to the Examiner's arguments, claim 21 is cancelled, rendering the Examiner's rejection moot. Accordingly, Applicant respectfully requests the Examiner withdraw this rejection.

Claim 50

The Examiner rejected claim 50 under 35 U.S.C. § 112(b) for allegedly being indefinite because the claim recites "PD-L1-positive melanoma tumor" but the Examiner contends that it is unknown how PD-L1 positivity is defined. Office Action, page 3. Applicant respectfully disagrees.

However, solely to advance prosecution, and without acquiescing to the Examiner's arguments, claim 50 is amended to recite "wherein the PD-L1-positive melanoma tumor is characterized by having at least about 1% of tumor cells showing cell-surface binding to an anti-PD-L1 antibody or an antigen-binding portion thereof." A person of ordinary skill in the art would be able to readily understand how PD-L1 positivity is defined by the claim, and thus amended claim 50 is definite. Accordingly, Applicant respectfully requests the Examiner reconsider and withdraw this rejection.

Rejections under 35 U.S.C. § 112(a)

Claims 2-3, 8, 14, 16-18, 20-21, 32, 34-38, 46, and 48-49 are rejected under 35 U.S.C. § 112(a) for allegedly failing to comply with the written description requirement. Office Action, pages 3-6. Though the Examiner notes that the specification provides written description support for administering nivolumab at the recited doses, the Examiner contends that the specification does not support recitation of any anti-PD-1 antibody, generically. *Id.* Applicant respectfully disagrees.

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However, solely to advance prosecution, and without acquiescing to the Examiner's arguments, claims 21, 48, and 49 are cancelled, rendering the Examiner's rejection of these claims moot. In addition, claim 2 is amended to recite a method for treating a melanoma in a human patient afflicted with a melanoma tumor comprising administering to the patient afflicted with a melanoma tumor nivolumab at a flat dose of 480 mg once every four weeks. Amended claim 2 recites that the anti-PD-1 antibody is nivolumab. As the Examiner notes, the specification provides written description support for a method for treating a melanoma comprising administering to a patient afflicted with a melanoma tumor nivolumab at a flat dose of 480 mg once every four weeks. It also would have been readily apparent to a person of ordinary skill in the art that the inventors had full possession of amended claim 2 in view of the specification as filed. For at least these reasons, amended claim 2 meets the written description requirement.

Insofar as the Examiner's rejection of claims 3, 8, 14, 16-18, 20, 32, 34-38, and 46 are based on their dependency from claim 2, claims 3, 8, 14, 16-18, 20, 32, 34-38, and 46 depend from amended claim 2 and thus include every element of amended claim 2. Therefore claims 3, 8, 14, 16-18, 20, 32, 34-38, and 46 also meet the written description requirement for the same reasons as amended claim 2. Accordingly, Applicant respectfully requests the Examiner reconsider and withdraw these rejections of claims 2-3, 8, 14, 16-18, 20-21, 32, 34-38, 46, and 48-49.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 2, 8, 14, 16-18, 21, 25, and 50 under 35 U.S.C. § 102(a)(1) for allegedly being anticipated by “Opdivo FDA Label,” March 2015 (the “Label”); and rejected claims

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2-3, 8, 14, 16-18, 20-21, 25, 32, 34-38, 46, 48, and 50 under 35 U.S.C. § 102(a)(2) for allegedly being anticipated by U.S. Patent Application Publication No. 2015/0125463 to Cogswell et al. (“Cogswell”). Office Action, pages 6-9. Applicant respectfully disagrees.

However, solely to advance prosecution, and without acquiescing to the Examiner's arguments, claims 21 and 25 are cancelled rendering the Examiner's rejection of these claims moot. In addition, claim 2 is amended to recite method for treating a melanoma in a human patient afflicted with a melanoma tumor comprising administering to the patient afflicted with a melanoma tumor nivolumab at a flat dose of 480 mg once every four weeks. Similarly, claim 50 is amended to recite a method for treating a melanoma in a human patient afflicted with a melanoma tumor, comprising administering to the patient nivolumab as a monotherapy at a flat dose of 480 mg once every four weeks, wherein the patient is identified as having a PD-L1-positive melanoma tumor prior to the administration, wherein the PD-L1-positive melanoma tumor is characterized by having at least about 1% of tumor cells showing cell-surface binding to an anti-PD-L1 antibody or an antigen-binding portion thereof.

The Examiner has pointed to no part of the Label or Cogswell that discloses a method for treating melanoma comprising administering nivolumab at a flat dose of 480 mg once every 4 weeks. Therefore, the Examiner has not established that either the Label or Cogswell discloses every element of amended claims 2 and 50. Therefore, amended claims 2 and 50 are novel over the Label and Cogswell.

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For at least these reasons, the methods of amended claims 2 and 50 are novel in view of the alleged disclosure of the Label. Claims 3, 8, 14, 16-18, 20-21, 25, 32, 34-38, and 46 depend directly or indirectly from amended claim 2 or 50 and thus include every element of amended claim 2 or 50. Therefore, amended claims 3, 8, 14, 16-18, 20-21, 25, 32, 34-38, and 46 are also novel over the Label. Accordingly, Applicant respectfully requests the Examiner reconsider and withdraw these rejections.

Alleged Double Patenting Rejections

Claims 2-3, 8, 25, 32, 34-38, 46, and 48

The Examiner rejected claims 2-3, 8, 25, 32, 34-38, 46, and 48 on the ground of nonstatutory double patenting for allegedly being unpatentable over claims 1-22 of U.S. Patent No. 9,856,320 ("the '320 patent"). Office Action, pages 9-11. Applicant respectfully disagrees.

As noted above, claim 2 is amended to recite a method for treating a melanoma comprising administering to a patient afflicted with a melanoma tumor nivolumab at a flat dose of 480 mg once every four weeks. The Examiner points to no claim of the '320 patent that recites a method of treating melanoma with nivolumab at a flat dose of 480 mg or an equivalent thereof. Nor does the Examiner provide any reason for a skilled artisan to modify one or more claims of the '320 patent in such a way as to arrive at the method of claim 2. Therefore, amended claim 2 is patentably distinct from the claims of the '320 patent.

Claims 3, 8, 14, 16-18, 20, 32, 34-38, and 46 depend directly or indirectly from amended claim 2 and thus include every element of amended claim 2. Therefore, claims 3, 8, 14, 16-18, 20, 32,

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34-38, and 46 are also patentable distinct from the claims of the '320 patent. Accordingly, Applicant respectfully requests the Examiner reconsider and withdraw this rejection.

Claims 2, 8, 14, 16-18, 20, 25, and 50

The Examiner rejected claims 2, 8, 14, 16-18, 20, 25, and 50 on the ground of nonstatutory double patenting for allegedly being unpatentable over claims 2-12 and 16 of U.S. Patent No. 10,174,113, which is the parent to this application. Office Action, pages 11-12. Solely to advance prosecution, and without acquiescing to the Examiner's arguments, Applicant submits herewith a terminal disclaimer to obviate the objection. Accordingly, Applicant respectfully requests that the rejection be reconsidered and withdrawn.

Claims 2, 8, 14, 16-18, 20-21, 25, and 50

The Examiner provisionally rejected claims 2, 8, 14, 16-18, 20-21, 25, and 50 on the ground of nonstatutory double patenting for allegedly being unpatentable over claims 3, 9, 15, 17-22, 26, 28-29, and 49 of copending U.S. Patent Application No. 16/430,106 ("the '106 application"), published as 2020/0010549. Office Action, page 12. Applicant respectfully disagrees.

As noted above, claim 2 is amended to recite a method for treating a melanoma comprising administering to a human patient afflicted with a melanoma tumor nivolumab at a flat dose of 480 mg once every four weeks. Claim 50 is similarly amended to recite, *inter alia*, administering to a human patient afflicted with a melanoma tumor nivolumab at a flat dose of 480 mg once every four weeks. The Examiner points to no claim of the '106 application that recites a method of treating

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melanoma with nivolumab at a dose of 480 mg or an equivalent thereof. Nor does the Examiner provide any reason for a skilled artisan to modify one or more claims of the '106 application in such a way as to arrive at the methods of amended claims 2 and 50. Therefore, amended claims 2 and 50 are patentably distinct from the pending claims of the '106 application.

Claims 21 and 25 are cancelled, rendering the Examiners provisional rejection of these claims moot. In addition, claims 8, 14, 16-18, and 20 depend directly or indirectly from amended claim 2 and thus include every element of amended claim 2. Therefore, claims 8, 14, 16-18, and 20 are also patentable distinct from the claims of the '106 application. Accordingly, Applicant respectfully requests the Examiner reconsider and withdraw this provisional rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant hereby respectfully requests that the Examiner reconsider all presently outstanding objections and 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.

/Brian M. Dudley/

Brian M. Dudley
Attorney for Applicant
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Date: June 24, 2021
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Atty. Dkt. No. 3338.0330003/ELE/C-K/BMD

Electronic Acknowledgement Receipt	
EFS ID:	43085016
Application Number:	16240316
International Application Number:	
Confirmation Number:	4170
Title of Invention:	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY
First Named Inventor/Applicant Name:	Arvin YANG
Customer Number:	115018
Filer:	Brian Mason Dudley/Jeanette Yando
Filer Authorized By:	Brian Mason Dudley
Attorney Docket Number:	3338.0330003/ELE/C-K/BMD
Receipt Date:	24-JUN-2021
Filing Date:	04-JAN-2019
Time Stamp:	18:31:31
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	Transmittal Letter	2021-06-24- Transmittal-3338-0330003.PDF	233102 7fcd80bbb23c79498cf7c15e5e9b3fda6bfe414d	no	2
Warnings:					

Information:					
2	Application Data Sheet	2021-06-24-Marked-up-ADS-3338-0330003.pdf	161315	no	8
			94e2f168d81160e7ade293517977f21ef1d7b5b7		
Warnings:					
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3		2021-06-24-Amendment-Reply-111-3338-0330003.pdf	164351	yes	16
			ea96cca3204f0637af388f506ae2d60b5ca194c1		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Specification		2	2	
	Claims		3	6	
	Applicant Arguments/Remarks Made in an Amendment		7	16	
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TRANSMITTAL FORM <i>(to be used for all correspondence after initial filing)</i>	Application Number	16/240,316
	Filing Date	January 4, 2019
	First Named Inventor	Arvin Yang
	Art Unit	1644
	Examiner Name	OUSPENSKI, Ilia I.
Total Number of Pages in This Submission	Attorney Docket Number	3338.0330003/ELE/C-K

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): Application Data Sheet
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	/Brian M. Dudley/	
Printed name	Brian M. Dudley	
Date	June 24, 2021	Reg. No. 77,546

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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.
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	3338.0330003/ELE/C-K/BMD
		Application Number	16/240,316
Title of Invention	~~TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-GTLA-4 ANTIBODY~~ TREATMENT OF MELANOMA USING AN ANTI-PD-1 ANTIBODY		
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.)
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Inventor 1 Remove				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Arvin		YANG	
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service				
City	Princeton	State/Province	NJ	Country of Residence US
Mailing Address of Inventor:				
Address 1		Rt. 206 & Province Line Road		
Address 2				
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All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. Add				

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Application Information:

Title of the Invention	~~TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-GTLA-4 ANTIBODY~~ TREATMENT OF MELANOMA USING AN ANTI-PD-1 ANTIBODY		
Attorney Docket Number	3338.0330003/ELE/C-K/BMD	Small Entity Status Claimed ☐	
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	6	Suggested Figure for Publication (if any)	

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	3338.0330003/ELE/C-K/BMD
		Application Number	16/240,316
Title of Invention	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY— TREATMENT OF MELANOMA USING AN ANTI-PD-1 ANTIBODY		

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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.

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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.

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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	15/141769	2016-04-28

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	3338.0330003/ELE/C-K/BMD
		Application Number	16/240,316
Title of Invention	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY TREATMENT OF MELANOMA USING AN ANTI-PD-1 ANTIBODY		
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/141769	Claims benefit of provisional	62/153973	2015-04-28
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			

Foreign Priority Information:

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	3338.0330003/ELE/C-K/BMD
		Application Number	16/240,316
Title of Invention	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY TREATMENT OF MELANOMA USING AN ANTI-PD-1 ANTIBODY		

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.

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	3338.0330003/ELE/C-K/BMD
		Application Number	16/240,316
Title of Invention	~~TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY~~ TREATMENT OF MELANOMA USING AN ANTI-PD-1 ANTIBODY		

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.

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	3338.0330003/ELE/C-K/BMD
		Application Number	16/240,316
Title of Invention	TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY TREATMENT OF MELANOMA USING AN ANTI-PD-1 ANTIBODY		

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	/Brian M. Dudley/		Date (YYYY-MM-DD)	2021-06-24	
First Name	Brian M.	Last Name	Dudley	Registration Number	77546
Additional Signature may be generated within this form by selecting the Add button.					

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	3338.0330003/ELE/C-K/BMD
		Application Number	<u>16/240,316</u>
Title of Invention	~~TREATMENT OF PD-L1-NEGATIVE MELANOMA USING AN ANTI-PD-1 ANTIBODY AND AN ANTI-CTLA-4 ANTIBODY~~ — <u>TREATMENT OF MELANOMA USING AN ANTI-PD-1 ANTIBODY</u>		

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.**

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:

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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 inspections 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.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/240,316	01/04/2019	Arvin YANG	3338.0330003/ ELE/C-K/BMD	4170
115018	7590	08/11/2021	EXAMINER	
Sterne, Kessler, Goldstein & Fox P.L.L.C. 1100 New York Avenue NW Washington, DC 20005			OUSPENSKI, ILIA I	
			ART UNIT	PAPER NUMBER
			1644	
			NOTIFICATION DATE	DELIVERY MODE
			08/11/2021	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

DETAILED ACTION

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

2. Applicant's amendment and remarks filed on 04/24/2021 are acknowledged. Claims 2, 3, 8, 14, 16-18, 20, 32, 34-38, 46 and 50-52 are pending.

3. The following is a quotation of **35 U.S.C. 112(a)**:

(a) IN GENERAL.—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 or joint inventor of carrying out the invention.

4. Claims 35 and 36 stand rejected under **35 U.S.C. 112(a)** because the specification, while being enabling for a method for treating melanoma comprising administering ipilimumab at 1 or 3 mg/kg every 3 weeks, or at about 80 mg, 160 mg, or 240 mg every 2, 3 or 4 weeks, does not reasonably provide enablement for a method for treating melanoma comprising administering a generically recited anti-CTLA4 antibody at 1 or 3 mg/kg every 3 weeks, or at about 80 mg, 160 mg, or 240 mg every 2, 3 or 4 weeks.

The rejection set forth in section 8 of the previous office action dated 03/24/2021 is maintained for the reasons of record, insofar as it applies to the recitation of administration of a generic anti-CTLA4 antibody at a specific dosing schedule.

Applicant does not appear to have addressed these grounds of rejection, which are maintained and incorporated by reference herein as if reiterated in full.

5. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, provisional application USSN 62153973 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for the claims of the present application. Specifically, sufficient support could not be identified for the limitation of administering nivolumab at a flat dose of 480 mg once every 4 weeks.

Consequently, presently pending claims have been accorded the priority of the filing date of parent application USSN 15141769, i.e. 04/28/2016. Should Applicant disagree with the Examiner's factual determination above, it is incumbent upon Applicant to provide a showing that specifically supports these claim limitations.

6. The following is a quotation of the appropriate paragraphs of **35 U.S.C. 102** that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

7. Claims 2 and 8 are rejected under **35 U.S.C. 102(a)(2)** as being anticipated by Cai et al. (US 20180237534; see entire document).

Cai teaches methods of treating cancer which comprise administering an anti-PD-1 antibody at 480 mg administered once every 4 weeks (e.g. [0595]), wherein the antibody is nivolumab (e.g. [0599]) and the cancer is melanoma (e.g. [0638]), thereby anticipating claim 2. Since Cai's method is within the scope of claim 2, it inherently produces the same outcomes as the method of claim 2, including those recited in claim 8.

8. Claims 2 and 8 are rejected under **35 U.S.C. 102(a)(2)** as being anticipated by Coric et al. (US Patent No. 10392442; see entire document).

Coric teaches and claims a method of treating cancer comprising administering nivolumab at a flat dose of about 480 mg once about every 4 weeks (e.g. claims 1, 7 and 18), wherein the cancer is melanoma (e.g. claim 2), thereby anticipating instant claims 2 and 8.

9. Claims 2, 3, 8, 14, 16-18, 32, 34-38, 46 and 50-52 are rejected under **35 U.S.C. 102(a)(2)** as being anticipated by Nathan et al. (US 20210206854; see entire document).

Nathan reviews that nivolumab has shown activity in a variety of advanced solid tumors including melanoma (e.g. [0005], [0149]), and that “[c]oncurrent therapy with nivolumab and ipilimumab in a Phase 1 clinical trial produced rapid and deep tumor regression in a substantial proportion of patients with advanced melanoma, and was significantly more effective than either antibody alone” ([0006], citing Wolchok et al. 2013; see also [0116], [0165]). Ipilimumab (Yervoy™) is approved for the treatment of melanoma at 3 mg/kg given intravenously once every 3 weeks, but may be used at 1 mg/kg when combined with nivolumab (e.g. [0123]).

Nathan further teaches that the anti-PD-1 antibody is administered at a flat dose of at least about 480 mg every 4 weeks (e.g. [0011], [0058], [0059], [0063], [0064], [0071], [0141]), and describes in Example 2 ([0574]-[0762], and Fig. 2) the design of a Phase 3b/4 dose frequency optimization study of nivolumab 240 mg every 2 weeks vs. nivolumab 480 mg every 4 weeks in subjects with non-small cell lung cancer.

Nathan discusses evaluation of PD-L1 expression as a predictive biomarker ([0182]-[0200]). Specifically, the proportion of cells in a tumor sample that express PD-L1 on the cell surface can be measured prior to the treatment (e.g. [0184]-[0185]). Cell surface expression of PD-L1 is assayed using automated IHC in FFPE tissue specimens [0187]-[0189].

In particular, “[i]n another embodiment, the PD-L1 status of a tumor is at least about 1%. In other embodiments, the PD-L1 status of the subject is at least about 5%” [0197]. Nathan further states: “PD-L1 positive” as used herein can be interchangeably used with “PD-L1 expression of at least about 1%” [0200]. And further: “Analyses based on archival specimens for subjects in CA209012 have shown that subjects with both PD-L1+ (IHC greater than or equal to 5%) and PD-L1 tumors may benefit from treatment with nivolumab” [0202].

Nathan reviews the nivolumab and ipilimumab dosing regimen used in clinical trials of melanoma patients and applies them to lung cancer patients (e.g. [0123]), i.e. Nathan assumes that the same regimen are applicable to these types of cancer. Accordingly, Nathan’s teachings include all of the limitations of the instant claims, and as such are anticipatory.

10. The following is a quotation of **35 U.S.C. 103** which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claims 2, 14, 16-18 and 20 are rejected under **35 U.S.C. 103** as being unpatentable over Nathan et al. (US 20210206854; see entire document) in view of Cogswell et al. (US Patent No. 10072082; cited on IDS; see entire document).

As addressed in section 8 above, Nathan teaches a method of treating cancer comprising administering to the patient nivolumab at a flat dose of 480 mg once every 4 weeks, wherein at least about 1% of tumor cells are PD-L1 positive, as determined by automated IHC in FFPE tumor specimen using an anti-PD-L1 antibody.

While Nathan does not specifically exemplify anti-PD-L1 antibody comprising SEQ ID NOS 1 and 2 recited in instant claim 20 (also known as antibody 28-8 – see e.g. p. 30 of the present specification), it was known in the art before the effective filing date of the claimed invention that this antibody is useful for quantifying PD-L1 expression in FFPE tumor specimen by automated IHC.

For example, Cogswell teaches and claims a method of treating cancer, comprising selecting a subject whose tumor cells comprise at least 1% of PD-L1-expressing cells, as determined by IHC with an anti-PD-L1 antibody, and administering an anti-PD-1 antibody to the subject (claim 1). The anti-PD-L1 antibody comprises SEQ ID NOS 35 and 36, which are identical to instant SEQ ID NOS 1 and 2, respectively (see SCORE). The cancer is melanoma, renal cell carcinoma, or NSCLC (e.g. claim 27), and the anti-PD-1 antibody is nivolumab (e.g. claim 16). The method further comprises administering an anti-CTLA4 antibody such as ipilimumab (e.g. claims 17-21), which is administered simultaneously or sequentially with nivolumab (e.g. claims 22-23).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had both motivation and expectation of success in using the anti-PD-L1 antibody taught by Cogswell in the presently claimed method, because it is taught to be useful for reliably quantifying cell surface expression of PD-L1 in FFPE

tumor specimen by automated IHC, a property which few antibodies possess, as a skilled artisan is aware.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention, as evidenced by the references, especially in the absence of evidence to the contrary.

12. The nonstatutory **double patenting** rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(I)(1) - 706.02(I)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-l.jsp.

13. Claims 2 and 8 are rejected on the ground of nonstatutory **double patenting** as being unpatentable over at least claims 1-2, 7 and 18 of U.S. Patent No. 10392442 (described in section 7 above).

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the claims of the '442 Patent (described in section 7 above), which are directed to a method of treating cancer comprising administering nivolumab at a flat dose of about 480 mg once about every 4 weeks (e.g. claims 1, 7 and 18), wherein the cancer is melanoma (e.g. claim 2).

14. Claims 2 and 8 are rejected on the ground of nonstatutory **double patenting** as being unpatentable over the claims of U.S. Patent No. 11078278.

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are obvious over the claims of the '278 Patent, which are directed to a method of treating renal cell carcinoma comprising administering nivolumab at a flat dose of about 480 mg once about every 4 weeks (e.g. claims 1, 11, 14 and 18). It would have been obvious to a person of ordinary skill in the art before the effective filing date of the claimed invention to apply the treatment to melanoma, because nivolumab was previously approved for that indication, and

because administering nivolumab every 4 weeks rather than every 2 weeks has obvious advantages.

15. Claims 2-3, 8, 14, 16-18, 37-38, 46 and 50-52 are rejected on the ground of nonstatutory **double patenting** as being unpatentable over the claims of U.S. Patent No. 10544224.

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are obvious over the claims of the '224 Patent, which are directed to a method of treating an HPV-positive squamous cell carcinoma head and neck cancer comprising administering nivolumab at a flat dose of about 480 mg once every 4 weeks (e.g. claims 1-2), wherein the tumor expresses PD-L1 (e.g. claims 7 and 19). The method further comprises administering an anti-CTLA4 antibody and/or chemotherapy (e.g. claims 8-14). It would have been obvious to a person of ordinary skill in the art before the effective filing date of the claimed invention to apply the treatment to melanoma, because nivolumab was previously approved for that indication, and because administering nivolumab every 4 weeks rather than every 2 weeks has obvious advantages. Although in stipulating that the tumor expresses PD-L1 the claims of the '224 Patent do not recite a specific percentage of PD-L1 positive cells required for the tumor to be considered PD-L1 positive, a skilled artisan would reasonably assume 1% to be the minimal reasonable cutoff level, and a 5% level was also known to have been used in the art. Claim 18 is included in the rejection, because IHC of FFPE specimen was one of the standard methods for ascertaining protein expression in tumor samples.

16. Claims 2, 3, 8, 32, 34-38 and 46 are provisionally rejected on the ground of nonstatutory **double patenting** as being unpatentable over at least claims 1, 5 and 12-13 of copending application USSN 16/649277, published as US 20210030739.

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the claims of the '277 application, directed to a method of treating melanoma (claims 1 and 5) comprising administering a combination of nivolumab at 480 mg every 4 weeks and ipilimumab at 3 mg/kg every 3 weeks (claims 12 and 13).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

17. Claims 2, 3, 8, 37 and 38 are provisionally rejected on the ground of nonstatutory **double patenting** as being unpatentable over at least claims 1, 11-15 and 21 of copending application USSN 16/499540, published as US 20210101980.

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the claims of the '540 application, directed to a method of treating a tumor such as melanoma (claims 1 and 11) comprising administering nivolumab at 480 mg every 4 weeks (claims 1, 12, 14 and 21) in combination with an anti-CTLA4 antibody (claim 15).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

18. Claims 2, 8, 14, 16-18, 20 and 51 are provisionally rejected on the ground of nonstatutory **double patenting** as being unpatentable over claims ## of copending application USSN 17/044753, published as US 20210147570, as evidenced e.g. by the present specification at p. 30.

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are anticipated by or obvious over the claims of the '753 application.

The latter are directed to a method of treating cancer comprising administering an anti-PD-1 antibody comprising SEQ ID NOS: 15 and 17 (i.e. nivolumab) once every four weeks at a fixed dose of 480 mg (claim 59), wherein the method comprises first measuring the expression level of PD-L1 by IHC with antibody "28-8", and treating the subject if the expression level of PD-L1 is at least 1% or at least 5% (claim 67). Although the claims of the '753 application do not specify the type of cancer to be treated, the skilled artisan would understand that melanoma is among them, since nivolumab was earlier approved for the treatment of melanoma.

The present specification discloses at p. 30, last paragraph, that "an anti-PD-L1 antibody useful for the present methods includes mAb 28-8 set forth in SEQ ID NOS: 1 and 2," i.e. the IHC assay recited in claim 67 of the '753 application utilizes the same anti-PD-L1 antibody as recited in instant claim 20.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

19. Claims **2 and 8** are provisionally rejected on the ground of nonstatutory **double patenting** as being unpatentable over at least claims 1, 2, 5, 18 and 21 of

copending application USSN 16/073676, published as US 20210206854 (discussed in section 8 above).

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are obvious over the claims of the '676 application.

The latter are directed to a method of treating lung cancer comprising administering an anti-PD-1 antibody such as nivolumab and an anti-CTLA4 antibody such as ipilimumab, wherein nivolumab is administered at a flat dose of about 480 mg once about every 4 weeks (e.g. claims 1, 2, 5, 18 and 21). Although the copending claims do not recite melanoma, a person of ordinary skill in the art would have been aware that nivolumab was initially approved for melanoma, and that clinical trials of nivolumab in other cancer types were using the same dosing regimen as a starting point. The skilled artisan would have been motivated to use the dosing regimen of the '676 application for treating melanoma because of the advantages of lower frequency of antibody infusions (every 4 weeks) as compared to previously used biweekly infusions.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

20. Claims 2-3, 8, 37-38 and 46 are provisionally rejected on the ground of nonstatutory **double patenting** as being unpatentable over the claims of copending application USSN 16/768838, published as US 20210054063.

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the claims of the '838 application, directed to a method of treating a solid tumor comprising administering nivolumab every 4 weeks or 28 days (claims 1 and 3) at a dose of 480 mg (claims 6 and

14), wherein the tumor is melanoma (claim 23), and further comprising administering an anti-CTLA4 antibody such as ipilimumab (claims 49-50).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

21. Claims 2 and 8 are provisionally rejected on the ground of nonstatutory **double patenting** as being unpatentable over the claims of copending application USSN 16/646690, published as US 20210009697.

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are obvious over the claims of the '690 application, which are directed to a method of treating pancreatic cancer comprising administering nivolumab at 480 mg once every four weeks (e.g. claims 53-55 and 61). It would have been obvious to a person of ordinary skill in the art before the effective filing date of the claimed invention to apply the treatment to melanoma, because nivolumab was previously approved for that indication, and because administering nivolumab every 4 weeks rather than every 2 weeks has obvious advantages.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

22. Claims 2, 8, 14, 16-18 and 50 are provisionally rejected on the ground of nonstatutory **double patenting** as being unpatentable over the claims of copending application USSN 16/306380, published as US 20200325226.

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are obvious over the claims of the '380 application, which are directed to a method of treating NSCLC comprising administering nivolumab at 480 mg once every four weeks (e.g. claims 1-2, 11, 20, 24 and 26), wherein at least 1% of tumor cells express PD-L1 (e.g. claim 8). It would have been obvious to a person of ordinary skill in the art before the effective filing date of the claimed invention to apply the treatment to melanoma, because nivolumab was previously approved for that indication, and because administering nivolumab every 4 weeks rather than every 2 weeks has obvious advantages.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

23. Claims 2, 8, 14, 16-18 and 50-52 are provisionally rejected on the ground of nonstatutory **double patenting** as being unpatentable over the claims of copending application USSN 16/617725, published as US 20200109204.

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are obvious over the claims of the '725 application, which are directed to a method of treating a subject afflicted with a tumor comprising administering nivolumab at 480 mg once every four weeks (e.g. claims 1, 12 and 14), wherein the tumor exhibits PD-L1 expression (e.g. claims 7-8). Although the claims of the '725 application do not specify the type of cancer being treated, a skilled artisan was aware that nivolumab was previously approved for treating melanoma. Although in stipulating that the tumor expresses PD-L1 the claims of the '725 application do not recite a specific percentage of PD-L1 positive cells required for the tumor to be considered PD-L1 positive, a skilled artisan would reasonably assume 1% to be the minimal reasonable cutoff level, and a 5% level was also known to have been used in the art. Claim 18 is included in the rejection, because IHC of FFPE specimen was one of the standard methods for ascertaining protein expression in tumor samples.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

24. Conclusion: no claim is allowed.

25. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA IOUSPENSKI 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 IOUSPENSKI/
Primary Examiner, Art Unit 1644

Notice of References Cited	Application/Control No. 16/240,316		Applicant(s)/Patent Under Reexamination YANG, Arvin	
	Examiner ILIA I OUSPENSKI		Art Unit 1644	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20180237534-A1	08-2018	CAI; Zhehong	C07K16/3069	1/1
*	B	US-10392442-B2	08-2019	Coric; Vladimir	C07K16/2818	1/1
*	C	US-20210206854-A1	07-2021	NATHAN; Faith	A61P35/00	1/1
*	D	US-11078278-B2	08-2021	Simon; Jason Samuel	C07K16/2803	1/1
*	E	US-10544224-B2	01-2020	Manekas; Demetrios	C12Q1/708	1/1
*	F	US-20210030739-A1	02-2021	BASCIANO; Paul Andrew	A61K9/0019	1/1
*	G	US-20210101980-A1	04-2021	BHAGAVATHEESWARAN; Prabhu Seshaiyer	C07K16/2818	1/1
*	H	US-20210147570-A1	05-2021	ALTURA; Rachel A.	C07K16/2827	1/1
*	I	US-20210054063-A1	02-2021	CARLETON; Michael	A61P35/00	1/1
*	J	US-20210009697-A1	01-2021	Lewis; Katherine E.	A61K31/337	1/1
*	K	US-20200325226-A1	10-2020	EDWARDS; Robin	A61P11/00	1/1
*	L	US-20200109204-A1	04-2020	EDWARDS; Robin	A61P35/00	1/1
	M					

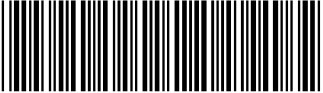
FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

<i>Search Notes</i> 	Application/Control No. 16/240,316	Applicant(s)/Patent Under Reexamination YANG, Arvin
	Examiner ILIA IOUSPENSKI	Art Unit 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	03/20/2021	io
Sequence search: in SCORE	03/20/2021	io
WEST: attached	03/20/2021	io
Dialog: attached	03/20/2021	io
Inventor search	03/20/2021	io
Sequence, WEST and Inventor searches updated	08/06/2021	io

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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WEST Search History

DATE: Friday, August 06, 2021

Hide?	<u>Set</u> <u>Name</u>	<u>Query</u>	<u>Hit</u> <u>Count</u>
	<i>DB=PGPB,USPT; THES=ASSIGNEE; PLUR=YES; OP=ADJ</i>		
☐	L63	L62 and melanoma.clm.	4
☐	L62	L61 and L48.clm.	12
☐	L61	L60 or L58	15
☐	L60	L56 and (28 day\$4).clm.	2
☐	L58	L56 and ((4 week\$) or (four week\$)).clm.	15
☐	L57	L54 and melanoma.clm.	10
☐	L56	L54 and (480 mg).clm.	18
☐	L55	L53 and L48.clm.	31
☐	L54	L53 and L46.clm.	34
☐	L53	L52 and (Bristol\$.as,aanm. or yang-a\$.in.)	43
☐	L52	L51 or L50	76
☐	L51	L48 near25 (480 mg)	55
☐	L50	L49 same L48	40
☐	L49	L47 near25 (480 mg)	63
☐	L48	(nivolumab or 5C4 or BMS-936558 or bms936558 or MDX-1106\$ or mdx1106 or (mdx 1106) or GTPL7335 or gtpl-7335 or ONO-4538 or ono4538 or Opdivo\$)	11651
☐	L47	((((programmed adj2 death adj2 1) or pd-1\$ or hpd-1\$ or pd1\$ or hpd1\$ or pdcd1\$ or pdcd-1\$ or hpdc1\$ or cd279\$) near10 (antibod\$10 or ab)) or (anti-pd-1\$ or anti-hpd-1\$ or anti-pd1\$ or anti-hpd1\$ or anti-pdcd1\$ or anti-cd279\$ or ".alpha.pd-1\$" or ".alpha.hpd-1\$" or ".alpha.pd1\$" or alpha-pd-1\$ or alpha-pd1\$)	13825
☐	L46	((programmed adj2 death adj2 1) or pd-1\$ or hpd-1\$ or pd1\$ or hpd1\$ or pdcd1\$ or pdcd-1\$ or hpdc1\$ or cd279\$ or anti-pd-1\$ or anti-hpd-1\$ or anti-pd1\$ or anti-hpd1\$ or anti-pdcd1\$ or anti-cd279\$ or ".alpha.pd-1\$" or ".alpha.hpd-1\$" or ".alpha.pd1\$" or alpha-pd-1\$ or alpha-pd1\$)	68337

END OF SEARCH HISTORY



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/240,316	01/04/2019	Arvin YANG	3338.0330003/ ELE/C-K/BMD	4170
115018	7590	02/18/2022	EXAMINER	
Sterne, Kessler, Goldstein & Fox P.L.L.C. 1100 New York Avenue NW Washington, DC 20005			OUSPENSKI, ILIA I	
			ART UNIT	PAPER NUMBER
			1644	
			NOTIFICATION DATE	DELIVERY MODE
			02/18/2022	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

<i>Notice of Abandonment</i>	Application No.	Applicant(s)
	16/240,316	YANG, Arvin
	Examiner	Art Unit
	ILIA I OUSPENSKI	1644

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

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on 11 August 2021.
 - (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
 - (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 to the final rejection. (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) if this is utility or plant application, a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. Note that RCEs are not permitted in design applications.)
 - (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a *bona fide* attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 8 below).
 - (d) ☒ No reply has been received.
2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
 - (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
 - (b) ☐ The submitted fee of \$ _____ is insufficient. A balance of \$ _____ is due.
The issue fee required by 37CFR 1.18 is \$ _____. The publication fee, if required by 37 CFR 1.18(d), is \$ _____.
 - (c) ☐ The issue fee and publication fee, if applicable, has not been received.
3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
 - (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
 - (b) ☐ No corrected drawings have been received.
4. ☐ The letter of express abandonment which is signed by the attorney or agent of record or other party authorized under 37 CFR 1.33 (b). See 37 CFR 1.138(b).
5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34) upon the filing of a continuing application.
6. ☐ The decision by the Patent Trial and Appeal Board rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.
7. ☐ The dismissal of the appeal in an application having no allowed claims. (When an appeal is dismissed in an application having no allowed claims the application stands abandoned. See MPEP 1215.04 subsections I-V for an explanation of the reasons why an appeal is dismissed.)
8. ☐ The reason(s) below:

/ILIA I OUSPENSKI/
Primary Examiner, Art Unit 1644

Petitions to revive under 37 CFR 1.137, or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.