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Placeholder Sheet for Supplemental Content

Application Number: 19346638 Document Date: 10/01/2025

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- Drawing

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Form Revision Date: March 1, 2024

Halozyme EX2002
Merck v. Halozyme
IPR2026-00314

Doc Code - SEQ.XML

WIPO Type Code -

SLIC Placeholder Sheet for P-ELP (CMS) Content

Application Number: 19346638 Document Date: 10/01/2025

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- Sequence Listing

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Form Revision Date: 07 January 2022

Application Number: 19346638

Reviewed by: 97ClN/eHe4jhmn5GMimwpAP70alPRU2kNiDwvOWHBrv8bqgC4kdzMg==

Note: This validation report concerns the sequence listing filed 10-01-2025 09:01:01 and indicates that NO errors were found by the USPTO during validation of the sequence listing. This validation report should not be construed as meaning that the sequence listing complies with all of the requirements of 37 CFR §§ 1.821-1.825, 37 CFR §§ 1.831-1.835 and 1.839, WIPO Standard ST.25, or WIPO Standard ST.26.

For any sequence listing related questions or concerns, the Applicant is invited to contact the USPTO Sequence Listing Help Desk at 571-272-2510 or SequenceHelpDesk@USPTO.GOV.

Timestamp: [year=2025; month=10; day=1; hr=10; min=1; sec=10; ms=566]

Validated By CRFValidator v 2.3.0

Application No: 19346638 Version No: 1.1

CRF Copy Request from application : Version :

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No. of SeqIDs Defined: **0**
Actual SeqID Count: **34**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Manoj K. SHARMA, *et al.*	Docket No.:	24439-US-CNT-4
Application No.:	To Be Assigned	Confirmation No.:	TBA
Filed:	Concurrently Herewith	Art Unit:	TBA
Title:	STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF	Examiner:	TBA

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Madam:

(a) Pursuant to the duty of disclosure under 37 C.F.R. § 1.56, it is requested that the documents listed on the accompanying form(s) PTO/SB/08a and/or PTO/SB/08b be considered and made of record in the above-identified patent application. Copies of each cited U.S. patent and published patent application are not enclosed herewith, pursuant to 37 C.F.R. § 1.98(a)(2)(ii).

(b) Pursuant to 37 C.F.R. § 1.98(d), copies of references listed on the accompanying form(s) PTO/SB/08a and/or PTO/SB/08b that were submitted to or cited by the Office in earlier filed applications upon which the instant application relies on for an earlier effective filing date under 35 U.S.C. § 120 are not enclosed. The earlier filed applications in which references were submitted to or cited the Office are as follows:

Earlier Filed Applications		
U.S. Application No.	Filing Date	Attorney Docket No.
18/182,135	March 10, 2023	24439-US-CNT-2
16/609,612	October 30, 2019	24439-US-PCT

Copies of these documents are not herewith transmitted, but will be provided upon request.

(c) In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in the Statement is, or is considered to be, material to patentability as defined under 37 C.F.R. § 1.56(b). In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made.

(d) Applicant(s) respectfully requests that the Examiner initial the attached form(s) PTO/SB/08a and/or PTO/SB/08b after reviewing the pertinence of each reference.

(e) ☒ No fee is believed due because:

- ☒ This Information Disclosure Statement is being submitted within three (3) months of the filing date of the above-identified application; **or**
- ☐ This Information Disclosure Statement is being submitted within three (3) months of the date of entry of the national stage as set forth in 37 C.F.R. § 1.491 in an international application, **or**
- ☐ This Information Disclosure Statement is being submitted before the mailing of a first Office Action on the merits, **or**
- ☐ This Information Disclosure Statement is being submitted before the mailing of a first Office Action after the filing of a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114.

(f) ☐ This Information Disclosure Statement is being submitted before the mailing date of any final action, notice of allowance or an action that otherwise closes prosecution; and

- ☐ Each item of information contained in this Information Disclosure Statement was first cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement, and no fee is due; **or**
- ☐ No item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned after making reasonable inquiry, no item of information contained in this Information Disclosure Statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement, and no fee is due; **or**
- ☐ The Commissioner is hereby authorized to charge the fee set forth in 37 C.F.R. § 1.17(p).

(g) ☐ This Information Disclosure Statement is being submitted after the period specified in (f) and on or before the payment of the issue fee; and

- ☐ Each item of information contained in this Information Disclosure Statement was first cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement, and the Commissioner is hereby authorized to charge the fee set forth in 37 C.F.R. § 1.17(p); **or**
- ☐ No item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned after making reasonable inquiry, no item of information contained in this Information Disclosure Statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement, and the Commissioner is hereby authorized to charge the fee set forth in 37 C.F.R. § 1.17(p).

(h) ☐ In accordance with 37 C.F.R. § 1.704(d), each item of information contained in this Information Disclosure Statement:

☐ was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than 30 days prior to the filing of this information disclosure statement; or

☐ is a communication from a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than 30 days prior to the filing of this information disclosure statement.

☒ The Commissioner is hereby authorized to charge any additional fees which may be required for this Information Disclosure Statement, or credit any overpayment to Deposit Account No. 13-2755.

Dated: September 19, 2025

Respectfully submitted,

By: /Patrick Rehfuss, Reg. No. 75,367/

Patrick Rehfuss
Registration No.: 75,367
Attorney for Applicant

MERCK SHARP & DOHME LLC
P.O. Box 2000
Rahway, NJ 07065-0907
732-594-5491

PTO/AIA/80 (07-17)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no person is required to respond to a collection of information unless it displays a valid OMB control number

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

[x] Practitioners associated with Customer Number: 210

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

[x] The address associated with Customer Number: 210

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: Merck Sharp & Dohme LLC
126 East Lincoln Avenue
Rahway, NJ 07065

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee.

Signature /Cynthia A. Francisco/	Date September 3, 2025
Name Cynthia A. Francisco	Telephone
Title Executive Director, IP Administration	

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 18 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.

MERCK & CO., INC.

CERTIFICATION

I, Kelly E.W. Grez, Corporate Secretary of Merck & Co., Inc., a corporation duly organized and existing under the laws of the State of New Jersey, United States of America (the "Company"), do hereby certify that the attached: (1) is a true and correct copy of General Corporate Resolution #5 - Patent Matters, as amended by the Board of Directors of the Company at a meeting thereof duly called and held on July 22, 2025; and (2) is in full force and effect as of the date hereof.

IN WITNESS WHEREOF, I have hereunto subscribed my signature and affixed the seal of the Company this 29th day of July, 2025.

Merck & Co., Inc. CORPORATE SEAL 1970 NEW JERSEY

By: Kelly E.W. Grez
Title: Corporate Secretary

United States of America)
State of New Jersey) ss
County of Union)

Before me personally appeared Kelly E.W. Grez personally known to me and known by me to be the person who executed the foregoing document in my presence this 29th day of July, 2025.

KAREN R. ETTELMAN
Notary Public, State of New Jersey
Comm. # 50041653
My Commission Expires 7/11/2026

General Corporate Resolution #5

PATENT MATTERS

RESOLVED, that any of the following:

Robert M. Davis – Chairman, Chief Executive Officer and President
Jennifer Zachary – Executive Vice President and General Counsel
Laura M. Ginkel – Senior Vice President and Assistant General Counsel
Mark Stewart – Vice President, Global IP Litigation
Anna L. Cocuzzo – Associate Vice President, Group Managing Counsel
Alysia Finnegan – Associate Vice President, Group Managing Counsel
Catherine D. Fitch – Managing Counsel, Patents
Emily K. Sauter – Managing Counsel, Patents
Jenny Cromsigt – Managing Counsel, Animal Health IP
John C. Todaro – Managing Counsel, Patents
Andrew W. Custer – Managing Counsel, Patents
Deeba Hussain – Assistant Managing Counsel, European Patents
James Horgan – Director, IP Litigation
Cynthia A. Francisco – Executive Director, IP Administration

are hereby authorized to execute and to revoke on behalf of Merck & Co., Inc. and its affiliates (including subsidiaries) the following documents relating to patent matters:

Powers of attorney as fully in law as may be necessary and proper in connection with the acquisition, registration, maintenance and enforcement of patents and applications for patents, including powers of attorney relating to the prosecution or defense of patent rights before courts of law or other governmental tribunals, agencies or departments; affidavits and declarations; and any other documents which are necessary and proper for the acquisition, registration, maintenance, litigation and protection of patents.

Attorney Docket No. 24439

Substitute for PTO/AIA/01

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

Title of Invention: STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

Inventors: Manoj K. Sharma, Wendy Benjamin, Sarita Mittal, Ashwin Basarkar, Chakravarthy Nachu Narasimhan, Ramesh S. Kashi, Mohommed Shameem, Soumendu Bhattacharya, William P. Forrest,Jr., Yogita Krishnamachari

As the below named inventor, I declare that:

This declaration is directed to:

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☐ The attached application;

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☐ As amended on (if applicable); or

☐ Application No. filed on ;

☐ As amended on (if applicable).

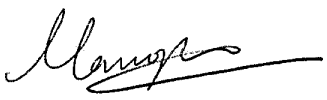
The above-identified application was made or authorized to be made by me.

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

I have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part 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.

LEGAL NAME OF INVENTOR	
Inventor: Manoj K. Sharma Signature: 	Date: 13 Nov 2019

Note: Use an additional PTO/AIA/01 (or substitute) form for each additional inventor.

Attorney Docket No. 24439

Substitute for PTO/AIA/01

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

Title of Invention: STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

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☐ Application No. , which is a 371 National Stage of PCT/ filed on ;

☐ As amended on (if applicable); or

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LEGAL NAME OF INVENTOR	
Inventor: Wendy Benjamin Signature: Wendy Benjamin	Date: 06 Nov 2019

Note: Use an additional PTO/AIA/01 (or substitute) form for each additional inventor.

Attorney Docket No. 24439

Substitute for PTO/AIA/01

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Title of Invention: STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

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LEGAL NAME OF INVENTOR	
Inventor: Sarita Mittal Signature: Sarita Mittal	Date: 12 NOV 2019

Note: Use an additional PTO/AIA/01 (or substitute) form for each additional inventor.

Attorney Docket No. 24439

Substitute for PTO/AIA/01

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Title of Invention: STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

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LEGAL NAME OF INVENTOR	
Inventor: Ashwin Basarkar Signature:	Date: 15 Nov 2019

Note: Use an additional PTO/AIA/01 (or substitute) form for each additional inventor.

Attorney Docket No. 24439

Substitute for PTO/AIA/01

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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.

LEGAL NAME OF INVENTOR	
Inventor: Chakravarthy Nachu Narasimhan Signature: CNarasimhan	Date: 31 Oct 2019

Note: Use an additional PTO/AIA/01 (or substitute) form for each additional inventor.

Attorney Docket No. 24439

Substitute for PTO/AIA/01

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LEGAL NAME OF INVENTOR	
Inventor: Ramesh S. Kashi Signature: Ramesh S. Kashi	Date: 21 NOV 2019

Note: Use an additional PTO/AIA/01 (or substitute) form for each additional inventor.

Attorney Docket No. 24439

Substitute for PTO/AIA/01

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

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LEGAL NAME OF INVENTOR	
Inventor: Mohammed Shameem Signature: M. Shameem	Date: 7 Nov. 2019

Note: Use an additional PTO/AIA/01 (or substitute) form for each additional inventor.

Attorney Docket No. 24439

Substitute for PTO/AIA/01

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

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LEGAL NAME OF INVENTOR	
Inventor: Soumendu Bhattaharya Signature: Bhattacharya	Date: 06 Nov 2019

Note: Use an additional PTO/AIA/01 (or substitute) form for each additional inventor.

Attorney Docket No. 24439

Substitute for PTO/AIA/01

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

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☐ Application No. filed on ;

☐ As amended on (if applicable).

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 the claimed invention of the application.

I have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part 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.

LEGAL NAME OF INVENTOR	
Inventor: William P. Forrest, Jr. Signature: William P. Forrest	Date: 31Oct2019

Note: Use an additional PTO/AIA/01 (or substitute) form for each additional inventor.

Attorney Docket No. 24439

Substitute for PTO/AIA/01

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

Title of Invention: STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

Inventors: Manoj K. Sharma, Wendy Benjamin, Sarita Mittal, Ashwin Basarkar, Chakravarthy Nachu Narasimhan, Ramesh S. Kashi, Mohommed Shameem, Soumendu Bhattacharya, William P. Forrest,Jr., Yogita Krishnamachari

As the below named inventor, I declare that:

This declaration is directed to:

☒ The application having the attorney docket number and Title of Invention noted above, which are on the specification;

☐ The attached application;

☐ Application No. , which is a 371 National Stage of PCT/ filed on ;

☐ As amended on (if applicable); or

☐ Application No. filed on ;

☐ As amended on (if applicable).

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 the claimed invention of the application.

I have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part 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.

LEGAL NAME OF INVENTOR	
Inventor: Yogita Krishnamachari Signature: Yogita. K	Date: 6-NOV-2019

Note: Use an additional PTO/AIA/01 (or substitute) form for each additional inventor.

PTO/AIA/14 (01-22)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24439-US-CNT-4
	Application Number	
Title of Invention	STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF	

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
	Manoj	K.	Sharma	

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

City	Littleton	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	7 Fraser Street		
Address 2			
City	Littleton	State/Province	MA
Postal Code	01460	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Wendy		Benjamin	

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

City	North Brunswick	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

Address 1	126 East Lincoln Avenue		
Address 2			
City	Rahway	State/Province	NJ
Postal Code	07065	Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Sarita		Mittal	

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24439-US-CNT-4
	Application Number	
Title of Invention	STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF	

City	Bridgewater	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

Address 1	126 East Lincoln Avenue
Address 2	

City	Rahway	State/Province	NJ
Postal Code	07065	Country	US

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Ashwin		Basarkar	

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

City	Keasbey	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

Address 1	2304 Sunnyview Oval
Address 2	

City	Keasbey	State/Province	NJ
Postal Code	08832	Country	US

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Chakravarthy	Nachu	Narasimhan	

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

City	Scotch Plains	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

Address 1	126 East Lincoln Avenue
Address 2	

City	Rahway	State/Province	NJ
Postal Code	07065	Country	US

Inventor 6 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Ramesh	S.	Kashi	

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

City	Warren	State/Province	NJ	Country of Residence	US

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24439-US-CNT-4
	Application Number	
Title of Invention	STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF	

Mailing Address of Inventor:

Address 1	5 Hickory Lane		
Address 2			
City	Warren	**State/Province**	NJ
Postal Code	07059	**Country**	US

Inventor 7 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Mohammed		Shameem	

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

City	Nanuet	**State/Province**	NY	**Country of Residence**	US

Mailing Address of Inventor:

Address 1	4 Surim Court		
Address 2			
City	Nanuet	**State/Province**	NY
Postal Code	10954	**Country**	US

Inventor 8 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Soumendu		Bhattacharya	

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

City	East Windsor	**State/Province**	NJ	**Country of Residence**	US

Mailing Address of Inventor:

Address 1	126 East Lincoln Avenue		
Address 2			
City	Rahway	**State/Province**	NJ
Postal Code	07065	**Country**	US

Inventor 9 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	William	P.	Forrest	Jr.

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

City	Middletown	**State/Province**	NJ	**Country of Residence**	US

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24439-US-CNT-4
	Application Number	
Title of Invention	STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF	

Mailing Address of Inventor:

Address 1	126 East Lincoln Avenue		
Address 2			
City	Rahway	**State/Province**	NJ
Postal Code	07065	**Country**	US

Inventor 10 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Yogita		Krishnamachari	

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

City	Scotch Plains	**State/Province**	NJ	**Country of Residence**	US

Mailing Address of Inventor:

Address 1	126 East Lincoln Avenue		
Address 2			
City	Rahway	**State/Province**	NJ
Postal Code	07065	**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	210		
Email Address	us_efs@merck.com	Add Email	Remove Email

Application Information:

Title of the Invention	STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF		
Attorney Docket Number	24439-US-CNT-4	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	11	**Suggested Figure for Publication (if any)**	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24439-US-CNT-4
	Application Number	
Title of Invention	STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF	

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	210		

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	18/182135	2023-03-10

PTO/AIA/14 (01-22)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24439-US-CNT-4
	Application Number	
Title of Invention	STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF	

Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
18/182135	Continuation of	16/609612	2019-10-30	11633476	2023-04-25

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16/609612	a 371 of international	PCT/US2018/030459	2018-05-01

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2018/030459	Claims benefit of provisional	62/500238	2017-05-02

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[i] (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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24439-US-CNT-4
	Application Number	
Title of Invention	STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF	

Authorization or Opt-Out of Authorization to Permit Access:

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

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

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

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

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

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

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

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

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

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

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

PTO/AIA/14 (01-22)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24439-US-CNT-4
	Application Number	
Title of Invention	STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF	

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. [X]

Organization Name	Merck Sharp & Dohme LLC		
Mailing Address Information For Applicant:			
Address 1	126 East Lincoln Avenue		
Address 2			
City	Rahway	**State/Province**	NJ
Country	US	Postal Code	07065
Phone Number		Fax Number	732-594-4720
Email Address	us_efs@merck.com		

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.

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	24439-US-CNT-4
	Application Number	
Title of Invention	STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF	

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	Merck Sharp & Dohme LLC

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	126 East Lincoln Avenue		
Address 2			
City	Rahway	**State/Province**	NJ
Country	US	Postal Code	07065
Phone Number		Fax Number	732-594-4720
Email Address	us_efs@merck.com		

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	/Patrick Rehfuss, Reg. No. 75,367/			Date (YYYY-MM-DD)	2025-09-19
First Name	Patrick	Last Name	Rehfuss	Registration Number	75,367

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	24439-US-CNT-4
	Application Number	
Title of Invention	STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF	

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:

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 the Freedom of Information Act requires disclosure of these records.

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 CooperationTreaty.

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.

STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Patent Application No. 18/182,135, filed March 10, 2023, which is a continuation of U.S. Patent Application No. 16/609,612, filed October 30, 2019 (now U.S. Patent No. 11,633,476, issued on April 25, 2023), which is a 371 national stage of International Application No. PCT/US2018/030459, filed May 1, 2018, which claims the benefit of U.S. Provisional Application No. 62/500,238, filed May 2, 2017, the contents of which are hereby incorporated by reference in their entirety.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[0002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. The XML file, created on March 6, 2023, is named 24439-US-CNT.XML and is 41,919 bytes in size.

FIELD OF THE INVENTION

[0003] The invention relates to stable formulations comprising antibodies or antigen binding fragments thereof that bind to human programmed death receptor 1 (PD-1). Also provided are methods of treating various cancers and chronic infections with the formulations of the invention.

BACKGROUND OF THE INVENTION

[0004] Immune checkpoint therapies targeting the programmed death receptor-1 (PD-1) axis have resulted in groundbreaking improvements in clinical response in multiple human cancers (Brahmer *et al.*, *N Engl J Med* 2012, 366: 2455-65; Garon *et al. N Engl J Med* 2015, 372: 2018-28; Hamid *et al.*, *N Engl J Med* 2013, 369: 134-44; Robert *et al.*, *Lancet* 2014, 384: 1109-17; Robert *et al.*, *N Engl J Med* 2015, 372: 2521-32; Robert *et al.*, *N Engl J Med* 2015, 372: 320-30; Topalian *et al.*, *N Engl J Med* 2012, 366: 2443-54; Topalian *et al.*, *J Clin Oncol* 2014, 32: 1020-30; Wolchok *et al.*, *N Engl J Med* 2013, 369: 122-33). The interaction of the PD-1 receptor on T-cells with its ligands, PD-L1 and PD-L2, on tumor and immune infiltrating cells regulates T-cell mediated immune responses and may play a role in immune escape by human tumors (Pardoll DM. *Nat Rev Cancer* 2012,12: 252-64). Binding of PD-1 to either of its ligands results in delivery of an inhibitory stimulus to the T cell. Immune therapies targeting the PD-1 axis

include monoclonal antibodies directed to the PD-1 receptor (KEYTRUDA™ (pembrolizumab), Merck and Co., Inc., Kenilworth, NJ and OPDIVO™ (nivolumab), Bristol-Myers Squibb, Princeton, NJ) and also those that bind to the PD-L1 ligand (MPDL3280A; TECENTRIQ™ (atezolizumab), Genentech, San Francisco, CA). Both therapeutic approaches have demonstrated anti-tumor effects in numerous cancer types.

[0005] Antibodies for use in human subjects must be stored prior to use and transported to the point of administration. Reproducibly attaining a desired level of antibody drug in a subject requires that the drug be stored in a formulation that maintains the bioactivity of the drug. The need exists for stable formulations of anti-human PD-1 antibodies for pharmaceutical use, *e.g.*, for treating various cancers and infectious diseases. Preferably, such formulations will exhibit a long shelf-life, be stable when stored and transported, and will be amenable to administration at high concentrations, *e.g.* for use in subcutaneous administration, as well as low concentrations, *e.g.* for intravenous administration.

SUMMARY OF THE INVENTION

[0006] The invention provides an anti-human PD-1 antibody formulation, comprising: a) about 5 mg/mL to about 200 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; b) about 5 mM to about 20 mM buffer; c) a stabilizer selected from the group consisting of: (i) about 6% to about 8% weight/volume (w/v) sucrose, trehalose or (2-hydroxypropyl)-β-cyclodextrin; (ii) about 3% to about 5% w/v mannitol, sorbitol, L-arginine, a pharmaceutically acceptable salt of L-arginine, L-proline, or a pharmaceutically acceptable salt of L-proline; and (iii) about 1.8 to about 2.2% w/v glycine, or a pharmaceutically acceptable salt thereof; d) about 0.01 % to about 0.10% non-ionic surfactant; and e) about 1 mM to about 20 mM anti-oxidant.

[0007] In embodiments of the invention, the buffer provides a pH of between 5.0 and 6.0.

[0008] In specific embodiments, the stabilizer of the anti-human PD-1 antibody formulation is selected from the group consisting of: (i) about 6% to about 8% w/v sucrose, trehalose or (2-hydroxypropyl)-β-cyclodextrin; (ii) about 3 % to about 5% mannitol, sorbitol, or L- proline, or a pharmaceutically acceptable salt of L-proline; and (iii) about 1.8 to about 2.2% w/v glycine, or a pharmaceutically acceptable salt thereof.

[0009] In certain embodiments, the anti-human PD-1 antibody formulation further comprises from about 1% to about 3% w/v L-arginine, or a pharmaceutically acceptable salt thereof.

[0010] The invention also provides an anti-human PD-1 antibody formulation comprising: a) about 25 mg/mL to about 200 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; b) about 5 mM to about 20 mM histidine buffer; c) about 6% to about 8% w/v

sucrose; d) about 0.01 % to about 0.04% w/v polysorbate 80; and e) about 1 mM to about 20 mM L-methionine, or a pharmaceutically acceptable salt thereof.

[0011] In specific embodiments, the anti-human PD-1 antibody formulation further comprises from about 1% to about 3% w/v L-arginine, or a pharmaceutically acceptable salt thereof.

[0012] The invention further provides an anti-human PD-1 antibody formulation comprising: a) about 75 to about 200 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; b) about 8 mM to about 12 mM histidine buffer; c) about 5 mM to about 10 mM methionine; d) about 6% to about 8% w/v sucrose; and e) 0.01 % to about 0.04% w/v polysorbate 80.

[0013] Also provided by the invention is an anti-human PD-1 antibody formulation, comprising: a) about 125 to about 200 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; b) about 10 mM histidine buffer; c) about 10 mM L-methionine or a pharmaceutically acceptable salt thereof; d) about 7 w/v sucrose; and e) about 0.02 % to w/v polysorbate 80.

[0014] In some embodiments, the anti-human PD-1 antibody formulation further comprises from about 1.25% to about 2.5% w/v L-arginine, or a pharmaceutically acceptable salt thereof. In some embodiments, the arginine is L-arginine. In other embodiments, the arginine is L-arginine HCL.

[0015] The invention also provides an anti-human PD-1 antibody formulation, comprising: a) about 5 mg/mL to about 75 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; b) about 8 mM to about 12 mM histidine buffer; c) a stabilizer selected from the group consisting of: (i) about 6% to about 8% w/v sucrose, trehalose or (2-hydroxypropyl)-β-cyclodextrin; (ii) about 3% to about 5% w/v mannitol, sorbitol, L-proline or a pharmaceutically acceptable salt of L-proline; and (iii) about 1.8 to about 2.2% w/v glycine, or a pharmaceutically acceptable salt thereof; d) about 0.01 % to about 0.04% polysorbate 80; and e) about 5 mM to about 10 mM methionine or a pharmaceutically acceptable salt thereof.

[0016] In certain embodiments, the anti-human PD-1 antibody formulation further comprises a metal chelator. In specific embodiments, the metal chelator is DTPA. In certain embodiments the DTPA is present at a concentration of about 10 μM to about 30 μM.

[0017] The invention also provides a liquid anti-human PD-1 antibody formulation that is reconstituted from a lyophilized formulation wherein the reconstituted solution comprises: a) about 125 mg/mL to about 175 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; b) about 8 mM to about 12 mM histidine buffer; c) a stabilizer selected from the group consisting of: (i) about 3% to about 8% w/v sucrose; (ii) about 2% to about 5% w/v L-

arginine, or a pharmaceutically acceptable salt thereof; (iii) about 3% to about 5% mannitol and about 1% to about 2% sucrose; and (iv) a combination of i) and ii); and d) about 0.01 % to about 0.04% polysorbate 80.

[0018] In specific embodiments of the invention the anti-PD-1 antibody is pembrolizumab or an antigen binding fragment of pembrolizumab.

[0019] Also provided herein are methods of treating cancer and methods of treating chronic infection in a human patient in need thereof comprising: administering an effective amount of the anti-human PD-1 antibody formulations of the invention to the patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] FIGURES 1A-1C show results of an HP-HIC study, which measures oxidation of Met-105, for high concentration pembrolizumab formulations over a 12-week time period. Results are provided for test formulations (see EXAMPLE 2) stored at 5°C (FIGURE 1A), 25°C (FIGURE 1B), and 40°C (FIGURE 1C).

[0021] FIGURES 2A-2C show results of an HP-HIC study of the formulations in EXAMPLE 3. Results are provided for test formulations stored at 5°C (FIGURE 2A), 25°C (FIGURE 2B), and 40°C (FIGURE 2C) over a 9-month period.

[0022] FIGURES 3A-3C show results of an HP-SEC analysis (measured as % mAb) of the formulations described in EXAMPLE 4. Results are provided for formulations stored at 5°C (FIGURE 3A), 25°C (FIGURE 3B) and 40°C (FIGURE 3C).

[0023] FIGURES 4A-4C show results of HP-HIC analysis of the formulations described in EXAMPLE 4. Results provided show the % of pre-peak 1 +2 (oxidized species) formulations stored at 5°C (FIGURE 3A), 25°C (FIGURE 3B) and 40°C (FIGURE 3C) over 12 weeks. The dashed lines in FIGURE 4B and FIGURE 4C shows results from Formulation 1, Example 3, as a comparator.

[0024] FIGURE 5 shows the amount of aggregation of each of the formulations in EXAMPLE 5 over an 8-week period of storage at 40°C as measured by HP-SEC.

[0025] FIGURE 6 shows the oxidation of Met-105 in the formulations in EXAMPLE 6, Study 2, at 40°C over an 8-week period as measured by HP-HIC.

[0026] FIGURE 7 shows oxidation of Met-105 in the formulations in EXAMPLE 6, Study 3 at 40°C over an 8-week period as measured by HP-HIC.

DETAILED DESCRIPTION OF THE INVENTION

[0027] The invention provides stable formulations comprising an anti-PD-1 antibody, or antigen binding fragment thereof that binds to human PD-1, which are useful for methods of

treatment of cancer or an immune disorder or immune condition which comprise intravenous or subcutaneous administration to a patient in need thereof. In certain embodiments of the invention, the anti-PD-1 antibody is pembrolizumab or an antigen binding fragment of pembrolizumab. The formulations of the invention address the issues of high viscosity and increased aggregation associated with antibody formulations comprising a high concentration of anti-PD1 antibodies. The invention further provides formulations comprising pembrolizumab or an antigen binding fragment thereof with reduced methionine oxidation, including reduced oxidation of methionine-105, which is located in CDR3 of the heavy chains of pembrolizumab.

[0028] The formulations of the invention are useful for subcutaneous delivery to a patient in need thereof. In order to deliver maximum therapeutic benefits to patients, it is desirable that formulations for subcutaneous (SC) delivery comprise a high antibody concentration (75-200 mg/ml). A high concentration of API is often required for SC formulations due to the historical bioavailability of 50-60% for SC injections and the expected dose range of an antibody product. However, high concentration of antibody, or antigen binding fragment thereof, may contribute to other properties of the product which would be undesirable, e.g. low injectability due to increased viscosity and higher than physiological osmolality and increased aggregation. Therefore, it is preferred that an antibody product intended for SC administration balances the effects of concentration while maintaining a level of drug that will provide the highest therapeutic benefit. An ideal product comprises a high protein concentration, low viscosity, an osmolality similar to physiological conditions, and a low level of aggregation under typical storage conditions. Increased viscosity at high protein concentration may not only make it difficult to extract the product from its container with a syringe, but also to inject the necessary dose into a patient from the syringe (syringeability). Advantageously, embodiments of the invention provide formulations that comprise a high concentration of antibody, or antigen binding fragment thereof, and a viscosity level that is acceptable for subcutaneous delivery. Additionally, the formulations of the invention do not lead to high levels of aggregation, as shown in more detail throughout the Examples.

[0029] Previous forced degradation studies were conducted on pembrolizumab drug substance (DS) to investigate product degradation pathways and to isolate and characterize impurities. In these studies, pembrolizumab DS was exposed to various stress conditions, and analysis of stressed samples indicated that, under the stress conditions employed, pembrolizumab DS was sensitive to light, peroxide, and high pH. Major degradation pathways of pembrolizumab included oxidation of methionine 105 (Met105) in the heavy chain CDR upon peroxide stress and oxidation of Met105 and Fc methionine residues when exposed to light. Pembrolizumab

maintained its bioactivity under most stress conditions for the degradation levels tested. However, reduction in affinity to PD-1 was observed for peroxide stressed samples by Surface Plasmon Resonance (SPR). An exposed methionine residue or a methionine residue in the CDR of an antibody has the potential of impacting the biological activity of the antibody through oxidation. It is shown herein that the formulations of the invention are able to reduce oxidation of Met105 within the pembrolizumab heavy chain CDR.

I. Definitions and Abbreviations

[0030] As used throughout the specification and appended claims, the following abbreviations apply:

API	active pharmaceutical ingredient
CDR	complementarity determining region in the immunoglobulin variable regions
CE-SDS	capillary electrophoresis-sodium dodecyl sulfate
CHO	Chinese hamster ovary
CI	confidence interval
DS	drug substance
EC50	concentration resulting in 50% efficacy or binding
ELISA	enzyme-linked immunosorbant assay
FFPE	formalin-fixed, paraffin-embedded
FR	framework region
HC	heavy chain
HNSCC	head and neck squamous cell carcinoma
HPBC	2-Hydroxypropyl)-β-cyclodextrin
HP-HIC	high performance hydrophobic interaction chromatography
HP-IEX	high performance ion-exchange chromatography
HP-SEC	high performance size exclusion chromatography
IC50	concentration resulting in 50% inhibition
IgG	immunoglobulin G
IHC	immunohistochemistry or immunohistochemical
mAb	monoclonal antibody
MES	2-(N-morpholino)ethanesulfonic acid
NCBI	National Center for Biotechnology Information
NSCLC	non-small cell lung cancer

PCR	polymerase chain reaction
PD-1	programmed death 1 (a.k.a. programmed cell death-1 and programmed death receptor 1)
PD-L1	programmed cell death 1 ligand 1
PD-L2	programmed cell death 1 ligand 2
PS80 or PS-80	polysorbate 80
SBEC	(sulfobutylether)-β-cyclodextrin
SWFI	sterile water for injection
TNBC	triple negative breast cancer
V_H	immunoglobulin heavy chain variable region
VK	immunoglobulin kappa light chain variable region
V_L	immunoglobulin light chain variable region
VP-DSC	Valerian-Plotnikov differential scanning calorimetry
v/v	volume per volume
WFI	water for injection
w/v	weight per volume

[0031] So that the invention may be more readily understood, certain technical and scientific terms are specifically defined below. Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

[0032] As used throughout the specification and in the appended claims, the singular forms "a," "an," and "the" include the plural reference unless the context clearly dictates otherwise.

[0033] Reference to "or" indicates either or both possibilities unless the context clearly dictates one of the indicated possibilities. In some cases, "and/or" was employed to highlight either or both possibilities.

[0034] "Treat" or "treating" a cancer as used herein means to administer a formulation of the invention to a subject having an immune condition or cancerous condition, or diagnosed with a cancer or pathogenic infection (e.g. viral, bacterial, fungal), to achieve at least one positive therapeutic effect, such as for example, reduced number of cancer cells, reduced tumor size, reduced rate of cancer cell infiltration into peripheral organs, or reduced rate of tumor metastasis or tumor growth. "Treatment" may include one or more of the following: inducing/increasing an antitumor immune response, stimulating an immune response to a pathogen, toxin, and/or self-antigen, stimulating an immune response to a viral infection, decreasing the number of one or

more tumor markers, halting or delaying the growth of a tumor or blood cancer or progression of disease associated with PD-1 binding to its ligands PD-L1 and/or PD-L2 ("PD-1-related disease") such as cancer, stabilization of PD-1-related disease, inhibiting the growth or survival of tumor cells, eliminating or reducing the size of one or more cancerous lesions or tumors, decreasing the level of one or more tumor markers, ameliorating, abrogating the clinical manifestations of PD-1-related disease, reducing the severity or duration of the clinical symptoms of PD-1-related disease such as cancer, prolonging the survival of a patient relative to the expected survival in a similar untreated patient, inducing complete or partial remission of a cancerous condition or other PD-1 related disease.

[0035] "Immune condition" or "immune disorder" encompasses, e.g., pathological inflammation, an inflammatory disorder, and an autoimmune disorder or disease. "Immune condition" also refers to infections, persistent infections, and proliferative conditions, such as cancer, tumors, and angiogenesis, including infections, tumors, and cancers that resist eradication by the immune system. "Cancerous condition" includes, *e.g.*, cancer, cancer cells, tumors, angiogenesis, and precancerous conditions such as dysplasia.

[0036] Positive therapeutic effects in cancer can be measured in a number of ways (See, W. A. Weber, *J. Nucl. Med.* 50:1S-10S (2009)). For example, with respect to tumor growth inhibition, according to NCI standards, a T/C $\leqq$42% is the minimum level of anti-tumor activity. A T/C < 10% is considered a high anti-tumor activity level, with T/C (%) = Median tumor volume of the treated/Median tumor volume of the control × 100. In some embodiments, the treatment achieved by administration of a formulation of the invention is any of progression free survival (PFS), disease free survival (DFS) or overall survival (OS). PFS, also referred to as "Time to Tumor Progression" indicates the length of time during and after treatment that the cancer does not grow, and includes the amount of time patients have experienced a complete response or a partial response, as well as the amount of time patients have experienced stable disease. DFS refers to the length of time during and after treatment that the patient remains free of disease. OS refers to a prolongation in life expectancy as compared to naive or untreated individuals or patients. While an embodiment of the formulations, treatment methods, and uses of the invention may not be effective in achieving a positive therapeutic effect in every patient, it should do so in a statistically significant number of subjects as determined by any statistical test known in the art such as the Student's t-test, the chi^2-test, the U-test according to Mann and Whitney, the Kruskal-Wallis test (H-test), Jonckheere-Terpstra-test and the Wilcoxon-test.

[0037] The term "patient" (alternatively referred to as "subject" or "individual" herein) refers to a mammal (*e.g.*, rat, mouse, dog, cat, rabbit) capable of being treated with the formulations of

the invention, most preferably a human. In some embodiments, the patient is an adult patient. In other embodiments, the patient is a pediatric patient. Those "in need of treatment" include those patients that may benefit from treatment with the formulations of the invention, e.g. a patient suffering from cancer or an immune condition.

[0038] The term "antibody" refers to any form of antibody that exhibits the desired biological activity. Thus, it is used in the broadest sense and specifically covers, but is not limited to, monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, humanized, fully human antibodies, and chimeric antibodies.

[0039] In general, the basic antibody structural unit comprises a tetramer. Each tetramer includes two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The variable regions of each light/heavy chain pair form the antibody binding site. Thus, in general, an intact antibody has two binding sites. The carboxy-terminal portion of the heavy chain may define a constant region primarily responsible for effector function. Typically, human light chains are classified as kappa and lambda light chains. Furthermore, human heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See generally, Fundamental Immunology Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989).

[0040] Typically, the variable domains of both the heavy and light chains comprise three hypervariable regions, also called complementarity determining regions (CDRs), which are located within relatively conserved framework regions (FR). The CDRs are usually aligned by the framework regions, enabling binding to a specific epitope. In general, from N-terminal to C-terminal, both light and heavy chains variable domains comprise FR1, CDR1, FR2 , CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is, generally, in accordance with the definitions of Sequences of Proteins of Immunological Interest, Kabat, *et al.*; National Institutes of Health, Bethesda, Md. ; 5th ed.; NIH Publ. No. 91-3242 (1991); Kabat (1978) *Adv. Prot. Chem.* 32:1-75; Kabat, *et al.*, (1977) *J. Biol. Chem.* 252:6609-6616; Chothia, *et al.*, (1987) *J Mol. Biol.* 196:901-917 or Chothia, *et al.*, (1989) *Nature* 342:878-883.

[0041] An antibody or antigen-binding fragment that "specifically binds to" a specified target protein is an antibody that exhibits preferential binding to that target as compared to other proteins, but this specificity does not require absolute binding specificity. An antibody is

considered "specific" for its intended target if its binding is determinative of the presence of the target protein in a sample, e.g. without producing undesired results such as false positives. Antibodies, or binding fragments thereof, useful in the invention will bind to the target protein with an affinity that is at least two fold greater, preferably at least ten times greater, more preferably at least 20-times greater, and most preferably at least 100-times greater than the affinity with non-target proteins. As used herein, an antibody is said to bind specifically to a polypeptide comprising a given amino acid sequence, e.g. the amino acid sequence of a mature human PD-1 or human PD-L1 molecule, if it binds to polypeptides comprising that sequence but does not bind to proteins lacking that sequence.

[0042] "Chimeric antibody" refers to an antibody in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in an antibody derived from a particular species (e.g., human) or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in an antibody derived from another species (e.g., mouse) or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity.

[0043] The term "pharmaceutically effective amount" or "effective amount" means an amount whereby sufficient therapeutic composition or formulation is introduced to a patient to treat a diseased or condition. One skilled in the art recognizes that this level may vary according the patient's characteristics such as age, weight, etc.

[0044] The term "about", when modifying the quantity (e.g., mM, or M) of a substance or composition, the percentage (v/v or w/v) of a formulation component, the pH of a solution/formulation, or the value of a parameter characterizing a step in a method, or the like refers to variation in the numerical quantity that can occur, for example, through typical measuring, handling and sampling procedures involved in the preparation, characterization and/or use of the substance or composition; through inadvertent error in these procedures; through differences in the manufacture, source, or purity of the ingredients employed to make or use the compositions or carry out the procedures; and the like. In certain embodiments, "about" can mean a variation of ± 0.1%, 0.5%, 1%, 2%, 3%, 4%, 5% or 10%.

[0045] The terms "cancer", "cancerous", or "malignant" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, leukemia, blastoma, and sarcoma. More particular examples of such cancers include squamous cell carcinoma, myeloma, small-cell lung cancer, non-small cell lung cancer, glioma, Hodgkin's lymphoma, non-Hodgkin's

lymphoma, gastrointestinal (tract) cancer, renal cancer, ovarian cancer, liver cancer, lymphoblastic leukemia, lymphocytic leukemia, colorectal cancer, endometrial cancer, kidney cancer, prostate cancer, thyroid cancer, melanoma, chondrosarcoma, neuroblastoma, pancreatic cancer, glioblastoma multiforme, cervical cancer, brain cancer, stomach cancer, bladder cancer, hepatoma, breast cancer, colon carcinoma, and head and neck cancer.

[0046] A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Anti-PD-1 antibodies can be used with any one or more suitable chemotherapeutic agent. Examples of such chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CBI-TMI); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as the enediyne antibiotics (e.g. calicheamicin, especially calicheamicin gamma1I and calicheamicin phiI1, see, e.g., Agnew, Chem. Intl. Ed. Engl., 33:183-186 (1994); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromomophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-

azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2, 2′,2″-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g. paclitaxel and doxetaxel; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen, raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (Fareston); aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, megestrol acetate, exemestane, formestane, fadrozole, vorozole, letrozole, and anastrozole; and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[0047] "Chothia" means an antibody numbering system described in Al-Lazikani *et al.*, *JMB* 273**:**927-948 (1997).

[0048] "Kabat" as used herein means an immunoglobulin alignment and numbering system pioneered by Elvin A. Kabat ((1991) Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md.).

[0049] A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially cancer cell over expressing any of the genes identified

herein, either *in vitro* or *in vivo*. Thus, the growth inhibitory agent is one which significantly reduces the percentage of cells over expressing such genes in S phase. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine) taxanes, and topo II inhibitors such as doxorubicin, epirubicin, daunorubicin, and etoposide. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as dacarbazine, mechlorethamine, and cisplatin. Further information can be found in *The Molecular Basis of Cancer*, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogens, and antineoplastic drugs" by Murakami et al. (WB Saunders: Philadelphia, 1995).

[0050] The terms "PD-1 binding fragment," "antigen binding fragment thereof," "binding fragment thereof" or "fragment thereof" encompass a fragment or a derivative of an antibody that still substantially retains its biological activity of binding to antigen (human PD-1) and inhibiting its activity (e.g., blocking the binding of PD-1 to PDL1 and PDL2). Therefore, the term "antibody fragment" or PD-1 binding fragment refers to a portion of a full length antibody, generally the antigen binding or variable region thereof. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments. Typically, a binding fragment or derivative retains at least 10% of its PD-1 inhibitory activity. In some embodiments, a binding fragment or derivative retains at least 25%, 50%, 60%, 70%, 80%, 90%, 95%, 99% or 100% (or more) of its PD-1 inhibitory activity, although any binding fragment with sufficient affinity to exert the desired biological effect will be useful. In some embodiments, an antigen binding fragment binds to its antigen with an affinity that is at least two fold greater, preferably at least ten times greater, more preferably at least 20-times greater, and most preferably at least 100-times greater than the affinity with unrelated antigens. In one embodiment the antibody has an affinity that is greater than about 10^9 liters/mol, as determined, e.g., by Scatchard analysis. Munsen *et al.* (1980) *Analyt. Biochem.* 107:220-239. It is also intended that a PD-1 binding fragment can include variants having conservative amino acid substitutions that do not substantially alter its biologic activity.

[0051] "Humanized antibody" refers to forms of antibodies that contain sequences from non-human (*e.g.*, murine) antibodies as well as human antibodies. Such antibodies contain minimal sequence derived from non-human immunoglobulin. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence.

The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. The humanized forms of rodent antibodies will generally comprise the same CDR sequences of the parental rodent antibodies, although certain amino acid substitutions may be included to increase affinity, increase stability of the humanized antibody, or for other reasons.

[0052] The antibodies of the invention also include antibodies with modified (or blocked) Fc regions to provide altered effector functions. *See, e.g.*, U.S. Pat. No. 5,624,821; WO2003/086310; WO2005/120571; WO2006/0057702; Presta (2006) *Adv. Drug Delivery Rev.* 58:640-656. Such modification can be used to enhance or suppress various reactions of the immune system, with possible beneficial effects in diagnosis and therapy. Alterations of the Fc region include amino acid changes (substitutions, deletions and insertions), glycosylation or deglycosylation, and adding multiple Fc. Changes to the Fc can also alter the half-life of antibodies in therapeutic antibodies, and a longer half-life would result in less frequent dosing, with the concomitant increased convenience and decreased use of material. *See* Presta (2005) *J. Allergy Clin. Immunol.*116:731 at 734-35.

[0053] "Fully human antibody" refers to an antibody that comprises human immunoglobulin protein sequences only. A fully human antibody may contain murine carbohydrate chains if produced in a mouse, in a mouse cell, or in a hybridoma derived from a mouse cell. Similarly, "mouse antibody" refers to an antibody which comprises mouse immunoglobulin sequences only. A fully human antibody may be generated in a human being, in a transgenic animal having human immunoglobulin germline sequences, by phage display or other molecular biological methods.

[0054] "Hypervariable region" refers to the amino acid residues of an antibody that are responsible for antigen-binding. The hypervariable region comprises amino acid residues from a "complementarity determining region" or "CDR" (*e.g.* residues 24-34 (CDRL1), 50-56 (CDRL2) and 89-97 (CDRL3) in the light chain variable domain and residues 31-35 (CDRH1), 50-65 (CDRH2) and 95-102 (CDRH3) in the heavy chain variable domain as measured by the Kabat numbering system (Kabat *et al.* (1991) Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md.) and/or those residues from a "hypervariable loop" (*i.e.* residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the light chain variable domain and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the heavy chain variable domain (Chothia and Lesk (1987) *J. Mol. Biol.* 196: 901-917). As used herein, the term "framework" or "FR" residues refers to those variable domain residues other than the hypervariable region residues defined herein as CDR residues. CDR and FR residues are

determined according to the standard sequence definition of Kabat. Kabat *et al.* (1987) Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda Md.

[0055] "Conservatively modified variants" or "conservative substitution" refers to substitutions of amino acids are known to those of skill in this art and may be made generally without altering the biological activity of the resulting molecule, even in essential regions of the polypeptide. Such exemplary substitutions are preferably made in accordance with those set forth in Table 1 as follows:

Table 1. Exemplary Conservative Amino Acid Substitutions

Original residue	Conservative substitution
Ala (A)	Gly; Ser
Arg (R)	Lys, His
Asn (N)	Gln; His
Asp (D)	Glu; Asn
Cys (C)	Ser; Ala
Gln (Q)	Asn
Glu (E)	Asp; Gln
Gly (G)	Ala
His (H)	Asn; Gln
Ile (I)	Leu; Val
Leu (L)	Ile; Val
Lys (K)	Arg; His
Met (M)	Leu; Ile; Tyr
Phe (F)	Tyr; Met; Leu
Pro (P)	Ala
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr; Phe
Tyr (Y)	Trp; Phe
Val (V)	Ile; Leu

[0056] In addition, those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity. *See, e.g.*, Watson *et al.* (1987) *Molecular Biology of the Gene*, The Benjamin/Cummings Pub. Co., p. 224 (4th Edition).

[0057] The phrase "consists essentially of," or variations such as "consist essentially of" or "consisting essentially of," as used throughout the specification and claims, indicate the inclusion of any recited elements or group of elements, and the optional inclusion of other elements, of similar or different nature than the recited elements, that do not materially change the basic or novel properties of the specified dosage regimen, method, or composition. As a

non-limiting example, a binding compound that consists essentially of a recited amino acid sequence may also include one or more amino acids, including substitutions of one or more amino acid residues, that do not materially affect the properties of the binding compound.

[0058] "Comprising" or variations such as "comprise", "comprises" or "comprised of" are used throughout the specification and claims in an inclusive sense, i.e., to specify the presence of the stated features but not to preclude the presence or addition of further features that may materially enhance the operation or utility of any of the embodiments of the invention, unless the context requires otherwise due to express language or necessary implication.

[0059] "Isolated antibody" and "isolated antibody fragment" refers to the purification status and in such context means the named molecule is substantially free of other biological molecules such as nucleic acids, proteins, lipids, carbohydrates, or other material such as cellular debris and growth media. Generally, the term "isolated" is not intended to refer to a complete absence of such material or to an absence of water, buffers, or salts, unless they are present in amounts that substantially interfere with experimental or therapeutic use of the binding compound as described herein.

[0060] "Monoclonal antibody" or "mAb" or "Mab", as used herein, refers to a population of substantially homogeneous antibodies, *i.e.*, the antibody molecules comprising the population are identical in amino acid sequence except for possible naturally occurring mutations that may be present in minor amounts. In contrast, conventional (polyclonal) antibody preparations typically include a multitude of different antibodies having different amino acid sequences in their variable domains, particularly their CDRs, which are often specific for different epitopes. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the invention may be made by the hybridoma method first described by Kohler *et al.* (1975) *Nature* 256: 495, or may be made by recombinant DNA methods (*see, e.g.*, U.S. Pat. No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.* (1991) *Nature* 352: 624-628 and Marks *et al.* (1991) *J. Mol. Biol.* 222: 581-597, for example. *See also* Presta (2005) *J. Allergy Clin. Immunol.* 116:731.

[0061] "Tumor" as it applies to a subject diagnosed with, or suspected of having, a cancer refers to a malignant or potentially malignant neoplasm or tissue mass of any size, and includes primary tumors and secondary neoplasms. A solid tumor is an abnormal growth or mass of tissue that usually does not contain cysts or liquid areas. Different types of solid tumors are

named for the type of cells that form them. Examples of solid tumors are sarcomas, carcinomas, and lymphomas. Leukemias (cancers of the blood) generally do not form solid tumors (National Cancer Institute, Dictionary of Cancer Terms).

[0062] The term "tumor size" refers to the total size of the tumor which can be measured as the length and width of a tumor. Tumor size may be determined by a variety of methods known in the art, such as, e.g. by measuring the dimensions of tumor(s) upon removal from the subject, e.g., using calipers, or while in the body using imaging techniques, e.g., bone scan, ultrasound, CT or MRI scans.

[0063] "Variable regions" or "V region" as used herein means the segment of IgG chains which is variable in sequence between different antibodies. It extends to Kabat residue 109 in the light chain and 113 in the heavy chain.

[0064] The term "buffer" encompasses those agents which maintain the solution pH of the formulations of the invention in an acceptable range, or, for lyophilized formulations of the invention, provide an acceptable solution pH prior to lyophilization.

[0065] The terms "lyophilization," "lyophilized," and "freeze-dried" refer to a process by which the material to be dried is first frozen and then the ice or frozen solvent is removed by sublimation in a vacuum environment. An excipient may be included in pre-lyophilized formulations to enhance stability of the lyophilized product upon storage.

[0066] The term "pharmaceutical formulation" refers to preparations which are in such form as to permit the active ingredients to be effective, and which contains no additional components which are toxic to the subjects to which the formulation would be administered. The term "formulation" and "pharmaceutical formulation" are used interchangeably throughout.

[0067] "Pharmaceutically acceptable" refers to excipients (vehicles, additives) and compositions that can reasonably be administered to a subject to provide an effective dose of the active ingredient employed and that are "generally regarded as safe" *e.g.*, that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset and the like, when administered to a human. In another embodiment, this term refers to molecular entities and compositions approved by a regulatory agency of the federal or a state government or listed in the U.S. Pharmacopeia or another generally recognized pharmacopeia for use in animals, and more particularly in humans.

[0068] A "reconstituted" formulation is one that has been prepared by dissolving a lyophilized protein formulation in a diluent such that the protein is dispersed in the reconstituted formulation. The reconstituted formulation is suitable for administration, *e.g.* parenteral administration), and may optionally be suitable for subcutaneous administration.

[0069] "Reconstitution time" is the time that is required to rehydrate a lyophilized formulation with a solution to a particle-free clarified solution.

[0070] A "stable" formulation is one in which the protein therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage. Various analytical techniques for measuring protein stability are available in the art and are reviewed in Peptide and Protein Drug Delivery, 247-301, Vincent Lee Ed., Marcel Dekker, Inc., New York, N.Y., Pubs. (1991) and Jones, A. Adv. Drug Delivery Rev. 10:29-90 (1993). Stability can be measured at a selected temperature for a selected time period.

[0071] A "stable" formulation is one in which the protein therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage. Various analytical techniques for measuring protein stability are available in the art and are reviewed in Peptide and Protein Drug Delivery, 247-301, Vincent Lee Ed., Marcel Dekker, Inc., New York, N.Y., Pubs. (1991) and Jones, A. Adv. Drug Delivery Rev. 10:29-90 (1993). Stability can be measured at a selected temperature for a selected time period. For example, in one embodiment, a stable formulation is a formulation with no significant changes observed at a refrigerated temperature (2-8° C) for at least 12 months. In another embodiment, a stable formulation is a formulation with no significant changes observed at a refrigerated temperature (2-8° C) for at least 18 months. In another embodiment, stable formulation is a formulation with no significant changes observed at room temperature (23-27°C) for at least 3 months. In another embodiment, stable formulation is a formulation with no significant changes observed at room temperature (23-27°C) for at least 6 months. In another embodiment, stable formulation is a formulation with no significant changes observed at room temperature (23-27°C) for at least 12 months. In another embodiment, stable formulation is a formulation with no significant changes observed at room temperature (23-27°C) for at least 18 months. The criteria for stability for an antibody formulation are as follows. Typically, no more than 10%, preferably 5%, of antibody monomer is degraded as measured by SEC-HPLC. Typically, the formulation is colorless, or clear to slightly opalescent by visual analysis. Typically, the concentration, pH and osmolality of the formulation have no more than +/-10% change. Potency is typically within 60-140%, preferably 80-120% of the control or reference. Typically, no more than 10%, preferably 5% of clipping of the antibody is observed, i.e., % low molecular weight species as determined, for example, by HP-SEC. Typically, no more than 10%, preferably no more than 5% of aggregation of the antibody is observed, i.e. % high molecular weight species as determined, for example, by HP-SEC.

[0072] An antibody "retains its physical stability" in a pharmaceutical formulation if it shows no significant increase of aggregation, precipitation and/or denaturation upon visual examination of color and/or clarity, or as measured by UV light scattering, size exclusion chromatography (SEC) and dynamic light scattering. The changes of protein conformation can be evaluated by fluorescence spectroscopy, which determines the protein tertiary structure, and by FTIR spectroscopy, which determines the protein secondary structure.

[0073] An antibody "retains its chemical stability" in a pharmaceutical formulation, if it shows no significant chemical alteration. Chemical stability can be assessed by detecting and quantifying chemically altered forms of the protein. Degradation processes that often alter the protein chemical structure include hydrolysis or clipping (evaluated by methods such as size exclusion chromatography and SDS-PAGE), oxidation (evaluated by methods such as by peptide mapping in conjunction with mass spectroscopy or MALDI/TOF/MS), deamidation (evaluated by methods such as ion-exchange chromatography, capillary isoelectric focusing, peptide mapping, isoaspartic acid measurement), and isomerization (evaluated by measuring the isoaspartic acid content, peptide mapping, etc.).

[0074] An antibody "retains its biological activity" in a pharmaceutical formulation, if the biological activity of the antibody at a given time is within a predetermined range of the biological activity exhibited at the time the pharmaceutical formulation was prepared. The biological activity of an antibody can be determined, for example, by an antigen binding assay. Formulations of the invention include antibodies and fragments thereof that are biologically active when reconstituted or in liquid form

[0075] The term "isotonic" means that the formulation of interest has essentially the same osmotic pressure as human blood. Isotonic formulations will generally have an osmotic pressure from about 270-328 mOsm. Slightly hypotonic pressure is 250-269 and slightly hypertonic pressure is 328-350 mOsm. Osmotic pressure can be measured, for example, using a vapor pressure or ice-freezing type osmometer.

[0076] A “non-reducing sugar” is a sugar not capable of acting as a reducing agent because it does not contain or cannot be converted to contain a free aldehyde group or a free ketone group. Examples of non-reducing sugars include but are not limited to dissacharrides such as sucrose and trehalose.

[0077] “Pembrolizumab” (formerly known as MK-3475, SCH 900475 and lambrolizumab) alternatively referred to herein as “pembro,” is a humanized IgG4 mAb with the structure described in *WHO Drug Information*, Vol. 27, No. 2, pages 161-162 (2013) and which comprises the heavy and light chain amino acid sequences and CDRs described in Table 2.

Pembrolizumab has been approved by the U.S. FDA for the treatment of patients with unresectable or metastatic melanoma and for the treatment of certain patients with recurrent or metastatic head and neck squamous cell cancer (HNSCC), classical Hodgkin lymphoma (cHL), urothelial carcinoma, gastric cancer, microsatellite instability-high (MSI-H) cancer and non-small cell lung cancer, as described in the Prescribing Information for KEYTRUDA™ (Merck & Co., Inc., Whitehouse Station, NJ USA; initial U.S. approval 2014, updated September 2017).

Formulations of the Invention

[0078] The formulations of the invention minimize the formation of antibody aggregates and particulates, high and low molecular weight species, minimize oxidation of methionine residues, and Met105 of pembrolizumab in particular, and ensure that the antibody retains biological activity over time.

[0079] The invention includes various formulations of a PD-1 antibody, or antigen binding fragment thereof, as described in more detail, *infra*. For example, the invention includes formulations comprising (i) an anti-PD-1 antibody or antigen binding fragment thereof, (ii) a buffer (e.g., histidine or acetate), (iii) a stabilizer (e.g., a non-reducing sugar such as sucrose or trehalose, or sorbitol, mannitol, (2-hydroxypropyl)-β-cyclodextrin, arginine, proline, or glycine); (iv) a non-ionic surfactant (e.g., polysorbate 80); and (v) an antioxidant (e.g., methionine). In further embodiments, the formulations of the invention comprise a viscosity-reducer (e.g. arginine, or a pharmaceutically acceptable salt thereof) and/or a metal chelator (e.g. DTPA).

Anti-PD-1 Antibodies and Antigen-Binding Fragments Thereof

[0080] The invention provides stable biological formulations comprising antibodies or antigen binding fragments thereof, which specifically bind to human PD-1 (e.g. a human or humanized anti-PD-1 antibody) as the active pharmaceutical ingredient (API), as well as methods for using the formulations of the invention. Any anti-PD-1 antibody or antigen binding fragment thereof can be used in the formulations and methods of the invention. In particular embodiments, the API is an anti-PD-1 antibody, which is selected from pembrolizumab and nivolumab. In specific embodiments, the anti-PD-1 antibody is pembrolizumab. In alternative embodiments, the anti-PD-1 antibody is nivolumab. Table 2 provides amino acid sequences for exemplary anti-human PD-1 antibodies pembrolizumab and nivolumab. Alternative PD-1 antibodies and antigen-binding fragments that are useful in the formulations and methods of the invention are shown in Table 3.

[0081] In some embodiments, an anti-human PD-1 antibody or antigen binding fragment thereof for use in the formulations of the invention comprises three light chain CDRs of CDRL1, CDRL2 and CDRL3 and/or three heavy chain CDRs of CDRH1, CDRH2 and CDRH3.

[0082] In one embodiment of the invention, CDRL1 is SEQ ID NO:1 or a variant of SEQ ID NO:1, CDRL2 is SEQ ID NO:2 or a variant of SEQ ID NO:2, and CDRL3 is SEQ ID NO:3 or a variant of SEQ ID NO:3.

[0083] In one embodiment, CDRH1 is SEQ ID NO:6 or a variant of SEQ ID NO:6, CDRH2 is SEQ ID NO: 7 or a variant of SEQ ID NO:7, and CDRH3 is SEQ ID NO:8 or a variant of SEQ ID NO:8.

[0084] In one embodiment, the three light chain CDRs are SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and the three heavy chain CDRs are SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8.

[0085] In an alternative embodiment of the invention, CDRL1 is SEQ ID NO:11 or a variant of SEQ ID NO:11, CDRL2 is SEQ ID NO:12 or a variant of SEQ ID NO:12, and CDRL3 is SEQ ID NO:13 or a variant of SEQ ID NO:13.

[0086] In one embodiment, CDRH1 is SEQ ID NO:16 or a variant of SEQ ID NO:16, CDRH2 is SEQ ID NO:17 or a variant of SEQ ID NO:17, and CDRH3 is SEQ ID NO:18 or a variant of SEQ ID NO:18.

[0087] In one embodiment, the three light chain CDRs are SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and the three heavy chain CDRs are SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8.

[0088] In an alternative embodiment, the three light chain CDRs are SEQ ID NO:11, SEQ ID NO:12, and SEQ ID NO:13 and the three heavy chain CDRs are SEQ ID NO:16, SEQ ID NO:17 and SEQ ID NO:18.

[0089] In a further embodiment of the invention, CDRL1 is SEQ ID NO:21 or a variant of SEQ ID NO:21, CDRL2 is SEQ ID NO:22 or a variant of SEQ ID NO:22, and CDRL3 is SEQ ID NO:23 or a variant of SEQ ID NO:23.

[0090] In yet another embodiment, CDRH1 is SEQ ID NO:24 or a variant of SEQ ID NO:24, CDRH2 is SEQ ID NO: 25 or a variant of SEQ ID NO:25, and CDRH3 is SEQ ID NO:26 or a variant of SEQ ID NO:26.

[0091] In another embodiment, the three light chain CDRs are SEQ ID NO:21, SEQ ID NO:22, and SEQ ID NO:23 and the three heavy chain CDRs are SEQ ID NO:24, SEQ ID NO:25 and SEQ ID NO:26.

[0092] Some antibody and antigen binding fragments of the formulations of the invention comprise a light chain variable region and a heavy chain variable region. In some embodiments, the light chain variable region comprises SEQ ID NO:4 or a variant of SEQ ID NO:4, and the heavy chain variable region comprises SEQ ID NO:9 or a variant of SEQ ID NO:9. In further embodiments, the light chain variable region comprises SEQ ID NO:14 or a variant of SEQ ID NO:14, and the heavy chain variable region comprises SEQ ID NO:19 or a variant of SEQ ID NO:19. In further embodiments, the heavy chain variable region comprises SEQ ID NO:27 or a variant of SEQ ID NO:27 and the light chain variable region comprises SEQ ID NO:28 or a variant of SEQ ID NO:28, SEQ ID NO:29 or a variant of SEQ ID NO:29, or SEQ ID NO:30 or a variant of SEQ ID NO:30. In such embodiments, a variant light chain or heavy chain variable region sequence is identical to the reference sequence except having one, two, three, four or five amino acid substitutions. In some embodiments, the substitutions are in the framework region (i.e., outside of the CDRs). In some embodiments, one, two, three, four or five of the amino acid substitutions are conservative substitutions.

[0093] In one embodiment of the formulations of the invention, the antibody or antigen binding fragment comprises a light chain variable region comprising or consisting of SEQ ID NO:4 and a heavy chain variable region comprising or consisting SEQ ID NO:9. In a further embodiment, the antibody or antigen binding fragment comprises a light chain variable region comprising or consisting of SEQ ID NO:14 and a heavy chain variable region comprising or consisting of SEQ ID NO:19. In one embodiment of the formulations of the invention, the antibody or antigen binding fragment comprises a light chain variable region comprising or consisting of SEQ ID NO:28 and a heavy chain variable region comprising or consisting SEQ ID NO:27. In a further embodiment, the antibody or antigen binding fragment comprises a light chain variable region comprising or consisting of SEQ ID NO:29 and a heavy chain variable region comprising or consisting SEQ ID NO:27. In another embodiment, the antibody or antigen binding fragment comprises a light chain variable region comprising or consisting of SEQ ID NO:30 and a heavy chain variable region comprising or consisting SEQ ID NO:27.

[0094] In another embodiment, the formulations of the invention comprise an antibody or antigen binding protein that has a V_L domain and/or a V_H domain with at least 95%, 90%, 85%, 80%, 75% or 50% sequence homology to one of the V_L domains or V_H domains described above, and exhibits specific binding to PD-1. In another embodiment, the antibody or antigen binding protein of the formulations of the invention comprises V_L and V_H domains having up to 1, 2, 3, 4, or 5 or more amino acid substitutions, and exhibits specific binding to PD-1.

[0095] In any of the embodiments above, the API may be a full-length anti-PD-1 antibody or an antigen binding fragment thereof that specifically binds human PD-1. In certain embodiments, the API is a full-length anti-PD-1 antibody selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA, and IgE. Preferably, the antibody is an IgG antibody. Any isotype of IgG can be used, including IgG_1, IgG_2, IgG_3, and IgG_4. Different constant domains may be appended to the V_L and V_H regions provided herein. For example, if a particular intended use of an antibody (or fragment) of the invention were to call for altered effector functions, a heavy chain constant domain other than IgG1 may be used. Although IgG1 antibodies provide for long half-life and for effector functions, such as complement activation and antibody-dependent cellular cytotoxicity, such activities may not be desirable for all uses of the antibody. In such instances an IgG4 constant domain, for example, may be used.

[0096] In embodiments of the invention, the API is an anti-PD-1 antibody comprising a light chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:5 and a heavy chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:10. In alternative embodiments, the API is an anti-PD-1 antibody comprising a light chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:15 and a heavy chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:20. In further embodiments, the API is an anti-PD-1 antibody comprising a light chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:32 and a heavy chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:31. In additional embodiments, the API is an anti-PD-1 antibody comprising a light chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:33 and a heavy chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:31. In yet additional embodiments, the API is an anti-PD-1 antibody comprising a light chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:34 and a heavy chain comprising or consisting of a sequence of amino acid residues as set forth in SEQ ID NO:31. In some formulations of the invention, the API is pembrolizumab or a pembrolizumab biosimilar. In some formulations of the invention, the API is nivolumab or a nivolumab biosimilar.

[0097] Ordinarily, amino acid sequence variants of the anti-PD-1 antibodies and antigen binding fragments of the invention will have an amino acid sequence having at least 75% amino acid sequence identity with the amino acid sequence of a reference antibody or antigen binding fragment (e.g. heavy chain, light chain, V_H, V_L, or humanized sequence), more preferably at least 80%, more preferably at least 85%, more preferably at least 90%, and most preferably at

least 95, 98, or 99%. Identity or homology with respect to a sequence is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the anti-PD-1 residues, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. None of N-terminal, C-terminal, or internal extensions, deletions, or insertions into the antibody sequence shall be construed as affecting sequence identity or homology.

[0098] Sequence identity refers to the degree to which the amino acids of two polypeptides are the same at equivalent positions when the two sequences are optimally aligned. Sequence identity can be determined using a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences. The following references relate to BLAST algorithms often used for sequence analysis: BLAST ALGORITHMS: Altschul, S.F., *et al.*, (1990) J. Mol. Biol. 215:403-410; Gish, W., *et al.*, (1993) Nature Genet. 3:266-272; Madden, T.L., *et al.*, (1996) Meth. Enzymol. 266:131-141; Altschul, S.F., *et al.*, (1997) Nucleic Acids Res. 25:3389-3402; Zhang, J., *et al.*, (1997) Genome Res. 7:649-656; Wootton, J.C., *et al.*, (1993) Comput. Chem. 17:149-163; Hancock, J.M. *et al.*, (1994) Comput. Appl. Biosci. 10:67-70; ALIGNMENT SCORING SYSTEMS: Dayhoff, M.O., *et al.*, "A model of evolutionary change in proteins." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3. M.O. Dayhoff (ed.), pp. 345-352, Natl. Biomed. Res. Found., Washington, DC; Schwartz, R.M., *et al.*, "Matrices for detecting distant relationships." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3." M.O. Dayhoff (ed.), pp. 353-358, Natl. Biomed. Res. Found., Washington, DC; Altschul, S.F., (1991) J. Mol. Biol. 219:555-565; States, D.J., *et al.*, (1991) Methods 3:66-70; Henikoff, S., *et al.*, (1992) Proc. Natl. Acad. Sci. USA 89:10915-10919; Altschul, S.F., *et al.*, (1993) J. Mol. Evol. 36:290-300; ALIGNMENT STATISTICS: Karlin, S., *et al.*, (1990) Proc. Natl. Acad. Sci. USA 87:2264-2268; Karlin, S., *et al.*, (1993) Proc. Natl. Acad. Sci. USA 90:5873-5877; Dembo, A., *et al.*, (1994) Ann. Prob. 22:2022-2039; and Altschul, S.F. "Evaluating the statistical significance of multiple distinct local alignments." in Theoretical and Computational Methods in Genome Research (S. Suhai, ed.), (1997) pp. 1-14, Plenum, New York.

[0099] Likewise, either class of light chain can be used in the compositions and methods herein. Specifically, kappa, lambda, or variants thereof are useful in the present compositions and methods.

Table 2. Exemplary PD-1 Antibody Sequences

Antibody Feature	Amino Acid Sequence	SEQ ID NO.
Pembrolizumab Light Chain		
CDR1	RASKGVSTSGYSYLH	1
CDR2	LASYLES	2
CDR3	QHSRDLPLT	3
Variable Region	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWY QQKPGQAPRLLIYLASYLESGVPARFSGSGSGTDFTLTISS LEPEDFAVYYCQHSRDLPLTFGGGTKVEIK	4
Light Chain	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWY QQKPGQAPRLLIYLASYLESGVPARFSGSGSGTDFTLTISS LEPEDFAVYYCQHSRDLPLTFGGGTKVEIKRTVAAPSVFI FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC	5
Pembrolizumab Heavy Chain		
CDR1	NYYMY	6
CDR2	GINPSNGGTNFNEKFKN	7
CDR3	RDYRFDMGFDY	8
Variable Region	QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWV RQAPGQGLEWMGGINPSNGGTNFNEKFKNRVTLTTDSST TTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQG TTVTVSS	9
Heavy Chain	QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWV RQAPGQGLEWMGGINPSNGGTNFNEKFKNRVTLTTDSST TTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQG TTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPE VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGK	10
Nivolumab Light Chain		
CDR1	RASQSVSSYLA	11
CDR2	DASNRAT	12
CDR3	QQSSNWPRT	13
Variable Region	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKP GQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPE DFAVYYCQQSSNWPRTFGQGTKVEIK	14
Light Chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKP GQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPE DFAVYYCQQSSNWPRTFGQGTKVEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC	15
Nivolumab Heavy Chain		
CDR1	NSGMH	16

Antibody Feature	Amino Acid Sequence	SEQ ID NO.
CDR2	VIWYDGSKRYYADSVKG	17
CDR3	NDDY	18
Variable Region	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVR QAPGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSK NTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSS	19
Heavy Chain	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVR QAPGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSK NTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTY TCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH YTQKSLSLSLGK	20

Table 3. Additional PD-1 Antibodies and Antigen Binding Fragments Useful in the Formulations, Methods and Uses of the Invention.

A. Antibodies and antigen binding fragments comprising light and heavy chain CDRs of hPD-1.08A in WO2008/156712	
CDRL1	SEQ ID NO:21
CDRL2	SEQ ID NO:22
CDRL3	SEQ ID NO:23
CDRH1	SEQ ID NO:24
CDRH2	SEQ ID NO:25
CDRH3	SEQ ID NO:26
C. Antibodies and antigen binding fragments comprising the mature h109A heavy chain variable region and one of the mature K09A light chain variable regions in WO 2008/156712	
Heavy chain VR	SEQ ID NO:27
Light chain VR	SEQ ID NO:28 or SEQ ID NO:29 or SEQ ID NO:30
D. Antibodies and antigen binding fragments comprising the mature 409 heavy chain and one of the mature K09A light chains in WO 2008/156712	
Heavy chain	SEQ ID NO:31
Light chain	SEQ ID NO:32 or SEQ ID NO:33 or SEQ ID NO:34

[0100] In some embodiments of the formulations of the invention, the API (i.e. the anti-PD-1 antibody or antigen binding fragment thereof) is present in a concentration of about 25 mg/mL to about 200 mg/mL. In additional embodiments, the API is present in a concentration of from about 5 mg/mL to about 25 mg/mL. In some embodiments of the formulations of the invention, the API (i.e. the anti-PD-1 antibody or antigen binding fragment thereof) is present in a concentration of about 5 mg/mL to about 200 mg/mL. In alternative embodiments, the API is present in a concentration of about 5 mg/mL, about 10 mg/mL, about 25 mg/mL, about 50 mg/mL, about 75 mg/mL, about 100 mg/mL, about 125 mg/mL, about 130 mg/mL about 150 mg/mL, about 165 mg/mL, about 167 mg/mL about 175 mg/mL, about 200 mg/mL.

[0101] In one embodiment, the API is present in a concentration of about 165 to about 170 mg/mL.

[0102] In one embodiment, the API is present in a concentration of about 167 mg/mL.

[0103] In one embodiment, the API is present in a concentration of about 130 mg/mL.

[0104] In additional embodiments, the API is present in a concentration of from about 5 mg/mL to about 75 mg/mL, from about 50 mg/mL to about 200 mg/mL; from about 75 mg/mL to about 200 mg/mL; from about 100 mg/mL to about 200 mg/mL; from about 25 mg/mL to about 175 mg/mL; from about 50 mg/mL to about 175 mg/mL; from about 75 mg/mL to about 175 mg/mL; from about 100 mg/mL to about 175 mg/mL; from about 25 mg/mL to about 150 mg/mL; from about 50 mg/mL to about 150 mg/mL; from about 75 mg/mL to about 150 mg/mL; from about 100 mg/mL to about 150 mg/mL; from about 25 mg/mL to about 125 mg/mL; from about 50 mg/mL to about 125 mg/mL; from about 75 mg/mL to about 125 mg/mL; from about 25 mg/mL to about 100 mg/mL, from about 125 mg/mL to about 175 mg/mL, from about 125 mg/mL to about 200 mg/mL, or from about 5 mg/mL to 200 mg/mL.

Formulation Excipients

[0105] The formulations of the invention comprise at least one excipient that stabilizes the formulation. In some embodiments, the formulation comprises more than one stabilizer.

[0106] In some embodiments of the formulations of the invention, the stabilizer is a non-reducing sugar. In embodiments of the invention, the non-reducing sugar is glucose. In further embodiments, the non-reducing sugar is sucrose. In additional embodiments, the non-reducing sugar is trehalose. In still further embodiments, the non-reducing sugar is lactose. In other embodiments, the non-reducing sugar is raffinose.

[0107] In some embodiments, the anti-human PD-1 antibody formulations of the invention comprise a stabilizer selected from the group consisting of: about 6% to about 8%

weight/volume (w/v) sucrose, trehalose or (2-hydroxypropyl)-β-cyclodextrin; about 3% to about 5% w/v mannitol, sorbitol, L-arginine, or a pharmaceutically acceptable salt of L-arginine, or L-proline, or a pharmaceutically acceptable salt of L-proline; and about 1.8 to about 2.2% w/v glycine, or a pharmaceutically acceptable salt thereof.

[0108] In some embodiments, the stabilizer is about 6% to about 8% w/v sucrose.

[0109] In some embodiments, the stabilizer is about 6% to about 8% w/v trehalose.

[0110] In some embodiments, the stabilizer is about 6% to about 8% w/v (2-hydroxypropyl)-β-cyclodextrin.

[0111] In some embodiments, the stabilizer is sucrose, trehalose or (2-hydroxypropyl)-β-cyclodextrin, which is present in an amount of about 6% to about 8% w/v. In further embodiments, the sucrose, trehalose or (2-hydroxypropyl)-β-cyclodextrin is present in an amount of about 6.5% to about 7.5% w/v. In still further embodiments, the sucrose, trehalose or (2-hydroxypropyl)-β-cyclodextrin is present in an amount of about 6% w/v, about 6.25% w/v, about 6.5% w/v, about 6.75% w/v, about 7% w/v, about 7.25% w/v, about 7.5% w/v, about 7.75% w/v or about 8% w/v.

[0112] In some embodiments, the stabilizer is about 3% to about 5% w/v mannitol.

[0113] In some embodiments, the stabilizer is about 3% to about 5% w/v sorbitol.

[0114] In some embodiments, the stabilizer is about 3% to about 5% w/v L-arginine, or a pharmaceutically acceptable salt thereof.

[0115] In certain embodiments, the formulation of the invention comprises arginine, e.g., L-arginine or a pharmaceutically acceptable salt thereof. In additional embodiments, the formulations of the invention comprise arginine hydrochloride (i.e. arginine HCl). In further embodiments, the formulations comprise arginine succinate. In further embodiments, the arginine is L-arginine.

[0116] In some embodiments, the stabilizer is about 3% to about 5% w/v proline, e.g., L-proline, or a pharmaceutically acceptable salt thereof. In additional embodiments, the formulations of the invention comprise proline hydrochloride (i.e. proline HCl). In further embodiments, the formulations comprise L-proline.

[0117] In some embodiments, the stabilizer is mannitol, sorbitol, L-arginine, a pharmaceutically acceptable salt of L-arginine, L-proline, or a pharmaceutically acceptable salt of L-proline, which is present in an amount of about 3% to about 5% w/v. In further embodiments, the mannitol, sorbitol, L-arginine, pharmaceutically acceptable salt of L-arginine, L-proline, or a pharmaceutically acceptable salt of L-proline, is present in an amount of about 3.5% to about 4.5% w/v. In still further embodiments, the mannitol, sorbitol, L-arginine,

pharmaceutically acceptable salt of L-arginine, L-proline, or pharmaceutically acceptable salt of L-proline, is present in an amount of about 3% w/v, about 3.25% w/v, about 3.5% w/v, about 3.75% w/v, about 4% w/v, about 4.25% w/v, about 4.5% w/v, about 4.75% w/v, or about 5% w/v.

[0118] In some embodiments, the stabilizer is about 1.8 to about 2.2 % w/v glycine, or a pharmaceutically acceptable salt thereof.

[0119] In certain embodiments, the formulation of the invention comprises glycine or a pharmaceutically acceptable salt thereof. In additional embodiments, the formulations of the invention comprise sodium glycinate.

[0120] In specific embodiments, the stabilizer is glycine, which is present in an amount of about 150 mM to about 200 mM, or about 150 mM, about 160 mM, about 170 mM, about 175 mM, about 180 mM, about 190 mM or about 200 mM.

[0121] In certain embodiments, the stabilizer is glycine, which is present in an amount of about 1.8 to about 2.2% w/v, about 1.5 to about 2.5%, or about 1.8 to about 2.5% or about 1.5 to about 2.2%. In specific embodiments, the glycine is present in an amount of about 1.8%, about 2.0% about 2.2%, or about 2.5%.

[0122] In some embodiments, the anti-human PD-1 antibody formulations of the invention comprise a stabilizer selected from the group consisting of (1) about 6% to about 8% w/v sucrose, trehalose or (2-hydroxypropyl)-β-cyclodextrin; (2) about 3 % to about 5% mannitol, sorbitol, L-proline, or a pharmaceutically acceptable salt of L-proline; and (3) about 1.8 to about 2.2 % w/v glycine, or a pharmaceutically acceptable salt thereof.

[0123] The formulations of the invention optionally comprise arginine, e.g., L-arginine, or a pharmaceutically acceptable salt thereof, which may provide additional stability to the formulation, as well as control viscosity, which allows formulation at high API concentration. In some embodiments of the invention, the L-arginine or pharmaceutically acceptable salt is present in the formulations in an amount of 0.25% to about 3% weight/volume. In additional embodiments, the L-arginine or pharmaceutically acceptable salt is present in an amount of about 0.25% w/v, about 0.50% w/v, about 0.75% w/v, about 1.0% w/v, about 1.25% w/v, about 1.5% w/v, about 1.75% w/v, about 2.0% w/v, about 2.25% w/v, about 2.5% w/v, about 2.75% w/v or about 3.0% w/v. In further embodiments, the L-arginine or pharmaceutically acceptable salt is present in an amount of about 0 to about 2.75% w/v, 0 to about 2.5% w/v, 0 to about 2.25% w/v, 0 to about 2% w/v, 0 to about 1.75% w/v, 0 to about 1.5% w/v, 0 to about 1.25% w/v, 0 to about 1.0% w/v, about 0.5% to about 3.0% w/v, about 0.5% to about 2.75% w/v, about 0.5% to about 2.5% w/v, about 0.5% to about 2.25% w/v, about 0.5% to about 2% w/v, about

0.5% to about 1.75% w/v, about 0.5% to about 1.5% w/v, about 0.5% to about 1.25% w/v, about 0.5% to about 1.0% w/v, about 1.0% to about 3.0% w/v, about 1.0% to about 2.75% w/v, about 1.0% to about 2.5% w/v, about 1.0% to about 2.25% w/v, about 1.0% to about 2% w/v, about 1.0% to about 1.75% w/v, about 1.0% to about 1.5% w/v, about 1.5% to about 3.0% w/v, about 1.5% to about 2.75% w/v, about 1.5% to about 2.5% w/v, about 1.5% to about 2.25% w/v, about 1.5% to about 2% w/v, or about 2% to about 3% w/v.

[0124] In some embodiments of the invention, the stabilizer is selected from the group consisting of: about 6% to about 8% w/v sucrose, trehalose or (2-hydroxypropyl)-β-cyclodextrin; about 3% to about 5% w/v mannitol, sorbitol, or proline, or a pharmaceutically acceptable salt thereof; and about 1.8 to about 2.2% w/v glycine, or a pharmaceutically acceptable salt thereof, and the formulation further comprises L-arginine or a pharmaceutically acceptable salt thereof, which can be added in any of the amounts above to reduce viscosity of the formulation, especially when the API is present in high concentration (e.g. 75 mg/mL-200 mg/mL). It is understood that although L-arginine, or pharmaceutically acceptable salt thereof, may be added to reduce viscosity in such embodiments, the L-arginine or pharmaceutically acceptable salt, may also be serving to stabilize the formulation and may impart additional stability relative to the formulation without L-arginine or pharmaceutically acceptable salt.

[0125] As noted above, in specific embodiments, the formulations of the invention comprise a high concentration of API (e.g. about 75 mg/mL to about 200 mg/mL). In particular embodiments wherein a high concentration of API is employed, the formulations of the invention also comprise arginine, e.g., L-arginine, or a pharmaceutically acceptable salt thereof, e.g. an amount of L-arginine from about 0.25% to about 3.0% w/v.

[0126] In addition to an anti-PD-1 antibody or antigen binding fragment thereof, and a stabilizer in the amounts/concentrations specified above, the formulations of the invention also comprise a buffer. In some embodiments the buffer is present in an amount of about 5 mM to about 20 mM, which provides for a pH in the range of about 4.5 to 6.4.

[0127] In some embodiments of the invention, the buffer provides the formulation a pH in the range from about 4.5 to about 6.5. In further embodiments, the buffer has a pH in a range of about 5.0 to about 6.0. In still further embodiments, the pH is from about 5.3 to about 5.8. In other embodiments, the pH is from about 6.0 to about 6.4.

[0128] In particular embodiments, the buffer has a pH of about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.2 or about 6.4. Examples of buffers that will control the pH in this range include succinate (sodium or potassium), histidine, sodium acetate, phosphate (sodium or potassium), Tris (tris

(hydroxymethyl) aminomethane), diethanolamine, citrate (sodium) and other organic acid buffers.

[0129] In specific embodiments of the invention, the buffer is histidine or acetate at a pH of about 5.0 to about 6.0. In some embodiments, the buffer is an L-histidine buffer. In some preferred embodiments, the buffer is acetate. In embodiments where the formulation is lyophilized, it is preferred that the buffer is not acetate because acetate buffer systems are not compatible with the lyophilization process.

[0130] When a range of pH values is recited, such as "a pH between pH 5.5 and 6.0," the range is intended to be inclusive of the recited values. Unless otherwise indicated, for lyophilized formula the pH refers to the pH after reconstitution of the lyophilized formulations of the invention. The pH is typically measured at 25°C using standard glass bulb pH meter. As used herein, a solution comprising "histidine buffer at pH X" refers to a solution at pH X and comprising the histidine buffer, *i.e.* the pH is intended to refer to the pH of the solution.

[0131] In addition to an anti-PD-1 antibody or antigen binding fragment thereof, a stabilizer, and a buffer in the amounts/concentrations specified above, the formulations of the invention also comprise an anti-oxidant. In embodiments of the invention, the anti-oxidant is methionine. In embodiments of the invention, the anti-oxidant is L-methionine, or a pharmaceutically acceptable salt thereof. In further embodiments, the methionine is L-methionine. In other embodiments, the anti-oxidants is L-methionine HCl. In other embodiments, the anti-oxidant is histidine.

[0132] In some embodiments, the anti-oxidant (e.g. L-methionine) is present in the formulations of the invention in an amount of amount 1 mM to about 20 mM. In further embodiments, the anti-oxidant is present in an amount of about 5 mM to about 20 mM, about 5 mM to about 15 mM, about 5 mM to about 10 mM. In additional embodiments, the anti-oxidant is present in an amount of about 1 mM, about 2 mM, about 3 mM, about 4 mM, about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM or about 20 mM.

[0133] In embodiments wherein the anti-oxidant is histidine, the histidine can be present in amounts up to 100 mM. In such embodiments, histidine can serve as a buffer and as an anti-oxidant in the formulations of the invention.

[0134] In addition to an anti-PD-1 antibody or antigen binding fragment thereof, a stabilizer, a buffer, and an anti-oxidant in the amounts/concentrations specified above, the formulations of the invention also comprise a surfactant. Surfactants are typically added to formulations to

provide stability, reduce and/or prevent aggregation or to prevent and/or inhibit protein damage during processing conditions such as purification, filtration, freeze-drying, transportation, storage, and delivery. In some embodiments of the invention, a surfactant is useful for providing additional stability to the active ingredient(s), i.e. the anti-PD-1 antibody or antigen binding fragment thereof.

[0135] Surfactants that may be useful in the formulations of the invention include, but are not limited to: nonionic surfactants such as polyoxyethylene sorbitan fatty acid esters (Polysorbates, sold under the trade name Tween® (Uniquema Americas LLC, Wilmington, DE)) including Polysorbate-20 (polyoxyethylene sorbitan monolaurate), Polysorbate-40 (polyoxyethylene sorbitan monopalmitate), Polysorbate-60 (polyoxyethylene sorbitan monostearate), and Polysorbate-80 (polyoxyethylene sorbitan monooleate); polyoxyethylene alkyl ethers such as Brij® 58 (Uniquema Americas LLC, Wilmington, DE) and Brij® 35; poloxamers (e.g., poloxamer 188); Triton® X-100 (Union Carbide Corp., Houston, TX) and Triton® X-114; NP40; Span 20, Span 40, Span 60, Span 65, Span 80 and Span 85; copolymers of ethylene and propylene glycol (e.g., the pluronic® series of nonionic surfactants such as pluronic® F68, pluronic® 10R5, pluronic® F108, pluronic® F127, pluronic® F38, pluronic® L44, pluronic® L62 (BASF Corp., Ludwigshafen, Germany); and sodium dodecyl sulfate (SDS).

[0136] The amount of surfactant to be included in the formulations of the invention is an amount sufficient to perform the desired function, i.e. a minimal amount necessary to stabilize the active pharmaceutical ingredient (i.e. the anti-PD-1 antibody or antigen binding fragment thereof) in the formulation. Typically, the surfactant is present in a concentration of from about 0.008% to about 0.1% w/v% w/v. In some embodiments of this aspect of the invention, the surfactant is present in the formulation in an amount from about 0.01% to about 0.04%; from about 0.01% to about 0.03%, from about 0.01% to about 0.02%, from about 0.015% to about 0.04%; from about 0.015% to about 0.03%, from about 0.015% to about 0.02%, from about 0.02% to about 0.04%, from about 0.02% to about 0.035%, or from about 0.02% to about 0.03%. In specific embodiments, the surfactant is present in an amount of about 0.02%. In alternative embodiments, the surfactant is present in an amount of about 0.01%, about 0.015%, about 0.025%, about 0.03%, about 0.035%, or about 0.04%.

[0137] In exemplary embodiments of the invention, the surfactant is a nonionic surfactant selected from the group consisting of: Polysorbate 20, Polysorbate 80 and F127. In preferred embodiments, the surfactant is Polysorbate 80.

[0138] In specific embodiments, the PD-1 formulations of the invention comprise about 0.01% to about 0.04% PS80. In further embodiments, the formulations of the invention comprise PS80

in an amount of about 0.008%, about 0.01%, about 0.015%, about 0.02%, about 0.025%, about 0.03%, about 0.035%, about 0.04% or about 0.045%. In particular embodiments, the formulations of the invention comprise about 0.02% PS80.

[0139] The invention also provides an anti-human PD-1 antibody formulation as described herein, wherein the formulation is contained in a glass vial or injection device (e.g. a syringe).

[0140] In embodiments of the formulations of the invention, the anti-human PD-1 antibody formulation has one or more of the following attributes after storage at 2-8 °C for 12 months:

a) the % heavy chain and light chain as measured by reducing CE-SDS is ≥ 90.0%,

b) the % intact IgG as measured by non-reducing CE-SDS is ≥ 90.0%, and

c) the % monomer as measured by HP-SEC is ≥95%.

[0141] In further embodiments, the invention provides anti-human PD-1 antibody formulations as described herein, wherein after storage of the formulation at 2-8 °C for 12 months, the % heavy chain and light chain measured by reducing CE-SDS is ≥ 96%.

[0142] In further embodiments, the invention provides anti-human PD-1 antibody formulations as described herein, wherein after storage of the formulation at 2-8 °C for 12 months the % intact IgG in the formulation measured by non-reducing CE-SDS is ≥ 97%.

[0143] In further embodiments, the invention provides anti-human PD-1 antibody formulations as described herein, wherein after storage of the formulation at 2-8 °C for 12 months, the % monomer as measured by HP-SEC is ≥98.5.

[0144] In additional embodiments, the invention provides anti-human PD-1 antibody formulations as described herein, wherein after storage of the formulation at 2-8 °C for 12 months, the % high molecular weight species as measured by HP-SEC is ≤ 1.5%.

[0145] In further embodiments, the invention provides anti-human PD-1 antibody formulations as described herein, wherein after storage of the formulation at 25 °C for 12 months, the % monomer as measured by HP-SEC is ≥98.0 %.

[0146] In additional embodiments, the invention provides anti-human PD-1 antibody formulations as described herein, wherein after storage of the formulation at 25 °C for 6 months, the % high molecular weight species as measured by HP-SEC is ≤ 2 %.

[0147] In further embodiments, the invention provides anti-human PD-1 antibody formulations as described herein, wherein after storage of the formulation at 40 °C for 3 months, the % monomer as measured by HP-SEC is ≥94.0 %, ≥94.5 % or ≥95.0 %.

[0148] In additional embodiments, the invention provides anti-human PD-1 antibody formulations as described herein, wherein after storage of the formulation at 40 °C for 3 months, the % high molecular weight species as measured by HP-SEC is ≤ 5.5 %, ≤ 5.0 %, or ≤ 4.4 %.

Specific Aspects and Embodiments of the Invention

[0149] In one aspect (A1), the invention provides an anti-human PD-1 antibody formulation, comprising: (a) about 5 mg/mL to about 200 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; (b) about 5 mM to about 20 mM buffer; (c) a stabilizer selected from the group consisting of: (i) about 6% to about 8% weight/volume (w/v) sucrose, trehalose or (2-hydroxypropyl)-β-cyclodextrin; (ii) about 3% to about 5% w/v mannitol, sorbitol, L-arginine, a pharmaceutically acceptable salt of L-arginine, L-proline, or a pharmaceutically acceptable salt of L-proline; and (iii) about 1.8 to about 2.2 % w/v glycine, or a pharmaceutically acceptable salt thereof; (d) about 0.01 % to about 0.10% non-ionic surfactant; and (e) about 1 mM to about 20 mM anti-oxidant.

[0150] In one embodiment of aspect (A1), formulation has a pH between 4.5 and 6.4.

[0151] In one embodiment of aspect (A1), formulation has a pH between 5.0 and 6.0.

[0152] In one embodiment of aspect (A1), formulation has a pH between 5.3 and 5.8.

[0153] In one embodiment of aspect (A1), formulation has a pH around 5.5.

[0154] In one embodiment of aspect (A1), the buffer is histidine or acetate.

[0155] In one embodiment of aspect (A1), the buffer is about 10 mM histidine.

[0156] In one embodiment of aspect (A1), the buffer is about 10 mM L-histidine.

[0157] In one embodiment of aspect (A1), the buffer is about 10 mM acetate.

[0158] In one embodiment of aspect (A1), the stabilizer is about 6% to about 8% w/v sucrose.

[0159] In one embodiment of aspect (A1), the stabilizer is about 6% to about 8% w/v trehalose.

[0160] In one embodiment of aspect (A1), the stabilizer is about 6% to about 8% w/v (2-hydroxypropyl)-β-cyclodextrin.

[0161] In one embodiment of aspect (A1), the stabilizer is about 3% to about 5% w/v mannitol.

[0162] In one embodiment of aspect (A1), the stabilizer is about 3% to about 5% w/v sorbitol.

[0163] In one embodiment of aspect (A1), the stabilizer is about 3% to about 5% w/v L-arginine, or a pharmaceutically acceptable salt thereof.

[0164] In one embodiment of aspect (A1), the stabilizer is about 3% to about 5% w/v L-arginine, or a pharmaceutically acceptable salt thereof, and the pH of the formulation is from about 6.0 to about 6.4.

[0165] In one embodiment of aspect (A1), the stabilizer is about 3% to about 5% w/v L-arginine.

[0166] In one embodiment of aspect (A1), the stabilizer is about 3% to about 5% w/v arginine-HCl.

[0167] In one embodiment of aspect (A1), the stabilizer is about 3% to about 5% w/v L-proline, or a pharmaceutically acceptable salt thereof.

[0168] In one embodiment of aspect (A1), the stabilizer is about 3% to about 5% w/v L-proline.

[0169] In one embodiment of aspect (A1), the stabilizer is about 3% to about 5% w/v L-proline HCl.

[0170] In one embodiment of aspect (A1), the stabilizer is about 160 mM to about 200 mM glycine, or a pharmaceutically acceptable salt thereof.

[0171] In one embodiment of aspect (A1), the stabilizer is about 1.8 to about 2.2% w/v glycine, or pharmaceutically acceptable salt thereof.

[0172] In one embodiment of aspect (A1), the non-ionic surfactant is about 0.01 % to about 0.04% polysorbate 80.

[0173] In one embodiment of aspect (A1), the non-ionic surfactant is about 0.02 % polysorbate 80.

[0174] In one embodiment of aspect (A1), the anti-oxidant is about 1 mM to about 20 mM L-methionine or a pharmaceutically acceptable salt thereof.

[0175] In one embodiment of aspect (A1), the anti-oxidant is about 5 mM to about 15 mM L-methionine or a pharmaceutically acceptable salt thereof.

[0176] In one embodiment of aspect (A1), the anti-oxidant is about 10 mM L-methionine or a pharmaceutically acceptable salt thereof.

[0177] In one embodiment of aspect (A1), the anti-oxidant is L-methionine.

[0178] In one aspect (A2), the invention provides an anti-human PD-1 antibody formulation, comprising: (a) about 5 mg/mL to about 200 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; (b) about 5 mM to about 20 mM buffer; (c) a stabilizer selected from the group consisting of: (i) about 6% to about 8% weight/volume (w/v) sucrose, trehalose or (2-hydroxypropyl)-β-cyclodextrin; (ii) about 3% to about 5% w/v mannitol, sorbitol, L-proline, or a pharmaceutically acceptable salt of L-proline; and (iii) about 1.8 to about 2.2 % w/v glycine, or a pharmaceutically acceptable salt thereof; (d) about 0.01 % to about 0.10% non-ionic surfactant; and (e) about 1 mM to about 20 mM anti-oxidant.

[0179] In one embodiment of aspect (A2), the formulation further comprises from about 1% to about 3% w/v L-arginine, or a pharmaceutically acceptable salt thereof.

[0180] In one aspect (A3), the invention provides an anti-human PD-1 antibody formulation comprising: (a) about 25 mg/mL to about 200 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; (b) about 5 mM to about 20 mM histidine buffer; (c) about 6% to about 8% w/v sucrose; (d) about 0.01 % to about 0.04% w/v polysorbate 80; and (e) about 1 mM to about 20 mM L-methionine, or a pharmaceutically acceptable salt thereof.

[0181] In one embodiment of aspect (A3), the formulation further comprises from about 1% to about 3% w/v L-arginine, or a pharmaceutically acceptable salt thereof.

[0182] In one embodiment of aspect (A3), the formulation further comprises from about 1.25% to about 2.5% w/v L-arginine, or a pharmaceutically acceptable salt thereof.

[0183] In one embodiment of aspect (A3), the histidine buffer is present at a concentration of about 8 mM to about 12 mM.

[0184] In one embodiment of aspect (A3), the histidine buffer is L-histidine.

[0185] In one embodiment of aspect (A3), the L-methionine or pharmaceutically acceptable salt is present at a concentration of about 5 mM to about 15 mM.

[0186] In one embodiment of aspect (A3), the polysorbate 80 is present at a weight ratio of approximately 0.02% w/v.

[0187] In one embodiment of aspect (A3), the sucrose is present at a weight ratio of approximately 7% w/v.

[0188] In one aspect (A4), the invention provides an anti-human PD-1 antibody formulation, comprising: (a) about 75 to about 200 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; (b) about 8 mM to about 12 mM histidine buffer; (c) about 5 mM to about 10 mM L-methionine, or a pharmaceutically acceptable salt thereof; (d) about 6% to about 8% w/v sucrose; and (e) 0.01 % to about 0.04% w/v polysorbate 80.

[0189] In one aspect (A5), the invention provides an anti-human PD-1 antibody formulation, comprising: (a) about 125 to about 200 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; (b) about 10 mM histidine buffer; (c) about 10 mM L-methionine or pharmaceutically acceptable salt thereof; (d) about 7 % w/v sucrose; and (e) about 0.02 % to w/v polysorbate 80.

[0190] In one embodiment of aspect (A5), the formulation further comprises from about 1.25% to about 2.5% w/v L-arginine, or a pharmaceutically acceptable salt thereof.

[0191] In one embodiment of aspect (A5), the formulation further comprises from about 1.25% to about 2.5% w/v L-arginine.

[0192] In one embodiment of aspect (A5), the formulation further comprises from about 1.25% to about 2.5% w/v L-arginine-HCl.

[0193] In one embodiment of aspect (A5), the formulation has a pH between 5.0 and 6.0.

[0194] In one embodiment of aspect (A5), the formulation has a pH between 5.3 and 5.8.

[0195] In one aspect (A6), the invention provides an anti-human PD-1 antibody formulation, comprising: (a) about 5 mg/mL to about 75 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; (b) about 8 mM to about 12 mM histidine buffer; (c) a stabilizer selected from the group consisting of: (i) about 6% to about 8% weight/volume (w/v) sucrose, trehalose or (2-hydroxypropyl)-β-cyclodextrin; (ii) about 3% to about 5% w/v mannitol, sorbitol, L-arginine, a pharmaceutically acceptable salt of L-arginine, L-proline, or a pharmaceutically acceptable salt of L-proline; and (iii) about 1.8 to about 2.2% w/v glycine, or a pharmaceutically acceptable salt thereof; (d) about 0.01 % to about 0.04% polysorbate 80; and (e) about 5 mM to about 10 mM L-methionine or a pharmaceutically acceptable salt thereof.

[0196] In one embodiment of aspect (A6), the anti- human PD-1 antibody, or antigen binding fragment thereof is present at a concentration of about 5 mg/mL to about 25 mg/mL.

[0197] In one aspect (A7), the invention provides an anti-human PD-1 antibody formulation, comprising: (a) about 5 mg/mL to about 75 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; (b) about 8 mM to about 12 mM histidine buffer; (c) about 6% to about 8% weight/volume w/v sucrose; (d) about 0.01 % to about 0.04% polysorbate 80; and (e) about 5 mM to about 10 mM L-methionine or a pharmaceutically acceptable salt thereof.

[0198] In one embodiment of aspect (A7), the anti- human PD-1 antibody, or antigen binding fragment thereof is present at a concentration of about 5 mg/mL to about 25 mg/mL.

[0199] In one embodiment of aspect (A7), the L-methionine or a pharmaceutically acceptable salt thereof is L-methionine-HCl.

[0200] In one aspect (A8), the invention provides an anti-human PD-1 antibody formulation, comprising: (a) about 5 mg/mL to about 75 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; (b) about 8 mM to about 12 mM histidine buffer; (c) about 6% to about 8% w/v trehalose; (d) about 0.01 % to about 0.04% polysorbate 80; and (e) about 5 mM to about 10 mM methionine or a pharmaceutically acceptable salt thereof.

[0201] In one embodiment of aspect (A8), the anti- human PD-1 antibody, or antigen binding fragment thereof is present at a concentration of about 5 mg/mL to about 25 mg/mL.

[0202] In one aspect (A9), the invention provides an anti-human PD-1 antibody formulation, comprising: (a) about 5 mg/mL to about 75 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; (b) about 8 mM to about 12 mM histidine buffer; (c) about 6% to

about 8% w/v (2-hydroxypropyl)-β-cyclodextrin; (d) about 0.01 % to about 0.04% polysorbate 80; and (e) about 5 mM to about 10 mM L-methionine or a pharmaceutically acceptable salt thereof.

[0203] In one embodiment of aspect (A9), the anti- human PD-1 antibody, or antigen binding fragment thereof is present at a concentration of about 5 mg/mL to about 25 mg/mL.

[0204] In one aspect (A10), the invention provides an anti-human PD-1 antibody formulation, comprising: (a) about 5 mg/mL to about 75 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; (b) about 8 mM to about 12 mM histidine buffer; (c) about 3% to about 5% w/v mannitol; (d) about 0.01 % to about 0.04% polysorbate 80; and (e) about 5 mM to about 10 mM L-methionine or a pharmaceutically acceptable salt thereof.

[0205] In one embodiment of aspect (A10), the anti- human PD-1 antibody, or antigen binding fragment thereof is present at a concentration of about 5 mg/mL to about 25 mg/mL.

[0206] In one aspect (A11), the invention provides an anti-human PD-1 antibody formulation, comprising: (a) about 5 mg/mL to about 75 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; (b) about 8 mM to about 12 mM histidine buffer; (c) about 3% to about 5% w/v sorbitol; (d) about 0.01 % to about 0.04% polysorbate 80; and (e) about 5 mM to about 10 mM L-methionine or a pharmaceutically acceptable salt thereof.

[0207] In one embodiment of aspect (A11), the anti- human PD-1 antibody, or antigen binding fragment thereof is present at a concentration of about 5 mg/mL to about 25 mg/mL.

[0208] In one aspect (A12), the invention provides an anti-human PD-1 antibody formulation, comprising: (a) about 5 mg/mL to about 75 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; (b) about 8 mM to about 12 mM histidine buffer; (c) about 3% to about 5% w/v L-proline, or a pharmaceutically acceptable salt thereof; (d) about 0.01 % to about 0.04% polysorbate 80; and (e) about 5 mM to about 10 mM L-methionine or a pharmaceutically acceptable salt thereof.

[0209] In one embodiment of aspect (A12), the anti- human PD-1 antibody, or antigen binding fragment thereof is present at a concentration of about 5 mg/mL to about 25 mg/mL.

[0210] In one embodiment of aspect (A12), the L-proline, or a pharmaceutically acceptable salt thereof is L-proline.

[0211] In one embodiment of aspect (A12), the L-proline, or a pharmaceutically acceptable salt thereof is L-proline HCl.

[0212] In one aspect (A13), the invention provides an anti-human PD-1 antibody formulation, comprising: (a) about 5 mg/mL to about 75 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; (b) about 8 mM to about 12 mM histidine buffer; (c) about 3% to

about 5% w/v L-arginine, or a pharmaceutically acceptable salt thereof; (d) about 0.01 % to about 0.04% polysorbate 80; and (e) about 5 mM to about 10 mM L-methionine or a pharmaceutically acceptable salt thereof.

[0213] In one embodiment of aspect (A13), the anti- human PD-1 antibody, or antigen binding fragment thereof is present at a concentration of about 5 mg/mL to about 25 mg/mL.

[0214] In one embodiment of aspect (A13), the pH of the formulation is about 6.0 to about 6.4.

[0215] In one embodiment of aspect (A13), the L-arginine, or a pharmaceutically acceptable salt thereof is L-arginine.

[0216] In one embodiment of aspect (A13), the L-arginine, or a pharmaceutically acceptable salt thereof is L-arginine HCl.

[0217] In one aspect (A14), the invention provides an anti-human PD-1 antibody formulation, comprising: (a) about 5 mg/mL to about 75 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; (b) about 8 mM to about 12 mM histidine buffer; (c) about 160 mM to about 200 mM glycine, or a pharmaceutically acceptable salt thereof; (d) about 0.01 % to about 0.04% polysorbate 80; and (e) about 5 mM to about 10 mM L-methionine or a pharmaceutically acceptable salt thereof.

[0218] In one embodiment of aspect (A14), the anti- human PD-1 antibody, or antigen binding fragment thereof is present at a concentration of about 5 mg/mL to about 25 mg/mL.

[0219] In one embodiment of aspect (A14), the glycine, or pharmaceutically acceptable salt thereof is glycine.

[0220] In one embodiment of aspect (A14), the glycine, or pharmaceutically acceptable salt thereof is glycine HCl.

[0221] In one embodiment of aspect (A14), the glycine, or pharmaceutically acceptable salt thereof is glycine succinate.

[0222] In one embodiment of any of aspects (A6) – (A14), the formulation further comprises a metal chelator.

[0223] In one embodiment of any of aspects (A6) – (A14), the formulation further comprises DTPA, which is present at a concentration of about 10 μM to about 30 μM.

[0224] In some embodiments of any of aspects (A1) – (A14), the formulation is a liquid.

[0225] In some embodiments of any of aspects (A1) – (A14), the formulation is a reconstituted solution from a lyophilized formulation.

[0226] In any of the specific aspects and embodiments described herein, any anti-PD-1 antibody or antigen binding fragment thereof (i.e. an antibody or antigen binding fragment that specifically binds human PD-1, e.g. pembrolizumab or an antigen-binding fragment thereof) can

be used. In particular embodiments, one of the anti-PD-1 antibodies, or antigen binding fragments thereof, described herein, e.g. described in the section entitled Anti-PD-1 Antibodies and Antigen-Binding Fragments Thereof, is used.

[0227] In some embodiments of the invention, any of the formulations described herein is in aqueous solution. In alternative embodiment, the invention provides lyophilized formulations made by lyophilizing an aqueous formulation to provide a reconstituted formulation of the invention, as discussed more fully, *infra*.

Lyophilized Pharmaceutical Compositions

[0228] Lyophilized formulations of therapeutic proteins provide several advantages. Lyophilized formulations in general offer better chemical stability than solution formulations, and thus increased half-life. A lyophilized formulation may also be reconstituted at different concentrations depending on clinical factors, such as route of administration or dosing. For example, a lyophilized formulation may be reconstituted at a high concentration (i.e. in a small volume) if necessary for subcutaneous administration, or at a lower concentration if administered intravenously. High concentrations may also be necessary if high dosing is required for a particular subject, particularly if administered subcutaneously where injection volume must be minimized. One such lyophilized antibody formulation is disclosed at U.S. Pat. No. 6,267,958, which is hereby incorporated by reference in its entirety. Lyophilized formulations of another therapeutic protein are disclosed at U.S. Pat. No. 7,247,707, which is hereby incorporated by reference in its entirety.

[0229] Typically, the lyophilized formulation is prepared in anticipation of reconstitution at high concentration of drug product (DP, in an exemplary embodiment humanized anti-PD-1 antibody pembrolizumab, or antigen binding fragment thereof), *i.e.* in anticipation of reconstitution in a low volume of water. Subsequent dilution with water or isotonic buffer can then readily be used to dilute the DP to a lower concentration. Typically, excipients are included in a lyophilized formulation of the invention at levels that will result in a roughly isotonic formulation when reconstituted at high DP concentration, *e.g.* for subcutaneous administration. Reconstitution in a larger volume of water to give a lower DP concentration will necessarily reduce the tonicity of the reconstituted solution, but such reduction may be of little significance in non-subcutaneous, *e.g.* intravenous, administration. If isotonicity is desired at lower DP concentration, the lyophilized powder may be reconstituted in the standard low volume of water and then further diluted with isotonic diluent, such as 0.9% sodium chloride.

[0230] In an embodiment of the invention, humanized anti-PD-1 antibody (or antigen binding fragment thereof) is formulated as a lyophilized powder for reconstituting and utilizing for intravenous administration. In certain embodiments, the antibody (or antigen binding fragment thereof) is provided at about 50 mg/vial, and is reconstituted with sterile water for injection prior to use. If desired, the reconstituted antibody may be aseptically diluted with 0.9% sodium chloride Injection USP in a sterile IV container. In some embodiments, the target pH of the reconstituted formulation is 5.5±0.5. In various embodiments, the lyophilized formulation of the invention enables reconstitution of the anti-PD-1 antibody to high concentrations, such as about 20, 25, 30, 40, 50, 60, 75, 100, 125, 150, 175 or more mg/mL.

[0231] Lyophilized formulations are by definition essentially dry, and thus the concept of concentration is not useful in describing them. Describing a lyophilized formulation in the terms of the weight of the components in a unit dose vial is more useful, but is problematic because it varies for different doses or vial sizes. In describing the lyophilized formulations of the invention, it is useful to express the amount of a component as the ratio of the weight of the component compared to the weight of the drug substance (DS) in the same sample (e.g. a vial). This ratio may be expressed as a percentage. Such ratios reflect an intrinsic property of the lyophilized formulations of the invention, independent of vial size, dosing, and reconstitution protocol.

[0232] In other embodiments, the lyophilized formulation of anti-human PD-1 antibody, or antigen binding fragment, is defined in terms of the pre-lyophilization solution used to make the lyophilized formulation, such as the pre-lyophilization solution. In one embodiment the pre-lyophilization solution comprises antibody, or antigen-binding fragment thereof, at a concentration of about 10 mg/mL about 25 mg/mL or about 50 mg/mL. Such pre-lyophilization solutions may be at pH 4.4 – 5.2 (including about 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1. and 5.2), e.g. preferably about pH 4.8, or about pH 5.5.

[0233] In yet other embodiments, the lyophilized formulation of anti-human PD-1 antibody, or antigen binding fragment, is defined in terms of the reconstituted solution generated from the lyophilized formulation.

[0234] Reconstituted solutions may comprise antibody, or antigen-binding fragment thereof, at concentrations of about 10, 15, 20, 25, 30, 40, 50, 60, 75, 80, 90 or 100 mg/mL or higher concentrations such as 150 mg/mL, 167 mg/mL, 200 mg/mL, or up to about 250 mg/mL. Such reconstituted solutions may be at about pH 5.5, or range from about pH 5.0 to about 6.0

[0235] The lyophilized formulations of the invention are formed by lyophilization (freeze-drying) of a pre-lyophilization solution. Freeze-drying is accomplished by freezing the

formulation and subsequently subliming water at a temperature suitable for primary drying. Under this condition, the product temperature is below the eutectic point or the collapse temperature of the formulation. Typically, the shelf temperature for the primary drying will range from about -30 to 25°C (provided the product remains frozen during primary drying) at a suitable pressure, ranging typically from about 50 to 250 mTorr. The formulation, size and type of the container holding the sample (e.g., glass vial) and the volume of liquid will dictate the time required for drying, which can range from a few hours to several days (e.g. 40-60 hrs). A secondary drying stage may be carried out at about 0-40°C, depending primarily on the type and size of container and the type of protein employed. The secondary drying time is dictated by the desired residual moisture level in the product and typically takes at least about 5 hours. Typically, the moisture content of a lyophilized formulation is less than about 5%, and preferably less than about 3%. The pressure may be the same as that employed during the primary drying step. Freeze-drying conditions can be varied depending on the formulation and vial size.

[0236] In some instances, it may be desirable to lyophilize the protein formulation in the container in which reconstitution of the protein is to be carried out in order to avoid a transfer step. The container in this instance may, for example, be a 3, 5, 10, 20, 50 or 100 cc vial.

[0237] The lyophilized formulations of the invention are reconstituted prior to administration. The protein may be reconstituted at a concentration of about 10, 15, 20, 25, 30, 40, 50, 60, 75, 80, 90 or 100 mg/mL or higher concentrations such as 150 mg/mL, 200 mg/mL, 250 mg/mL, or 300 mg/mL up to about 500 mg/mL. High protein concentrations are particularly useful where subcutaneous delivery of the reconstituted formulation is intended. However, for other routes of administration, such as intravenous administration, lower concentrations of the protein may be desired (*e.g.* from about 5-50 mg/mL).

[0238] Reconstitution generally takes place at a temperature of about 25°C to ensure complete hydration, although other temperatures may be employed as desired. The time required for reconstitution will depend, *e.g.*, on the type of diluent, amount of excipient(s) and protein. Exemplary diluents include sterile water, bacteriostatic water for injection (BWFI), a pH buffered solution (e.g. phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution.

[0239] The invention provides a liquid anti-human PD-1 antibody formulation that is reconstituted from a lyophilized formulation wherein the reconstituted solution comprises: a) about 125 mg/mL to about 175 mg/mL of an anti-human PD-1 antibody, or antigen binding fragment thereof; b) about 8 mM to about 12 mM histidine buffer; c) a stabilizer selected from

the group consisting of: (i) about 3% to about 8% weight/volume (w/v) sucrose; (ii) about 2% to about 5% w/v L-arginine, or a pharmaceutically acceptable salt thereof; (iii) about 3% to about 5% mannitol and about 1% to about 2% sucrose, and (iv) a combination of i) and ii); and d)about 0.01 % to about 0.04% polysorbate 80.

[0240] In embodiments of the invention, the stabilizer comprises about 3% to about 8% weight/volume (w/v) sucrose.

[0241] In embodiments of the invention, the stabilizer comprises about 2% to about 5% w/v L-arginine, or a pharmaceutically acceptable salt thereof.

[0242] In embodiments of the invention, the stabilizer comprises about 3% to about 5% mannitol and about 1% to about 2% sucrose.

[0243] In embodiments of the invention, the stabilizer comprises about 4% to about 4.5% mannitol and about 1% to about 2% sucrose.

[0244] In embodiments of the invention, the stabilizer comprises about 3% to about 8% weight/volume (w/v) sucrose and about 2% to about 5% w/v L-arginine, or a pharmaceutically acceptable salt thereof. In specific embodiments, the stabilizer comprises sucrose and L-arginine. In other embodiments, the stabilizer comprises sucrose and L-arginine-HCl.

[0245] In specific embodiments, the stabilizer comprises a combination of 2-4% w/v L-arginine, or a pharmaceutically acceptable salt thereof and 3.5-6 % w/v sucrose. In other embodiments, the stabilizer comprises a combination of about 3% L-arginine or a pharmaceutically acceptable salt thereof and about 5.5% sucrose. In other embodiments, the stabilizer comprises a combination of about 2% L-arginine or a pharmaceutically acceptable salt thereof and about 5 % sucrose. In other embodiments, the stabilizer comprises a combination of about 2% L-arginine or a pharmaceutically acceptable salt thereof and about 3.7% sucrose.

Liquid Pharmaceutical Compositions

[0246] A liquid antibody formulation can be made by taking the drug substance (*e.g.*, anti-humanized PD-1) which is in liquid form (*e.g.*, pembrolizumab in an aqueous pharmaceutical formulation) and buffer exchanging it into the desired buffer as the last step of the purification process. There is no lyophilization step in this embodiment. The drug substance in the final buffer is concentrated to a desired concentration. Excipients such as sucrose, methionine and polysorbate 80 are added to the drug substance and it is diluted using the appropriate buffer to final protein concentration. The final formulated drug substance is filtered, e.g. using 0.22μm filters, and filled into a final container (*e.g.* glass vials or syringes). Such a liquid formulation is exemplified by a final liquid formulation comprising 10 mM histidine pH 5.5, 7% sucrose,

0.02% polysorbate 80, 25-200 mg/mL pembrolizumab and 1.5-2.5% arginine, or a pharmaceutically acceptable salt thereof.

II. Methods of Use

[0247] The invention also relates to a method of treating cancer in a subject, the method comprising administering an effective amount of any of the formulations of the invention; i.e., any formulation described herein (including the formulations of the invention defined as aspects (A1)-(A14) in the Specific Aspects and Embodiments of the Invention section herein (referred to hereafter as "aspects (A1)-(A14)")), to the subject. In some embodiments of this method, the formulation is administered to the subject via intravenous administration. In other embodiments, the formulation is administered to the subject by subcutaneous administration.

[0248] In any of the methods of the invention, the cancer can be selected from the group consisting of: melanoma, lung cancer, head and neck cancer, bladder cancer, breast cancer, gastrointestinal cancer, multiple myeloma, hepatocellular cancer, lymphoma, renal cancer, mesothelioma, ovarian cancer, esophageal cancer, anal cancer, biliary tract cancer, colorectal cancer, cervical cancer, thyroid cancer, salivary cancer, prostate cancer (e.g. hormone refractory prostate adenocarcinoma), pancreatic cancer, colon cancer, esophageal cancer, liver cancer, thyroid cancer, glioblastoma, glioma, and other neoplastic malignancies.

[0249] In some embodiments the lung cancer in non-small cell lung cancer.

[0250] In alternate embodiments, the lung cancer is small-cell lung cancer.

[0251] In some embodiments, the lymphoma is Hodgkin lymphoma.

[0252] In other embodiments, the lymphoma is non-Hodgkin lymphoma. In particular embodiments, the lymphoma is mediastinal large B-cell lymphoma. In some embodiments, the lymphoma is diffuse large B-cell lymphoma (DLBCL).

[0253] In some embodiments, the breast cancer is triple negative breast cancer.

[0254] In further embodiments, the breast cancer is ER+/HER2- breast cancer.

[0255] In some embodiments, the bladder cancer is urothelial cancer.

[0256] In some embodiments, the head and neck cancer is nasopharyngeal cancer. In some embodiments, the cancer is thyroid cancer. In other embodiments, the cancer is salivary cancer. In other embodiments, the cancer is squamous cell carcinoma of the head and neck.

[0257] In some embodiments, the cancer is metastatic colorectal cancer with high levels of microsatellite instability (MSI-H).

[0258] In some embodiments, the cancer is a solid tumor with a high level of microsatellite instability (MSI-H).

[0259] In some embodiments, the cancer is a solid tumor with a high mutational burden.

[0260] In some embodiments, the cancer is selected from the group consisting of: melanoma, non-small cell lung cancer, relapsed or refractory classical Hodgkin lymphoma, head and neck squamous cell carcinoma, urothelial cancer, esophageal cancer, gastric cancer, DLBCL and hepatocellular cancer.

[0261] In other embodiments of the above treatment methods, the cancer is a Heme malignancy. In certain embodiments, the Heme malignancy is acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), DLBCL, EBV-positive DLBCL, primary mediastinal large B-cell lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, follicular lymphoma, Hodgkin's lymphoma (HL), mantle cell lymphoma (MCL), multiple myeloma (MM), myeloid cell leukemia-1 protein (Mcl-1), myelodysplastic syndrome (MDS), non-Hodgkin lymphoma (NHL), or small lymphocytic lymphoma (SLL).

[0262] Malignancies that demonstrate improved disease-free and overall survival in relation to the presence of tumor-infiltrating lymphocytes in biopsy or surgical material, *e.g.* melanoma, colorectal, liver, kidney, stomach/esophageal, breast, pancreas, and ovarian cancer are encompassed in the methods and treatments described herein. Such cancer subtypes are known to be susceptible to immune control by T lymphocytes. Additionally, included are refractory or recurrent malignancies whose growth may be inhibited using the antibodies described herein.

[0263] In some embodiments, the formulations of the invention (e.g. aspects (A1)-(A14)) are administered to a subject having a cancer characterized by elevated expression of PD-L1 and/or PD-L2 in tested tissue samples, including: ovarian, renal, colorectal, pancreatic, breast, liver, gastric, esophageal cancers and melanoma. Additional cancers that can benefit from treatment with anti-PD-1 antibodies such as humanized anti-PD-1 antibody pembrolizumab include those associated with persistent infection with viruses such as human immunodeficiency viruses, hepatitis viruses class A, B and C, Epstein Barr virus, human papilloma viruses that are known to be causally related to for instance Kaposi's sarcoma, liver cancer, nasopharyngeal cancer, lymphoma, cervical, vulval, anal, penile and oral cancers.

[0264] In one embodiment, the invention comprises a method of treating cancer in a human patient comprising administering any formulation of the invention (e.g. aspects (A1)-(A14)) to the patient.

[0265] In one embodiment, the invention comprises a method of treating unresectable or metastatic melanoma in a human patient comprising administering any formulation of the invention (e.g. aspects (A1)-(A14)) to the patient.

[0266] In one embodiment, the invention comprises a method of treating metastatic non-small cell lung cancer (NSCLC) in a human patient comprising administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient. In specific embodiments, the patient has a tumor with high PD-L1 expression [(Tumor Proportion Score (TPS) ≥50%)] and was not previously treated with platinum-containing chemotherapy. In other embodiments, the patient has a tumor with PD-L1 expression (TPS ≥1%) and was previously treated with platinum-containing chemotherapy. In still other embodiments, the patient has a tumor with PD-L1 expression (TPS ≥1%) and was not previously treated with platinum-containing chemotherapy. In specific embodiments, the patient had disease progression on or after receiving platinum-containing chemotherapy.

[0267] In certain embodiments, the PD-L1 TPS is determined by an FDA-approved test.

[0268] In certain embodiments, the patient's tumor has no EGFR or ALK genomic aberrations.

[0269] In certain embodiments, the patient's tumor has an EGFR or ALK genomic aberration and had disease progression on or after receiving treatment for the EGFR or ALK aberration(s) prior to receiving the anti-PD-1 antibody, or antigen binding fragment thereof.

[0270] In one embodiment, the invention comprises a method of treating metastatic non-small cell lung cancer (NSCLC) in a human patient comprising: (1) administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient, and (2) administering pemetrexed and carboplatin to the patient. In specific embodiments, the patient was not previously treated with an anti-cancer therapeutic prior to starting the combination treatment regimen with the formulation of the invention, pemetrexed and carboplatin.

[0271] In a certain embodiments, the patient has nonsquamous non-small cell lung cancer.

[0272] In certain embodiments, pemetrexed is administered to the patient in an amount of 500 mg/m^2. In sub-embodiments, pemetrexed is administered to the patient via intravenous infusion every 21 days. In specific embodiments, the infusion time is about 10 minutes.

[0273] In embodiments of the invention where the patient is treated with a formulation of the invention in combination with pemetrexed, the invention further comprises administering about 400 μg to about 1000 μg of folic acid to the patient once per day, beginning about 7 days prior to administering pemetrexed to the patient and continuing until about 21 days after the patient is administered the last dose of pemetrexed. In certain embodiments the folic acid is administered orally. In some embodiments, the invention further comprises administering about 1 mg of vitamin B_{12} to the patient about 1 week prior to the first administration of pemetrexed and about every three cycles of pemetrexed administration (i.e., approximately every 9 weeks). In certain embodiments the vitamin B_{12} is administered intramuscularly. In certain embodiments, the

invention further comprises administering about 4 mg of dexamethasone to the patient twice a day on the day before, the day of, and the day after pemetrexed administration. In certain embodiments the dexamethasone is administered orally.

[0274] In one embodiment, the invention comprises a method of treating recurrent or metastatic head and neck squamous cell cancer (HNSCC) in a human patient comprising administering any formulation of the invention (e.g. aspects (A1)-(A14)) to the patient. In certain embodiments, the patient was previously treated with platinum-containing chemotherapy. In certain embodiments, the patient had disease progression on or after platinum-containing chemotherapy.

[0275] In one embodiment, the invention comprises a method of treating refractory classical Hodgkin lymphoma (cHL) in a human patient comprising administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient. In certain embodiments, the patient has relapsed after 3 or more lines of therapy for cHL. In specific embodiments, the patient is an adult patient. in alternative embodiments, the patient is a pediatric patient.

[0276] In one embodiment, the invention comprises a method of treating locally advanced or metastatic urothelial carcinoma in a human patient comprising administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient. In certain embodiments, the patient is not eligible for cisplatin-containing chemotherapy. In certain embodiments, the patient has disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

[0277] In one embodiment, the invention comprises a method of treating unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors in a human patient comprising administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient. In specific embodiments, the patient had disease progression following prior anti-cancer treatment.

[0278] In one embodiment, the invention comprises a method of treating unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient colorectal cancer in a human patient comprising administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient. In specific embodiments, the patient had disease progression following prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

[0279] In one embodiment, the invention comprises a method of treating recurrent locally advanced or metastatic gastric cancer in a human patient comprising administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient.

[0280] In one embodiment, the invention comprises a method of treating recurrent locally advanced or metastatic gastroesophageal junction adenocarcinoma in a human patient comprising administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient. In specific embodiments, the patient's tumor expresses PD-L1 [Combined Positive Score (CPS) $\geq$1]. In specific embodiments, the patient has disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy. In specific embodiments, the patient has disease progression on or after two or more prior lines of therapy including HER2/neu-targeted therapy.

[0281] In one embodiment, the invention comprises a method of treating cancer in a human patient comprising administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient, wherein the patient has a cancer selected from the group consisting of: melanoma, lung cancer, head and neck cancer, bladder cancer, breast cancer, gastrointestinal cancer, multiple myeloma, hepatocellular cancer, lymphoma, renal cancer, mesothelioma, ovarian cancer, esophageal cancer, anal cancer, biliary tract cancer, colorectal cancer, cervical cancer, thyroid cancer, and salivary cancer.

[0282] In one embodiment, the invention comprises a method of treating small cell lung cancer in a human patient comprising administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient.

[0283] In one embodiment, the invention comprises a method of treating non-Hodgkin lymphoma in a human patient comprising administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient. In specific embodiments, the non-Hodgkin lymphoma is mediastinal large B-cell lymphoma. In specific embodiments, the non-Hodgkin lymphoma is diffuse large B-cell lymphoma.

[0284] In one embodiment, the invention comprises a method of treating breast cancer in a human patient comprising administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient. In certain embodiments, the breast cancer is triple negative breast cancer. In certain embodiments, the breast cancer is ER+/HER2- breast cancer.

[0285] In one embodiment, the invention comprises a method of treating nasopharyngeal cancer in a human patient comprising administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient.

[0286] In one embodiment, the invention comprises a method of treating thyroid cancer in a human patient comprising administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient.

[0287] In one embodiment, the invention comprises a method of treating salivary cancer in a human patient comprising administering a formulation of the invention (e.g. aspects (A1)-(A14)) to the patient.

[0288] Antagonist anti-PD-1 antibodies or antibody fragments can also be used to prevent or treat infections and infectious disease. Thus, the invention provides a method for treating chronic infection in a mammalian subject comprising administering an effective amount of a formulation of the invention to the subject. In some specific embodiments of this method, the formulation is administered to the subject via intravenous administration. In other embodiments, the formulation is administered to the subject by subcutaneous administration.

[0289] These agents can be used alone, or in combination with vaccines, to stimulate the immune response to pathogens, toxins, and self-antigens. The antibodies or antigen-binding fragment thereof can be used to stimulate immune response to viruses infectious to humans, including but not limited to: human immunodeficiency viruses, hepatitis viruses class A, B and C, Epstein Barr virus, human cytomegalovirus, human papilloma viruses, and herpes viruses. Antagonist anti-PD-1 antibodies or antibody fragments can be used to stimulate immune response to infection with bacterial or fungal parasites, and other pathogens. Viral infections with hepatitis B and C and HIV are among those considered to be chronic viral infections.

[0290] The formulations of the invention may be administered to a patient in combination with one or more "additional therapeutic agents". The additional therapeutic agent may be a biotherapeutic agent (including but not limited to antibodies to VEGF, EGFR, Her2/neu, VEGF receptors, other growth factor receptors, CD20, CD40, CD-40L, OX-40, 4-1BB, and ICOS), a growth inhibitory agent, an immunogenic agent (for example, attenuated cancerous cells, tumor antigens, antigen presenting cells such as dendritic cells pulsed with tumor derived antigen or nucleic acids, immune stimulating cytokines (for example, IL-2, IFNα2, GM-CSF), and cells transfected with genes encoding immune stimulating cytokines such as but not limited to GM-CSF).

[0291] As noted above, in some embodiments of the methods of the invention, the method further comprises administering an additional therapeutic agent. In particular embodiments, the additional therapeutic agent is an anti-LAG3 antibody or antigen binding fragment thereof, an anti-GITR antibody, or antigen binding fragment thereof, an anti-TIGIT antibody, or antigen binding fragment thereof, an anti-CD27 antibody or antigen binding fragment thereof. In one embodiment, the additional therapeutic agent is a Newcastle disease viral vector expressing IL-12. In a further embodiment, the additional therapeutic agent is dinaciclib. In still further embodiments, the additional therapeutic agent is a STING agonist.

[0292] Suitable routes of administration may, for example, include parenteral delivery, including intramuscular, subcutaneous, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal. Drugs can be administered in a variety of conventional ways, such as intraperitoneal, parenteral, intraarterial or intravenous injection. Modes of administration in which the volume of solution must be limited (*e.g.* subcutaneous administration) require a lyophilized formulation to enable reconstitution at high concentration.

[0293] Selecting a dosage of the additional therapeutic agent depends on several factors, including the serum or tissue turnover rate of the entity, the level of symptoms, the immunogenicity of the entity, and the accessibility of the target cells, tissue or organ in the individual being treated. The dosage of the additional therapeutic agent should be an amount that provides an acceptable level of side effects. Accordingly, the dose amount and dosing frequency of each additional therapeutic agent (e.g. biotherapeutic or chemotherapeutic agent) will depend in part on the particular therapeutic agent, the severity of the cancer being treated, and patient characteristics. Guidance in selecting appropriate doses of antibodies, cytokines, and small molecules are available. *See, e.g.*, Wawrzynczak (1996) *Antibody Therapy*, Bios Scientific Pub. Ltd, Oxfordshire, UK; Kresina (ed.) (1991) *Monoclonal Antibodies, Cytokines and Arthritis*, Marcel Dekker, New York, NY; Bach (ed.) (1993) *Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases*, Marcel Dekker, New York, NY; Baert *et al.* (2003) *New Engl. J. Med.* 348:601-608; Milgrom *et al.* (1999) *New Engl. J. Med.* 341:1966-1973; Slamon *et al.* (2001) *New Engl. J. Med.* 344:783-792; Beniaminovitz *et al.* (2000) *New Engl. J. Med.* 342:613-619; Ghosh *et al.* (2003) *New Engl. J. Med.* 348:24-32; Lipsky *et al.* (2000) *New Engl. J. Med.* 343:1594-1602; Physicians' Desk Reference 2003 (Physicians' Desk Reference, 57th Ed); Medical Economics Company; ISBN: 1563634457; 57th edition (November 2002). Determination of the appropriate dosage regimen may be made by the clinician, *e.g.*, using parameters or factors known or suspected in the art to affect treatment or predicted to affect treatment, and will depend, for example, the patient's clinical history (e.g., previous therapy), the type and stage of the cancer to be treated and biomarkers of response to one or more of the therapeutic agents in the combination therapy.

[0294] Various literature references are available to facilitate selection of pharmaceutically acceptable carriers or excipients for the additional therapeutic agent. *See, e.g.*, *Remington's Pharmaceutical Sciences* and *U.S. Pharmacopeia: National Formulary*, Mack Publishing Company, Easton, PA (1984); Hardman *et al.* (2001) *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, McGraw-Hill, New York, NY; Gennaro (2000) *Remington: The Science and Practice of Pharmacy*, Lippincott, Williams, and Wilkins, New

York, NY; Avis *et al.* (eds.) (1993) *Pharmaceutical Dosage Forms: Parenteral Medications*, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) *Pharmaceutical Dosage Forms: Tablets*, Marcel Dekker, NY; Lieberman *et al.* (eds.) (1990) *Pharmaceutical Dosage Forms: Disperse Systems*, Marcel Dekker, NY; Weiner and Kotkoskie (2000) *Excipient Toxicity and Safety*, Marcel Dekker, Inc., New York, NY.

[0295] A pharmaceutical antibody formulation can be administered by continuous infusion, or by doses at intervals of, *e.g.*, one day, 1-7 times per week, one week, two weeks, three weeks, monthly, bimonthly, etc. A preferred dose protocol is one involving the maximal dose or dose frequency that avoids significant undesirable side effects. A total weekly dose is generally at least 0.05 μg/kg, 0.2 μg/kg, 0.5 μg/kg, 1 μg/kg, 10 μg/kg, 100 μg/kg, 0.2 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 10 mg/kg, 25 mg/kg, 50 mg/kg body weight or more. *See, e.g.*, Yang *et al.* (2003) *New Engl. J. Med.* 349:427-434; Herold *et al.* (2002) *New Engl. J. Med.* 346:1692-1698; Liu *et al.* (1999) *J. Neurol. Neurosurg. Psych.* 67:451-456; Portielji *et al.* (20003) *Cancer Immunol. Immunother.* 52:133-144. The desired dose of a small molecule therapeutic, *e.g.*, a peptide mimetic, natural product, or organic chemical, is about the same as for an antibody or polypeptide, on a moles/kg basis.

[0296] In certain embodiments, dosing will comprise administering to a subject escalating doses of 1.0, 3.0, and 10 mg/kg of the pharmaceutical formulation, *i.e*, a formulation comprising pembrolizumab, over the course of treatment. The formulation comprising pembrolizumab can be a reconstituted liquid formulation, or it can be a liquid formulation not previously lyophilized. Time courses can vary and can continue as long as desired effects are obtained. In certain embodiments, dose escalation will continue up to a dose of about 10mg/kg. In certain embodiments, the subject will have a histological or cytological diagnosis of melanoma, or other form of solid tumor, and in certain instances, a subject may have non-measurable disease. In certain embodiments, the subject will have been treated with other chemotherapeutics, while in other embodiments, the subject will be treatment naïve.

[0297] In yet additional embodiments, the dosing regimen will comprise administering a dose of 1, 3, or 10 mg/kg of any of the pharmaceutical formulations described herein (*i.e*, a formulation comprising pembrolizumab), throughout the course of treatment. For such a constant dosing regimen, the interval between doses will be about 14 days (± 2 days). In certain embodiments, the interval between doses will be about 21 days (± 2 days).

[0298] In certain embodiments, the dosing regimen will comprise administering a dose of from about 0.005mg/kg to about 10mg/kg, with intra-patient dose escalation. In certain embodiments, a dose of 5 mg/kg or 10 mg/kg will be administered at intervals of every 3 weeks, or every 2

weeks. In yet additional embodiments, a dose of 3mg/kg will be administered at three week intervals for melanoma patients or patients with other solid tumors. In these embodiments, patients should have non-resectable disease; however, patients may have had previous surgery.

[0299] In certain embodiments, a subject will be administered a 30 minute IV infusion of any of the pharmaceutical formulations described herein. In certain embodiments for the escalating dose, the dosing interval will be about 28 days ((± 1 day) between the first and second dose. In certain embodiments, the interval between the second and third doses will be about 14 days (± 2 days). In certain embodiments, the dosing interval will be about 14 days (± 2 days), for doses subsequent to the second dose.

[0300] In certain embodiments, the use of cell surface markers and/or cytokine markers, as described in WO2012/018538 or WO2008/156712 will be used in bioassays for monitoring, diagnostic, patient selection, and/or treatment regimens involving blockade of the PD-1 pathway. Subcutaneous administration may performed by injected using a syringe, or using other injection devices (e.g. the Inject-ease® device); injector pens; or needleless devices (e.g. MediJector and BioJector®).

[0301] Embodiments of the invention also include one or more of the biological formulations described herein (i) for use in, (ii) for use as a medicament or composition for, or (iii) for use in the preparation of a medicament for: (a) therapy (e.g., of the human body); (b) medicine; (c) induction of or increasing of an antitumor immune response (d) decreasing the number of one or more tumor markers in a patient; (e) halting or delaying the growth of a tumor or a blood cancer; (f) halting or delaying the progression of PD-1-related disease; (g) halting or delaying the progression cancer; (h) stabilization of PD-1-related disease; (i) inhibiting the growth or survival of tumor cells; (j) eliminating or reducing the size of one or more cancerous lesions or tumors; (k) reduction of the progression, onset or severity of PD-1-related disease; (l) reducing the severity or duration of the clinical symptoms of PD-1-related disease such as cancer (m) prolonging the survival of a patient relative to the expected survival in a similar untreated patient n) inducing complete or partial remission of a cancerous condition or other PD-1 related disease, or o) treatment of cancer.

GENERAL METHODS

[0302] Standard methods in molecular biology are described Sambrook, Fritsch and Maniatis (1982 & 1989 2nd Edition, 2001 3rd Edition) *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Sambrook and Russell (2001) *Molecular Cloning, 3rd ed.,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Wu

(1993) *Recombinant DNA*, Vol. 217, Academic Press, San Diego, CA). Standard methods also appear in Ausbel, *et al.* (2001) *Current Protocols in Molecular Biology, Vols.1-4*, John Wiley and Sons, Inc. New York, NY, which describes cloning in bacterial cells and DNA mutagenesis (Vol. 1), cloning in mammalian cells and yeast (Vol. 2), glycoconjugates and protein expression (Vol. 3), and bioinformatics (Vol. 4).

[0303] Methods for protein purification including immunoprecipitation, chromatography, electrophoresis, centrifugation, and crystallization are described (Coligan, *et al.* (2000) *Current Protocols in Protein Science, Vol. 1*, John Wiley and Sons, Inc., New York). Chemical analysis, chemical modification, post-translational modification, production of fusion proteins, glycosylation of proteins are described (see, *e.g.*, Coligan, *et al.* (2000) *Current Protocols in Protein Science, Vol. 2*, John Wiley and Sons, Inc., New York; Ausubel, *et al.* (2001) *Current Protocols in Molecular Biology, Vol. 3*, John Wiley and Sons, Inc., NY, NY, pp. 16.0.5-16.22.17; Sigma-Aldrich, Co. (2001) *Products for Life Science Research*, St. Louis, MO; pp. 45-89; Amersham Pharmacia Biotech (2001) *BioDirectory*, Piscataway, N.J., pp. 384-391). Production, purification, and fragmentation of polyclonal and monoclonal antibodies are described (Coligan, *et al.* (2001) *Current Protocols in Immunology, Vol. 1*, John Wiley and Sons, Inc., New York; Harlow and Lane (1999) *Using Antibodies*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Harlow and Lane, *supra*). Standard techniques for characterizing ligand/receptor interactions are available (see, *e.g.*, Coligan, *et al.* (2001) *Current Protocols in Immunology, Vol. 4*, John Wiley, Inc., New York).

[0304] Monoclonal, polyclonal, and humanized antibodies can be prepared (see, *e.g.*, Sheperd and Dean (eds.) (2000) *Monoclonal Antibodies*, Oxford Univ. Press, New York, NY; Kontermann and Dubel (eds.) (2001) *Antibody Engineering*, Springer-Verlag, New York; Harlow and Lane (1988) *Antibodies A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pp. 139-243; Carpenter, *et al.* (2000) *J. Immunol.* 165:6205; He, *et al.* (1998) *J. Immunol.* 160:1029; Tang *et al.* (1999) J. Biol. Chem. 274:27371-27378; Baca *et al.* (1997) *J. Biol. Chem.* 272:10678-10684; Chothia *et al.* (1989) *Nature* 342:877-883; Foote and Winter (1992) *J. Mol. Biol.* 224:487-499; U.S. Pat. No. 6,329,511).

[0305] An alternative to humanization is to use human antibody libraries displayed on phage or human antibody libraries in transgenic mice (Vaughan *et al.* (1996) *Nature* Biotechnol. 14:309-314; Barbas (1995) *Nature Medicine* 1:837-839; Mendez *et al.* (1997) *Nature Genetics* 15:146-156; Hoogenboom and Chames (2000) *Immunol. Today* 21:371-377; Barbas *et al.* (2001) *Phage Display: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New

York; Kay *et al.* (1996) *Phage Display of Peptides and Proteins: A Laboratory Manual*, Academic Press, San Diego, CA; de Bruin *et al.* (1999) *Nature Biotechnol.* 17:397-399).

[0306] Purification of antigen is not necessary for the generation of antibodies. Animals can be immunized with cells bearing the antigen of interest. Splenocytes can then be isolated from the immunized animals, and the splenocytes can fused with a myeloma cell line to produce a hybridoma (see, *e.g.*, Meyaard *et al.* (1997) *Immunity* 7:283-290; Wright *et al.* (2000) *Immunity* 13:233-242; Preston *et al.*, *supra*; Kaithamana *et al.* (1999) *J. Immunol.* 163:5157-5164).

[0307] Antibodies can be conjugated, *e.g.*, to small drug molecules, enzymes, liposomes, polyethylene glycol (PEG). Antibodies are useful for therapeutic, diagnostic, kit or other purposes, and include antibodies coupled, *e.g.*, to dyes, radioisotopes, enzymes, or metals, *e.g.*, colloidal gold (see, *e.g.*, Le Doussal *et al.* (1991) *J. Immunol.* 146:169-175; Gibellini *et al.* (1998) *J. Immunol.* 160:3891-3898; Hsing and Bishop (1999) *J. Immunol.* 162:2804-2811; Everts *et al.* (2002) *J. Immunol.* 168:883-889).

[0308] Methods for flow cytometry, including fluorescence activated cell sorting (FACS), are available (see, *e.g.*, Owens, *et al.* (1994) *Flow Cytometry Principles for Clinical Laboratory Practice*, John Wiley and Sons, Hoboken, NJ; Givan (2001) *Flow Cytometry, 2nd ed.*; Wiley-Liss, Hoboken, NJ; Shapiro (2003) *Practical Flow Cytometry*, John Wiley and Sons, Hoboken, NJ). Fluorescent reagents suitable for modifying nucleic acids, including nucleic acid primers and probes, polypeptides, and antibodies, for use, *e.g.*, as diagnostic reagents, are available (Molecular Probesy (2003) *Catalogue*, Molecular Probes, Inc., Eugene, OR; Sigma-Aldrich (2003) *Catalogue*, St. Louis, MO).

[0309] Standard methods of histology of the immune system are described (see, *e.g.*, Muller-Harmelink (ed.) (1986) *Human Thymus: Histopathology and Pathology*, Springer Verlag, New York, NY; Hiatt, *et al.* (2000) *Color Atlas of Histology*, Lippincott, Williams, and Wilkins, Phila, PA; Louis, *et al.* (2002) *Basic Histology: Text and Atlas*, McGraw-Hill, New York, NY). Software packages and databases for determining, *e.g.*, antigenic fragments, leader sequences, protein folding, functional domains, glycosylation sites, and sequence alignments, are available (see, *e.g.*, GenBank, Vector NTI® Suite (Informax, Inc, Bethesda, MD); GCG Wisconsin Package (Accelrys, Inc., San Diego, CA); DeCypher® (TimeLogic Corp., Crystal Bay, Nevada); Menne, *et al.* (2000) *Bioinformatics* 16: 741-742; Menne, *et al.* (2000) *Bioinformatics Applications Note* 16:741-742; Wren, *et al.* (2002) *Comput. Methods Programs Biomed.* 68:177-181; von Heijne (1983) *Eur. J. Biochem.* 133:17-21; von Heijne (1986) *Nucleic Acids Res.* 14:4683-4690).

Analytical Methods

[0310] Analytical methods suitable for evaluating the product stability include size exclusion chromatography (SEC), dynamic light scattering test (DLS), differential scanning calorimetery (DSC), iso-asp quantification, potency, UV at 340 nm, UV spectroscopy, and FTIR. SEC (J. Pharm. Scien., 83:1645-1650, (1994); Pharm. Res., 11:485 (1994); J. Pharm. Bio. Anal., 15:1928 (1997); J. Pharm. Bio. Anal., 14:1133-1140 (1986)) measures percent monomer in the product and gives information of the amount of soluble aggregates. DSC (Pharm. Res., 15:200 (1998); Pharm. Res., 9:109 (1982)) gives information of protein denaturation temperature and glass transition temperature. DLS (American Lab., November (1991)) measures mean diffusion coefficient, and gives information of the amount of soluble and insoluble aggregates. UV at 340 nm measures scattered light intensity at 340 nm and gives information about the amounts of soluble and insoluble aggregates. UV spectroscopy measures absorbance at 278 nm and gives information of protein concentration. FTIR (Eur. J. Pharm. Biopharm., 45:231 (1998); Pharm. Res., 12:1250 (1995); J. Pharm. Scien., 85:1290 (1996); J. Pharm. Scien., 87:1069 (1998)) measures IR spectrum in the amide one region, and gives information of protein secondary structure.

[0311] The iso-asp content in the samples is measured using the Isoquant Isoaspartate Detection System (Promega). The kit uses the enzyme Protein Isoaspartyl Methyltransferase (PIMT) to specifically detect the presence of isoaspartic acid residues in a target protein. PIMT catalyzes the transfer of a methyl group from S-adenosyl-L-methionine to isoaspartic acid at the .alpha.-carboxyl position, generating S-adenosyl-L-homocysteine (SAH) in the process. This is a relatively small molecule, and can usually be isolated and quantitated by reverse phase HPLC using the SAH HPLC standards provided in the kit.

[0312] The potency or bioidentity of an antibody can be measured by its ability to bind to its antigen. The specific binding of an antibody to its antigen can be quantitated by any method known to those skilled in the art, for example, an immunoassay, such as ELISA (enzyme-linked immunosorbant assay).

[0313] All publications mentioned herein are incorporated by reference for the purpose of describing and disclosing methodologies and materials that might be used in connection with the invention.

[0314] Having described different embodiments of the invention herein with reference to the accompanying drawings, it is to be understood that the invention is not limited to those precise embodiments, and that various changes and modifications may be effected therein by one skilled

in the art without departing from the scope or spirit of the invention as defined in the appended claims.

EXAMPLE 1

Materials and Methods

[0315] CE-SDS: Samples were analyzed by a CE-SDS technique in which protein was denatured with sodium dodecyl sulfate (SDS) under reducing and non-reducing conditions and separated using capillary electrophoresis (CE) (Beckman-Coulter ProteomeLab PA800 CE system and IgG Purity/Heterogeneity Assay Kit). The method separates proteins based on their apparent molecular weight. Under non-reducing conditions, all species other than the main IgG peak were classified as impurities. Under reducing conditions, the IgG was resolved into the heavy and light chains. All other species were classified as impurities. In both cases, the result was reported as corrected area percent of each peak as calculated from the total corrected peak area percent.

[0316] HP-IEX: High performance ion-exchange chromatography (HP-IEX) was used to assess the charge profile. An ion exchange HPLC method was performed using a Dionex Dionex ProPac WCX-10 column and a UV detector at 280 nm. Samples were diluted in purified water, and 80 µg were injected for analysis. The mobile phase used for the IEX analysis was a gradient of the following mobile phases (mobile phase A: 24 mM MES, pH 6, 4% acetonitrile (v/v); mobile phase B: 20 mM phosphate, 95 mM NaCl, pH 8, 4% acetonitrile (v/v). The main peak is the major component of the chromatogram and it serves as a control for the characterization of acidic and basic variants. Acidic variants elute earlier than main peak and the main cause of the formation of acidic variants is due to the deamidation of the Asn in main peak and the presence of sialic acid compared to main peak. Basic variants elute later than main peak and the main cause of the formation of basic variants is due to the incomplete removal of C-terminal Lys from the main peak. Other causes are incomplete cyclization of the N-terminal glutamine (Gln) to pyroGlu of the light chain or heavy chain or both and also due to the Isomerization of Asp in the main peak to isoAsp.

[0317] HP-SEC: Purity of the sample was assessed by size exclusion chromatography (SEC) in which the percentage of monomer was determined, as well as the percentages of high molecular weight species (HMW) and late eluting peaks (LMW species). The presence of HMW species indicates protein aggregates and the presence of LMW species indicate protein fragments. High Performance - Size Exclusion Chromatography (HP-SEC) was performed by diluting the samples to 1.0 mg/mL with water. The diluted samples were injected (10 µL) into a

HPLC equipped with a YMC-pack-Diol 200 column and a UV detector. Proteins in the sample were separated by size and detected by UV absorption at 280 nm.

[0318] HP-SEC Arg: Purity of the sample was assessed by size exclusion chromatography (SEC) in which the percentage of monomer was determined, as well as the percentages of high molecular weight species (HMW) and late eluting peaks (LMW species). High Performance - Size Exclusion Chromatography (HP-SEC) was performed by diluting the samples to 5.0 mg/mL in mobile phase (50 mM sodium phosphate, 450 mM arginine mono hydrochloride, pH 7.0). The column temperature was set at 25°C and the flow rate was maintained at 0.5 mL/min using an isocratic elution. The diluted samples were injected (30 µL) into a HPLC equipped with YMC –PACK Diol-200 column and a UV detector. Proteins in the sample were separated by size and detected by UV absorption at 280 nm.

[0319] A350: UV absorption at 350 nm was measured using 96 well plate Spectramax reader as an indication of turbidity. The absorption readings were blanked against empty plate reading and normalized for sample pathlength.

[0320] HP-HIC: High performance hydrophobic interaction chromatography (HP-HIC) was used to assess oxidized products from the non-oxidized molecule. The percentage of pre-peaks, determined to be oxidized species comprising heavy chain Met105 oxidation on one heavy chain by previous analytical characterization, as well as the percentage of the main and percentage of the post peaks were determined. A HP-HIC method was performed by diluting the sample to 5.0 mg/mL in purified water. The sample was then injected (10 µL) into an HPLC equipped with a Tosoh Phenyl-5PW column and a UV detector at 280 nm. For the HIC analysis a mobile phase containing a gradient of the following components (mobile phase A: 5 mM sodium phosphate in 2% acetonitrile, pH 7.0; mobile phase B: 400 mM ammonium sulfate, 5 mM sodium phosphate in 2% acetonitrile, pH 6.9;) was used.

[0321] VP-DSC: Valerian-Plotnikov differential scanning calorimetry (VP-DSC) can be used to determine the thermal and conformational stability of monoclonal antibodies. DSC determines the heat capacity (C_p) of the protein solution relative to that of the placebo solution for increasing temperatures, producing a thermal transition upon protein unfolding. For monoclonal antibodies, multiple unfolding transitions (Tonset, Tm1, Tm2) are typically seen in the DSC thermogram corresponding to unfolding of individual domains

EXAMPLE 2

Evaluation of the Stability of High Concentration Pembrolizumab Formulations

[0322] An initial study was performed to evaluate the stability of formulations comprising a high (160 mg/ml) concentration of pembrolizumab and to evaluate the impact of different formulation excipients.

[0323] Pembrolizumab drug substance stock solutions were prepared in 10mM acetate pH 5.0 (189 mg/mL) and 10mM histidine pH 5.5 (187 mg/mL) by tangential flow filtration. Pembrolizumab formulations were prepared to 160 mg/mL target concentration by spiking the protein stock solution with excipient stock solutions and respective buffer. Test formulations comprising a high concentration of pembrolizumab (see Table 4) were prepared in 6R glass vials at a volume of between 3 mL and 4 mL. Excipients were spiked into the protein solution to achieve target levels of each excipient and brought to final volume using either acetate or histidine buffer. Formulation 2 was prepared at 125 mg/mL (without surfactant) and concentrated to greater than 160 mg/mL using a Millipore centricon device (10,000MWCO). PS80 was added after the concentration was adjusted to 160 mg/mL with placebo (i.e., formulated matrix, with all components except Ab and surfactant). Samples were stored at 2-8°C after preparation until they were filled into vials.

Table 4. High Concentration Pembrolizumab Formulations

Formulation	Pembro Concentration	Buffer	Stabilizer	Surfactant	Anti-Oxidant
1	160 mg/mL	Histidine	7% sucrose	0.02% PS80	—
2	160 mg/mL	Histidine	5% sorbitol	0.02% PS80	—
3	160 mg/mL	Histidine	7% sucrose	0.1% F127	—
4	160 mg/mL	Histidine	7% sucrose	0.02% PS80	10 mM Met
5	160 mg/mL	Acetate	7% sucrose	0.02% PS80	—

[0324] Pembrolizumab formulated solutions were filtered using Millex GV 0.22 μm PVDF 33mm filter and filled into glass low volume HPLC vials (Waters #186000384c, 12x32mm glass screw neck vial, 200 μL per vial). Vials were capped, and the caps were wrapped with parafilm to minimize potential evaporation. Samples were staged in 2-8°C, 25°C and 40°C environmental stability chambers. Each sample box was double bagged prior to placement into the stability chamber for a period of twelve weeks.

[0325] Stability of the formulations was evaluated using HP-SEC (to assess purity) and HP-IEX (charge profile) over a period of twelve weeks. Results demonstrate that there were no changes for any of the formulations that were stored at 5°C (as used herein and throughout the

Examples, the term "5°C" is used interchangeably with "2-8 °C", which indicates 5°C +/-3 °C (standard deviation) during the 12-week time period. Therefore, all formulations were considered stable at the 5°C storage condition. At 25°C, changes were observed via HP-SEC (a slight decrease in % mAb) and HP-IEX (slight decrease in % main) for each of the formulations over the time period tested. No differences were observed among results for the five formulations at 25°C using either of these two techniques (data not shown). More pronounced changes were observed for all of the formulations stored at 40°C evaluated by both techniques relative to the same formulations stored at 25°C. The lowest decrease in % mAb by HP-SEC after 12 weeks was observed with formulation 4 at 40°C compared to the other formulations stored at 40°C for 12 weeks, suggesting that this formulation may have improved stability (data not shown). There were no differences in charge profile among the five formulations at any of the temperatures for the length of the testing period (i.e. data at each 4-week interval was similar among the five formulations). Data not shown.

[0326] Oxidation of methionine-105 (Met-105) was also monitored by HP-HIC for each of the test formulations over the 12-week period. No changes in Met-105 oxidation were observed for any of the formulations at 5°C (Figure 1A). At 25°C, a trend of slight increase of % total pre-peak 1 +2 (representing approximately 50% oxidized Met-105 or one oxidized Met-105 per molecule) was observed among all five formulations (Figure 1B), which was more pronounced at 40°C (Figure 1C). The lowest amount of % total pre-peak 1 +2 was observed with formulation 4 over the 12-week period, suggesting that this formulation might be improving stability.

EXAMPLE 3

Evaluation of the Stability of High Concentration Pembrolizumab Formulations Comprising Arginine as a Viscosity-Lowering Agent

[0327] A further study was performed to evaluate the stability of formulations comprising an even higher concentration of pembrolizumab (200 mg/mL as compared to 160 mg/mL used in EXAMPLE 2). In this study, arginine (3%, 2%) was used as a viscosity lowering agent, alone or in combination with sucrose, and the impact on storage stability of pembrolizumab was evaluated.

[0328] For this study, pembrolizumab concentrated drug substance was prepared at 234 mg/mL in 10mM histidine pH 5.4 by concentration and diafiltration. Pembrolizumab drug product formulations (#1 to #3) were prepared to 200 mg/mL target concentration in 200 mL volumetric flasks by spiking the protein stock solution with excipient stock solutions and 10mM

histidine buffer (see Table 5). Each of the formulated solutions was filtered using 0.22μm PVDF membrane Stericup 250mL devices, and filled into 1mL syringes (Hypak SCF 1mL with BD Hypak SCF Stoppers) and 2 mL vials (Nuova Ompi 0612090.5657), with a 1 mL drug product fill volume. Samples were staged, protected from light, and placed in a 2-8°C environmental stability chamber for 12 months, a 25°C stability chamber for 9 months and a 40°C stability chamber for 5 months. The test formulations for this study did not contain any anti-oxidant.

Table 5. High Concentration Pembrolizumab Formulations for EXAMPLE 3

Antibody	Buffer	No.	Stabilizer 1	Stabilizer 2	Surfactant	Container (Fill)
200 mg/mL Pembro	10 mM His pH 5.5	1A	7% Sucrose	—	0.02% PS80	2 mL glass vials (1 mL)
		2A	—	3% Arginine	0.02% PS80	
		3A	2% Sucrose	2% Arginine	0.02% PS80	
		1B	7% Sucrose	—	0.02% PS80	1 mL BD syringes (1 mL)
		2B	—	3% Arginine	0.02% PS80	
		3B	2% Sucrose	2% Arginine	0.02% PS80	

[0329] The formulations were evaluated by visual observation, A350, HP-SEC (purity), HP-IEX (charge profile), HP-HIC (Met-105 oxidation) and CE-SDS. No changes were observed among the different formulations when stored at 5°C for up to 12 months, whether stored in vials or syringes, by visual observation, A350, HP-SEC, HP-IEX, HP-HIC, and CE-SDS (NR). Therefore, all formulations were considered stable at the 5°C storage condition.

[0330] Each of the test formulations were visually inspected for changes in coloration or precipitate formation (data not shown). All of the formulations showed some degree of yellow color at 25°C by visual assessment. The formulations containing sucrose without arginine (formulations 1A and 1B) began to show some yellow color after 3 months. By 9 months, some precipitates or particles were observed in all samples. The formulation comprising 2% sucrose and 2% arginine formed a gel in the vial (formulation 3A), which was evident in some vials as early as 1 month, but not in the syringe (formulation 3B). Rapid changes were observed for all formulations at 40°C over the 9-month testing period. Yellow coloration was observed in the sucrose-only formulations (1A and 1B) after 1 month, whether in a vial or a syringe.

[0331] A350 values were measured as an indication of turbidity (data not shown). At 25°C, a trend of increase in turbidity was observed over the 6-month testing period for sucrose-containing samples (formulations 1A and 1B) and samples comprising a sucrose-arginine combination in a vial (formulation 3A). An increase in A350 value of the sucrose samples at the

6-month timepoint correlated with the observation of yellow coloration. Additionally, the A350 of the sucrose-arginine samples were found to be atypically higher than samples containing the same combination in a syringe. At 40°C, a more pronounced trend of increased turbidity over time was observed for all formulations. Sucrose-containing samples (formulations 1A and 1B) turned amber and were therefore A350 was not measured at 6 months. The sucrose-arginine formulation in a vial (formulation 3A) was also not measured by A350 at 6 months due to gel formation. A350 results for arginine-containing formulations (no sucrose, formulations 2A and 2B) in either vials or syringes and sucrose-arginine formulations in syringes (formulation 3B) were comparable.

[0332] Purity of the formulations was determined by HP-SEC for a period of 9 months (data not shown). At 25°C, a trend of slight decrease in % mAb, with a corresponding increase in %HMW, was observed among all 5 formulations over time. The sucrose-containing formulations in vials and syringes (formulation 1A and 1B) showed the most changes as compared to the other formulations. %LMW data indicated significant variability at intermediate time points (3M, 6M) and was not conclusive. At 40°C, a trend of decrease in % mAb, with a corresponding increase in %HMW and %LMW, was observed among all the formulations over the 9-month period. There were no clear differences among the different formulations during the time tested.

[0333] Charge profile was determined by HP-IEX (data not shown). At 25°C, a trend of slight decrease in % main, and % total basic, with a corresponding increase in % acidic, was observed among all 5 formulations over 9 months. The most changes were observed for the sucrose-containing formulations (formulations 1A and 1B) in vials or syringes compared to the arginine-containing (formulations 2A and 2B) and sucrose + arginine-containing formulations (formulations 3A and 3B). At 40°C, a more pronounced trend of decrease in % main, and % total basic, with a corresponding increase in % acidic, was observed among all 5 formulations. There were no clear differences among the different formulations after 3 months. Additionally, there were no clear differences in stability profiles for formulations in vials compared to syringes.

[0334] Met-105 oxidation was measured by HP-HIC. Minimal changes in Met-105 oxidation were observed for any of the formulations at 5°C over a 9-month period (FIGURE 2A). At 25°C, a trend of slight increase in % total pre-peak 1+2 was observed among all formulations in vials, which was not observed for the corresponding formulations in syringes (FIGURE 2B). A higher increase in oxidation over 9 months was observed for the sucrose-containing formulations (no arginine) in vials as compared to formulations containing arginine (with or without sucrose).

At 40°C, a steep increase in the rate of oxidation was observed after 3 months for the arginine-containing formulations (vial and syringe) and the sucrose formulation in a syringe (FIGURE 2C). The other formulations were not tested after 3 months due to gel formation or amber coloration (see discussion above).

EXAMPLE 4

Evaluation of Formulations Comprising a High Concentration of Pembrolizumab with Alternative Viscosity Lowering Agents

[0335] An additional study was performed to test the utility of alternative excipients as viscosity lowering agents in high concentration pembrolizumab formulations. A series of formulations were prepared (Table 6) in micro-recovery HPLC vials with a 400 µL fill volume. The formulations in this study did not comprise any anti-oxidant. Samples were staged in a 5°C, 25°C and 40°C stability chambers for 12 weeks. The test formulations for this study did not contain any anti-oxidant.

Table 6. High Concentration Pembrolizumab Formulations for EXAMPLE 4

Formulation	Antibody	Buffer	Stabilizer 1	Stabilizer 2	Surfactant
1	200 mg/mL pembrolizumab	10 mM Histidine pH 5.5	2% Histidine	-	0.02% PS80
2			2% Histidine	2% Arginine	0.02% PS80
3			2% Histidine	2% Sucrose	0.02% PS80
4			150 mM Camphor sulfonic acid	-	0.02% PS80
5			150 mM Guanidine hydrochloride	-	0.02% PS80

[0336] No changes in purity were observed by HP-SEC analysis (measured as % mAb) for formulations stored at 5°C over a period of 12 weeks (FIGURE 3A). For samples stored at 25°C, a trend was observed among all five formulations which showed a slight decrease in % mAb, with formulation 4 (150 mM camphor sulfonic acid) showing the maximum decrease (~5%) among the 5 formulations (FIGURE 3B). The trend of decreased % mAb was also observed for formulations stored at 40°C, with no clear differences among the 5 formulations tested (FIGURE 3C).

[0337] Similar to results obtained by HP-SEC, no differences in charge profile were observed among the 5 formulations at 5°C for a 12 week period as evaluated by HP-IEX. Again, a trend was observed at 25°C which showed a decrease in % main for all five formulations over 12 weeks, with the most pronounced drop measured for formulations 3 and 4 (150 mM camphor sulfonic acid and 150 mM guanidine HCL). At 40°C, a more pronounced decrease in % main by HP-IEX was observed for each of the five formulations over the time tested, with no clear differences among the five formulations (data not shown).

[0338] No differences in % Met-105 oxidation (pre-peak 1+2) were observed for any of the five formulations after 12 weeks at the 5°C storage condition, as measured by HP-HIC (FIGURE 4A). However, for formulation 4, an increase in % pre-peak (other than pre-peak 1+2) was observed (data not shown). Pre peaks other than 1+2 contain contributions of molecules where both methionine residues are oxidized per molecule. A slight increase in % total pre-peak 1+2, indicating oxidized species, was observed for formulations 3(2% histidine, 2% sucrose) and 4 (150 mM camphor sulfonic acid) at 25°C (FIGURE 4B), as well as an increase in % pre-peak for peaks other than 1 + 2 (data not shown). Minimal changes in % total pre-peak 1 + 2 were detectable for formulations 1, 2, and 5 (FIGURE 4B). However, formulation 1 and formulation 2 did show significant increase in % pre-peaks other than 1+2 (data not shown).

[0339] A more pronounced increase was observed in % total pre-peak 1 + 2 among all 5 formulations at the 40°C storage condition over the 12 week period, with formulations 3 and 4 again showing the most changes in % total pre-peak 1 + 2 (FIGURE 4C) and % pre-peaks other than 1 +2 (data not shown). Formulations 1, 2, and 5 showed the least changes in % pre-peak 1+2 (FIGURE 4C), but significant changes in % pre-peaks other than 1+2 were observed, indicating oxidation of both Met-105 residues (data not shown).

EXAMPLE 5

Analysis of Formulations Comprising Arginine in Combination with Glutamine

[0340] Previous studies suggested that an equimolar mixture of arginine and glutamine can suppress temperature-induced aggregation of monoclonal antibodies in biological formulations (Kheddo *et al.*, *Int. J. Pharmaceutics* 473: 126-33(2014)). Fukuda *et al.* (*Pharm. Res.* 31:992-1001 (2014)) showed that Arg-HCl can suppress antibody aggregation at near-neutral pH, but promoted aggregation and degradation at acidic pH or high temperatures. In that study, the impact of Arg-HCl at high temperature could be mitigated by adding an equimolar mixture of arginine and aspartic acid or glutamic acid, which led to a suppression of aggregation (Fukuda *et al.*).

[0341] In order to investigate the impact of an equimolar mixture of glutamine and arginine on pembrolizumab formulations, a series of compositions were formulated and tested as described below. Concentrated pembrolizumab drug substance was prepared at 252.3 mg/mL in 10 mM histidine, pH 5.5 by concentration and dilafiltration. Formulations C1-C6 were prepared by spiking stock solutions of the following excipients: L-Arginine hydrochloride (475 mM stock), L-Glutamic Acid (170 mM stock), Polysorbate-80 (2%w/w stock), and sucrose (40% w/v stock) into pembrolizumab drug substance to achieve target compositions listed in Table 7.

[0342] Formulated drug substance batches were filtered using a 0.22 um PVDF syringe filter and filled into 2 mL glass vials (fill volume: 0.5 mL). Vials were capped using 13 mm serum stoppers and sealed using 13 mm flip-off seals. Vials were incubated in 40°C with 75% relative humidity (RH) walk-in incubator. Vials were tested at T0, 1 week, 2 week, 4 week, and 8 week time points.

[0343] Thermal unfolding was tested by DSC (Table 7) and viscosity of each formulation was measured (Table 7). Results indicate that there was no improvement in thermal unfolding behavior in the presence of an equimolar mixure of Arg and Glu. A reduction in viscosity was observed for all formulations comprising Arg, Glu or Arg: Glu (1:1) relative to C1, which contained no arginine or glutamine (Table 7). The amount of aggregation of each of these formulations over a 12-week period of storage at 40°C was also measured by HP-SEC. Results indicate that there was no reduction in aggregation for the formulations comprising an equimolar mixture of Arg:Glu (FIGURE 5).

Table 7. High Concentration Pembrolizumab Formulations for EXAMPLE 5

No.	Formulation	DSC (thermal unfolding)			Viscosity (cP)
		Tonset	Tm1	Tm2	
C1	167 mg/mL pembrolizumab, 7% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5	63.9	66.9	78.2	21.9
C2	C1 + 35 mM Arginine	64.2	64.5	76.8	18.2
C3	167 mg/mL pembrolizumab, 0.02% PS-80, 10mM Histidine buffer, pH 5.5 + 40 mM Arg + 40 mM Glu	62.3	64.7	75.9	16.0
C4	167 mg/mL pembrolizumab, 0.02% PS-80, 10mM Histidine buffer, pH 5.5 + 20 mM Arg + 20 mM Glu	61.8	65.2	76.0	16.8

C5	167 mg/mL pembrolizumab, 0.02% PS-80, 10mM Histidine buffer, pH 5.5 + 40 mM Arg	61.8	64.7	76.0	15.5
C6	167 mg/mL pembrolizumab, 0.02% PS-80, 10mM Histidine buffer, pH 5.5 + 40 mM Glu	62.8	64.8	75.8	17.9

EXAMPLE 6

Impact of Antioxidants and Chelators on Stability in the Presence of Metal Ions

Study 1:

[0344] Metal ions can be introduced during manufacturing of biological formulations, for example from steel tanks commonly used for processing monoclonal antibody products and related buffers. In order to determine the impact of antioxidants and chelators on formulation stability in the presence of metal ions, a series of test formulations were evaluated by HP-SEC (Table 8). Concentrated pembrolizumab drug substance was prepared at 252.3 mg/mL in 10 mM histidine, pH 5.5 by concentration and dilafiltration. Formulations D1-D5 were prepared by spiking stock solutions of the following excipients: methionine (100 mM stock), ferrous chloride (0.0227% w/v stock), polysorbate-80 (2% w/w stock), and sucrose (40% w/v stock) into pembrolizumab drug substance to achieve target compositions listed in Table 8.

[0345] Formulated drug substance batches were filtered using a 0.22 um PVDF syringe filter and filled into 2 mL glass vials (fill volume: 0.5 mL). Vials were capped using 13 mm serum stoppers and sealed using 13 mm flip-off seals. Vials were incubated in 40°C/ 75% RH walk-in incubator. Vials were tested at T0, 1 week, 2 week, 4 week, and 8 week time-points.

[0346] The base formulation tested in this study (Formulation 1) comprised a high concentration of pembrolizumab with sucrose and PS80 in histidine buffer (see Table 8, no. D1), whereas Formulation D3 comprised the base formulation + metal ions with an antioxidant (methionine) and Formulation D5 comprised the base formulation + metal ions and a chelator (DTPA).

Table 8. Formulations used for Example 6, Study 1

		% Aggregates (HP-SEC)				
	Formulation	T0	1 week	2 weeks	4 weeks	8 weeks
D1	167 mg/ml pembrolizumab, 7% Sucrose, 0.02% PS-80, 10 mM Histidine buffer, pH 5.5	0.8	1.1	1.4	2.1	3.1
D2	D1 + 1mM Methionine	0.8	1.1	1.4	2.1	3.1

D3	D1 + 1ppm Fe++, 1mM Methionine	0.8	1.3	1.6	2.5	4.0
D4	D1 + 1ppm Fe++	0.8	1.3	1.7	2.5	4.2
D5	D1 + 1ppm Fe++, 100µM DTPA	0.8	1.1	1.5	2.2	3.2

[0347] Results showed that methionine did not prevent aggregation in the presence of metal ions (Table 8, Formulation D3). A lower % aggregates was observed in the formulation comprising DTPA in the presence of metal ions (Formulation D5) compared with the base formulation in the presence of metal ions with no chelator/antioxidant (Formulation D4) or the formulation with methionine (Formulation D3) in the presence of metal ions after 8 weeks.

[0348] The formulations were also evaluated at 40°C over 8 weeks by HP-HIC to determine the impact of methionine and DTPA on oxidation in the presence of metal ions (data not shown). A slight reduction in oxidation was observed in the formulation comprising methionine and the formulation comprising DTPA in the presence of Fe^{2+} relative to controls.

Study 2:

[0349] The impact of additional antioxidants and chelators (Formulations E1-E9, Table 9) on stability and oxidation in the presence of metal ions at 40°C was evaluated by HP-SEC and HP-HIC.

Table 9. Formulations used for Example 6, Study 2

		% Aggregates (HP-SEC)				
		T0	1 week	2 weeks	4 weeks	8 weeks
	Lead formulation (D1)*	0.8	1.1	1.4	2.1	3.1
E1	D1 + 5mM Methionine	1.0	1.3	1.6	2.1	2.4
E2	D1 + 10mM Methionine	0.9	1.3	1.5	2.1	2.4
E3	D1 + 1ppm Fe++, 10mM Methionine	1.0	1.4	1.7	2.4	2.9
E6	D1 + 1ppm Fe++, 250uM EDTA	1.0	1.4	1.7	2.5	3.1
E7	D1 + 1ppm Fe++, 250uM DTPA	1.0	1.4	1.7	2.3	2.6
E8	D1 + 1ppm Fe++, 20mM Sodium Citrate	1.0	1.5	1.9	2.5	2.8
E9	D1 + 1ppm Fe++, 5mM Glutathione	0.8	2.4	3.3	4.6	5.0

* Data provided are from the Study summarized in Table 8.

[0350] HP-SEC results (see Table 9) indicate that formulations containing 5mM and 10 mM methionine (Formulations E1 and E2) showed a low increase in aggregates without metal ions. Formulations containing methionine and DTPA (Formulations E3 and E7) showed a lower increase in aggregate levels in presence of metal ions compared to EDTA (Formulation E6). The greatest increase in aggregates was observed in the formulation containing glutathione in the presence of metal ions (Formulation E9).

[0351] Oxidation of the formulations at 40°C was also tested over the 8-week period by HP-HIC (see FIGURE 6). Reduced oxidation levels over the 8-week period were observed by HP-HIC analysis for formulations containing 5 mM and 10 mM methionine (Formulations E1 and E2) compared to the other formulations tested. The formulations containing 10 mM methionine (Formulation E3) and 250 uM DTPA (Formulation E6) showed a low level of oxidation over the 8-week period in the presence of metal ions. Results also indicate that DTPA was more effective than EDTA at preventing oxidation over time. Sodium citrate and glutathione did not appear to be as effective at controlling oxidation in the presence of metal ions as methionine, DTPA or EDTA.

Study 3:

[0352] An additional study was undertaken to evaluate the impact of antioxidants and chelators separately and in combination (with or without metal ions) to further optimize excipient levels. Following formulation, the samples were stored at 40°C for 8 weeks and evaluated by HP-SEC at T=0, 4 weeks and 8 weeks (see Table 10).

Table 10. HMW (SEC) for Formulations Used in EXAMPLE 6, Study 3

	Formulation	T=0	4 weeks/ 40°C	8 weeks/ 40°C
H1	167 mg/mL pembrolizumab, 7% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5	1.01	2.01	2.81
H2	167 mg/mL pembrolizumab, 7% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5, 100 µM DTPA	1.01	2.07	2.84
H3	167 mg/mL pembrolizumab, 7% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5, 1ppm Fe++, 100 µM DTPA	1.01	2.10	2.88
H4	167 mg/mL pembrolizumab, 7% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5, 100 µM EDTA	0.90	1.63	2.18

	Formulation	T=0	4 weeks/ 40°C	8 weeks/ 40°C
H5	167 mg/mL pembrolizumab, 7% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5, 1ppm Fe++, 100 μM EDTA	0.92	1.98	3.13
H6	167 mg/mL pembrolizumab, 7% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5, 10 mM Methionine, 100uM DTPA	1.00	2.07	2.80
H7	167 mg/mL pembrolizumab, 7% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5, 1ppm Fe++, 10 mM Methionine, 100uM DTPA	0.99	2.07	2.81
H8	167 mg/mL pembrolizumab, 7% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5, 10 mM Methionine, 100uM EDTA	0.91	1.65	2.17
H9	167 mg/mL pembrolizumab, 7% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5, 1ppm Fe++, 10 mM Methionine, 100uM EDTA	0.91	1.83	2.67
H10	167 mg/mL pembrolizumab, 3% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5, 40mM Arg, 40 mM Glu	0.89	1.57	2.06
H11	167 mg/mL pembrolizumab, 3% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5, 10 mM Methionine, 40mM Arg, 40 mM Glu, 100 μM DTPA	0.89	1.68	2.12
H12	167 mg/mL pembrolizumab, 7% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5, 10 mM Methionine	1.06	1.99	2.70
H13	167 mg/mL pembrolizumab, 7% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5, 10 mM Methionine	1.06	2.00	2.70
H14	167 mg/mL pembrolizumab, 7% Sucrose, 0.02% PS-80, 10mM Histidine buffer, pH 5.5	1.06	2.05	2.79

[0353] In this study, the presence of arginine and glutamate (formulations H10 and H11) appeared to have an impact on the rate of aggregation.

[0354] Oxidation of the above samples at 40°C was also measured by HP-HIC over 8 weeks. Results indicate that the presence of 10 mM methionine resulted in a reduced rate of aggregation over the 8-week period compared to other formulations (see FIGURE 7).

[0355] Overall, studies 1-3 showed that the presence of L methionine in the pembrolizumab formulations was able to reduce the rate of oxidation in a concentration-dependent manner. No additional benefit of adding DTPA and EDTA along with methionine was observed.

EXAMPLE 7

Viscosity of High Concentration Anti-PD-1 Antibody Formulations

Study 1—Viscosity as a function of protein concentration

Study 1A:

[0356] In one experiment, the viscosity of unformulated pembrolizumab (pembrolizumab in 10 mM histidine buffer) as a function of protein concentration was measured. Samples were generated by ultrafiltration/diafiltration of pembrolizumab in 10 mM histidine buffer pH 5.4. Concentration values were measured by SoloVPE and the viscosity was measured using the MVROC instrument. Values are provided in Table 11 below.

Table 11. Viscosity of unformulated pembrolizumab (in 10 mM histidine buffer pH 5.5) as a function of protein concentration

Measured pembrolizumab concentration (mg/mL)	Viscosity at 20°C (cP)
25	1.3
46	1.7
54.7	1.8
90.2	3.1
135.6	7.6
153.8	11.3
206	52.3
223.4	88.1
234	173.4
263	425

Study 1B:

[0357] In another experiment, the viscosity of pembrolizumab formulated in 10 mM histidine pH 5.5 in the presence of 3% (w/v) arginine as a function of pembrolizumab concentration was also measured. The samples for this experiment were generated by ultrafiltration-diafiltration of pembrolizumab in 10 mM histidine pH 5.4 buffer in the presence of 3% (w/v) arginine. Samples were collected at different stages of UV/DF process and concentration and viscosity values were measured. Concentration values were measured by SoloVPE and the viscosity was measured using an MVROC instrument. Values are provided in Table 12.

Table 12: Viscosity of pembrolizumab formulated in 10 mM histidine pH 5.5 in the presence of 3% (w/v) arginine

Measured pembrolizumab concentration (mg/mL)	Viscosity at 20 °C (cP)
51.6	1.8
93.1	3.0
157.3	9.90
217.3	50.9
288	271.0

Study 1C:

[0358] In another experiment, the viscosity of formulated pembrolizumab samples was measured. Formulations of pembrolizumab were prepared at different concentrations in the range of 100-200 mg/mL with 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80, 10 mM methionine, in 10 mM histidine buffer pH 5.5. The formulations were prepared by mixing the following stock solutions: (1) pembrolizumab drug substance at 236 mg/mL in 10 mM histidine pH 5.5 buffer; (2) 49% (w/w) sucrose, 0.14% (w/w) polysorbate 80, 85 mM methionine in 10 mM histidine pH 5.4; and (3) 10 mM histidine pH 5.5. Viscosity measurements were performed using MVROC viscometer (see Table 13).

Table 13: Viscosity of fully formulated pembrolizumab as a function of protein concentration.

Measured concentration[1] (mg/mL)	Viscosity[2] at 20 °C, (cP)
100.2 (0.2)	4.2 (0.0)
125.6 (0.2)	7.1 (0.1)
148.1 (0.6)	13.1 (0.0)
174.8 (0.2)	26.8 (0.1)
186.1 (1.2)	34.7 (0.4)
204.1 (1.3)	54.9 (0.5)

[1] Concentration values of samples were measured in triplicate via absorption of UV A280 of diluted samples, and the average value along with the standard deviation was reported.
[2] Viscosity values were measured in triplicate and the average value along with the standard deviation was reported.

Study 2: Effect of different excipients on viscosity of high concentration pembrolizumab solutions

[0359] In this study, stock solutions of different excipients in 10 mM histidine pH 5.5 buffer were prepared. Subsequently, pembrolizumab drug substance samples in 10 mM histidine, pH 5.5 were spiked with these excipient stocks to achieve target excipient concentration. Pembrolizumab concentration values were measured by SoloVPE and the viscosity was measured using an MVROC instrument (Table 14). Sample pH was also measured.

Table 14: Effect of different excipients on viscosity of pembrolizumab solutions in 10 mM histidine pH 5.5 (target pH)

Excipient	Target excipient concentration (unit)	Measured pembrolizumab concentration (mg/mL)	Measured pH[1]	Viscosity [2] (cP) at 20°C
L-Arginine	200 mM	183	5.5	20.29
Poly-arginine (5-15 kDa)	0.5 mg/mL	202	5.6	51.354
Poly-arginine (15-70 kDa)	0.5 mg/mL	186	5.56	54.018
L-Alaninine	200 mM	197	5.47	30.641
L-Cysteine	200 mM	187	5.56	31.844
L-Glutamine	60 mM	193	5.6	53.825
Glycine	200 mM	175	5.52	42.769
L-Histidine	100 mM	186	5.05	19.402
L-Lysine	200 mM	179	5.52	27.431
L-Methionine	40 mM	200	5.45	38.501
O-phospho-L-serine	30 mM	151	5.56	34.42
Potassium Chloride	200 mM	195	5.59	38.246
Sodium Chloride	200 mM	208	5.69	58.192
Calcium Chloride	200 mM	178	5.56	33.593
Potassium Iodide	200 mM	180	5.7	34.626
Sodium Iodide	200 mM	197	5.77	35.92
Guanidine hydrochloride	200 mM	189	5.61	20.984
DMSO	10% (v/v)	180	5.4	13.056
Protamine	0.75 mg/mL	180	5.54	50.328
Camphor-10-sulfonic acid	200 mM	191	5.64	15.698
L-Glutamic acid	200 mM	173	5.55	52.368
Polysorbate 80	0.1% (w/v)	183	5.89	49.268
Pluronic F127	0.1% (w/v)	179	5.85	43.908
ATP	12.5 mg/mL	173	5.73	56.695

[1] Target pH of all samples was 5.5; however, in certain cases, the pH of the spiking solution influenced the pH of the spiked pembrolizumab samples
[2] The viscosity of control pembrolizumab solution in 10 mM histidine buffer only (non-spiked with any of the excipients) was not measured in this experiment; however, based on the other experiments, it was expected to be ~50 cP

Study 3: Effect of concentration of arginine, histidine, and methionine on viscosity of pembrolizumab solutions

[0360] In this study, the effect of arginine, histidine, sodium acetate, and methionine concentration on viscosity of pembrolizumab solutions was investigated. Pembrolizumab drug substance (>200 mg/mL) in 10 mM histidine pH 5.4 was mixed with different amounts of stock solutions of arginine, histidine, and methionine to achieve varying concentrations of excipients

in solutions containing pembrolizumab target concentrations of 200 mg/mL or 167 mg/mL. The results are summarized in Table 15.

Table 15. Effect of Excipient Concentration on Viscosity

		Target pembrolizumab concentration - 200 mg/mL		Target pembrolizumab concentration - 167 mg/mL	
	Target excipient conc. (mM)	Measured pembrolizumab concentration (mg/mL)	Viscosity at 20 °C (cP)	Measured pembrolizumab concentration (mg/mL)	Viscosity at 20 °C (cP)
No Excipient	0	191.6	37.847	163.4	18.512
	0[1]	202.5	58.7	-	-
L-Arginine HCl	15	193.4	37.268	164.8	17.427
	30	188.2	32.976	163.6	16.206
	45	196.4	30.041	166.3	17.950
	60	191.2	28.615	161.8	12.951
	75	190.7	26.697	168.7	13.758
	71[1]	193.3	27.1	-	-
	142[1]	201.8	26.1	-	-
	213.6[1]	203.5	26.7	-	-
	285[1]	205.7	26.8	-	-
	356[1]	211.7	25.6	-	-
	427[1]	205.5	25.3	-	-
L-Histidine Hydrochloride Monohydrate	5	183.6	37.142	165.1	18.209
	20	189.8	20.356	164.2	16.654
	35	190.1	30.337	166.4	16.877
	50	193.9	24.073	168.9	15.490
	65	190.2	27.341	166	13.303
L-Methionine	10	190.8	45.544	168.7	19.708
	20	188	46.901	160.8	19.926
	30	191.7	45.374	161.2	18.402
	40	194.3	41.235	161.3	18.304

[1]Value represents data from a separate experiment that evaluated arginine.HCl concentrations up to 9% (w/v) (equivalent to 427 mM)

[0361] Data from the studies above demonstrate that viscosity of pembrolizumab in 10 mM histidine buffer pH 5.5 increases exponentially with increase in protein concentration (Table 11). The data also show that the presence of 3% (w/v) arginine reduces the viscosity of pembrolizumab in 10 mM histidine pH 5.5 solution; however, the exponential increase in viscosity with increase in pembrolizumab concentration is still observed (Table 12). Viscosity values of pembrolizumab formulated in 10 mM histidine pH 5.5, along with 7% (w/v) sucrose, 0.02% polysorbate 80, 10 mM methionine in the protein concentration range of 100 – 200 mg/mL are similar to corresponding values measured in 10 mM pH 5.5 buffer alone. The

viscosity of formulated pembrolizumab shows significant increase around 150 mg/mL and higher concentrations (Table 13).

[0362] Different excipients impacted viscosity of pembrolizumab high concentration solutions to different extents (Table 14). The excipients that had the greatest impact on pembrolizumab viscosity include L-arginine, L-histidine, guanidine hydrochloride, DMSO, and camphor sulfonic acid (Table 14). In addition, Table 15 shows that L-arginine and L-hisitidine reduce pembrolizumab solution viscosity in a concentration dependent manner and that addition of L-methionine up to 40 mM does not reduce viscosity of pembrolizumab.

EXAMPLE 8

Long-Term Stability of High Concentration Anti-PD-1 Antibody Formulations

[0363] Additional studies were performed to determine the long term stability of high-concentration pembrolizumab formulations in the presence and absence of methionine. This study investigated the impact of concentration and presence of antioxidant (e.g., methionine) on the stability of pembrolizumab. Stock solutions of excipients were prepared and spiked into pembrolizumab drug substance to achieve the final composition presented in the Table 16. The formulations were staged in 5°C +/- 3°C, 25°C +/- 3°C/60% ± 5% relative humidity and 40°C +/- 2°C/75% ± 5% relative humidity environmental stability chambers. Formulations K2 and K3 were staged on limited stability compared to formulations K1 and K4. The planned duration of the study is 36 months, with 25°C ending after six months and 40°C ending after three months. Results for up to 12 months are presented below.

Table 16. Long Term Stability of Formulations Comprising Pembrolizumab

Formulation	Ab Concentration (mg/mL)		Formulation	Fill	Container/closure
	Target	Actual			
K1	167	143	10 mM histidine pH 5.5, 7% sucrose, 0.02% PS80 + 10mM Met	1.4 mL (label)	2R vial 12 mM serum stopper
K2	184	161			
K3	150	131			
K4	167	146	10 mM histidine pH 5.5, 7% sucrose, 0.02% PS80		

[0364] All test formulations were visually inspected and found to be essentially free from visible particles through 12 months at 5°C. The formulations were also evaluated by HP-SEC, HP-HIC and HP-IEX, and results are provided in Tables 17-19 and summarized below:

pH:

[0365] All formulations had the same initial pH value of 5.7. No change in the pH was observed for any of the formulations at any storage condition.

Potency by binding ELISA:

[0366] No change was observed in potency by binding ELISA for any of the formulations irrespective of the storage duration and condition. All the potency values were within the acceptance criteria of 60-140% of the reference (values ranged from 85-106 over the 12 month storage period for samples stored at 5°C, data not shown).

Reduced and Non-Reduced CE-SDS:

[0367] Purity by CE-SDS was measured under reducing and non-reducing conditions. There was no measurable change in % purity or % intact IgG as a function of time at 5°C up to 12 months for any of the formulations. At 5°C, the % purity by reducing CE-SDS (heavy chain and light chain) was >96.5% for formulations K1 and K4 through 12 months and ≥97.0% for formulations K2 and K3 over the same time period. At 25°C, there was a small decrease in purity for all the formulations. At 40°C, an expected drop in purity was observed after 3 months for all the formulations. The % purity at 5°C by non-reducing CE-SDS (intact IgG) was ≥98.2 for formulations K1 and K2, ≥97.1 for formulation K2 and ≥97.2 for formulation K4 through 12 months at the times tested. All results were within the clinical acceptance criteria of ≥ 90.0% for both reducing and non-reducing CE-SDS.

Purity by HP-SEC:

[0368] At the recommended storage condition of 5°C, no measurable changes in % HMW were noticed for any of the formulations up to 12 months from the initial levels. At 25°C over 6 months, %HMW increased with a corresponding decrease in monomer. No LMW species could be detected at either of the storage conditions for any formulation. At 40°C over 3 months, %HMW increased for different formulations with a corresponding drop in monomer. For formulations K1-K3, increase in HMW was observed with increase in concentration. LMW species were observed for all formulations at 40°C at 3 month time point.

Oxidation by HP-HIC:

[0369] Oxidation at Methionine 105 was quantified by monitoring pre-peak 1+2 by HP-HIC. Formulations K1-K4 exhibited no change in oxidation at 5°C over 12 months. At 25°C over 6

months, the levels of pre-peak 1+2 increased slightly, whereas at 40°C over 3 months, the increase was more evident. At 25 °C and 40 °C, change in oxidation was more pronounced for formulation K4. Since K4 is the only formulation which does not contain L-Methionine, these results demonstrate that inclusion of L-Methionine resulted in a significant decrease in the rate of oxidation.

Charge Heterogeneity by HP-IEX:

[0370] Charge heterogeneity was evaluated by monitoring the main peak along with different acidic and basic species. At 5°C up to 12 months, no measurable changes were found in any of the individual peaks including the main peak for any of the formulations. At 25°C for 6 months, the main peak decreased. There was an increase in all the acidic species (Acidic variants, Acidic 1, and pre main peak) and basic variants peak. There was a decrease observed in Basic 1and Basic 2 species. At 40°C for 3 months, the main peak showed an ever steeper decline. Similar to 25°C, increase was observed for Acidic variants, Acidic 1, pre main and basic variants peak and decrease was observed in Basic 1 and Basic 2 peaks.

Turbidity:

[0371] Turbidity of the drug product batches was determined on stability by measuring optical density at 350 nm. There was no measurable change in turbidity at 5°C for any of the formulations. Samples stored at 25°C showed a slight increase whereas those stored at 40°C showed an even larger increase in turbidity. The increase in turbidity at 25°C and 40°C is consistent with increasing high molecular weight species observed on stability.

[0372] Overall, based on twelve months of stability data, formulations K1-K4 were stable at 5°C for up to 12 months with no measurable changes in product quality attributes. Some degradation was observed upon monitoring the attributes at 25°C for 6 months and at 40°C for 3 months. Stability of products at 5°C will be further evaluated up to a duration of 36 months.

Table 17. Stability Data for Formulations K1-K4 at 5°C

Test	Form.	Stability Test Interval					
Time Interval		Initial	1 mo.	3 mos.	6 mos.	9 mos.	12 mos.
Purity by HP-SEC							
High Molecular Weight Species (%)	K1	1.4	1.4	1.5	1.4	1.4	1.4
	K2	1.5	N.A.	N.A.	1.5	N.A.	1.5

Test	Form.	Stability Test Interval					
Time Interval		Initial	1 mo.	3 mos.	6 mos.	9 mos.	12 mos.
	K3	1.5	N.A.	N.A.	1.4	N.A.	1.4
	K4	1.5	1.5	1.6	1.5	1.5	1.5
% Monomer	K1	98.5	98.5	98.5	98.5	98.5	98.5
	K2	98.5	N.A.	N.A.	98.5	N.A.	98.5
	K3	98.5	N.A.	N.A.	98.6	N.A.	98.5
	K4	98.5	98.5	98.4	98.5	98.5	98.5
Low Molecular Weight Species (%)	K1	0	0	0	<RL[1]	<RL[1]	<RL[1]
	K2	0	N.A.	N.A.	<RL[1]	N.A.	<RL[1]
	K3	0	N.A.	N.A.	<RL[1]	N.A.	<RL[1]
	K4	0	0	0	<RL[1]	<RL[1]	<RL[1]
Oxidation by HP-HIC							
Pre-peak 1 & 2 (%)	K1	6.26	6.34	6.50	6.35	6.05	5.73
	K2	6.28	N.A.	N.A.	6.38	N.A.	5.75
	K3	6.40	N.A.	N.A.	6.36	N.A.	5.78
	K4	6.36	6.58	6.86	6.64	6.31	6.15
Group Charge Variants by HP-IEX							
Acidic Variants (%)	K1	16.8	16.8	17.4	17.3	17.2	17.5
	K2	16.8	N.A.	N.A.	17.3	N.A.	17.5
	K3	16.9	N.A.	N.A.	17.4	N.A.	17.4
	K4	16.8	16.9	17.6	17.3	17.3	17.5
Main (%)	K1	59.5	59.4	59.2	59.4	59.6	58.7
	K2	59.5	N.A.	N.A.	59.4	N.A.	58.7
	K3	59.5	N.A.	N.A.	59.4	N.A.	58.8
	K4	59.5	59.4	59.1	59.6	59.5	58.6
Basic Variants (%)	K1	23.8	23.8	23.4	23.3	23.2	23.7
	K2	23.7	N.A.	N.A.	23.3	N.A.	23.8
	K3	23.7	N.A.	N.A.	23.2	N.A.	23.8
	K4	23.7	23.7	23.3	23.1	23.2	23.8
Turbidity (A350)	K1	0.187	0.185	0.190	0.189	0.192	0.200
	K2	0.200	N.A.	N.A.	0.207	N.A.	0.213
	K3	0.174	N.A.	N.A.	0.183	N.A.	0.191

Test	Form.	Stability Test Interval					
Time Interval		Initial	1 mo.	3 mos.	6 mos.	9 mos.	12 mos.
	K4	0.189	0.187	0.193	0.190	0.191	0.202

[1]<RL: Below reporting limit

Table 18. Stability Data for Formulations K1-K4 at 25°C

	Test	Form.	Stability Test Interval			
Time Interval			Initial	1 month	3 months	6 months
Purity by HP-SEC	High Molecular Weight Species (%)	K1	1.4	1.5	1.7	1.8
		K2	1.5	N.A.	1.8	1.9
		K3	1.5	N.A.	1.7	1.8
		K4	1.5	1.6	1.8	1.9
	% Monomer	K1	98.5	98.5	98.2	98.1
		K2	98.5	N.A.	98.2	98.1
		K3	98.5	N.A.	98.3	98.2
		K4	98.5	98.4	98.1	98.0
	Low Molecular Weight Species (%)	K1	0	0	0	<RL[1]
		K2	0	N.A.	0	<RL[1]
		K3	0	N.A.	0	<RL[1]
		K4	0	0	0	<RL[1]
Oxidation by HP-HIC	Pre-peak 1 & 2 (%)	K1	6.26	6.43	6.86	7.15
		K2	6.28	N.A.	6.88	7.15
		K3	6.4	N.A.	7.06	7.12
		K4	6.36	7.08	8.04	8.74
Group Charge Variants by HP-IEX	Acidic Variants (%)	K1	16.8	18.5	24.3	30.8
		K2	16.8	N.A.	23.7	30.8
		K3	16.9	N.A.	23.8	30.8
		K4	16.8	18.6	23.6	30.9
	Main (%)	K1	59.5	58.7	54.7	50.3
		K2	59.5	N.A.	55.4	50.3
		K3	59.5	N.A.	55.3	50.3
		K4	59.5	58.4	55.6	50.2
		K1	23.8	22.9	21.0	18.9

	Test	Form.	Stability Test Interval			
Time Interval			Initial	1 month	3 months	6 months
	Basic Variants (%)	K2	23.7	N.A.	20.8	18.9
		K3	23.7	N.A.	20.9	18.9
		K4	23.7	23.0	20.8	18.9
Turbidity (A350)		K1	0.187	0.197	0.217	0.231
		K2	0.200	N.A.	0.233	0.242
		K3	0.174	N.A.	0.200	0.212
		K4	0.189	0.199	0.219	0.244

[1]<RL: Below reporting limit, N/A: not available

Table 19. Stability Data for Formulations K1-K4 at 40°C

	Test	Form.	Stability Test Interval		
Time Interval			Initial	1 month	3 months
Purity by HP-SEC	High Molecular Weight Species (%)	K1	1.4	2.5	4.9
		K2	1.5	N.A.	5.2
		K3	1.5	N.A.	4.6
		K4	1.5	2.6	5.4
	% Monomer	K1	98.5	97.5	94.9
		K2	98.5	N.A.	94.7
		K3	98.5	N.A.	95.2
		K4	98.5	97.4	94.5
	Low Molecular Weight Species (%)	K1	0	0	0.2
		K2	0	N.A.	0.2
		K3	0	N.A.	0.2
		K4	0	0	0.2
Oxidation by HP-HIC	Pre-peak 1 & 2 (%)	K1	6.26	7.32	9.28
		K2	6.28	N.A.	9.25
		K3	6.4	N.A.	9.04
		K4	6.36	8.59	12.91
Group Charge Variants by HP-IEX	Acidic Variants (%)	K1	16.8	32.6	58.1
		K2	16.8	N.A.	58.5
		K3	16.9	N.A.	58.5

	Test	Form.	Stability Test Interval		
Time Interval			Initial	1 month	3 months
		K4	16.8	33.1	58.4
	Main (%)	K1	59.5	47.8	27.8
		K2	59.5	N.A.	27.7
		K3	59.5	N.A.	28.0
		K4	59.5	47.3	27.8
	Basic Variants (%)	K1	23.8	19.6	14.0
		K2	23.7	N.A.	13.8
		K3	23.7	N.A.	13.6
		K4	23.7	19.6	13.8
Turbidity (A350)		K1	0.187	0.231	0.322
		K2	0.200	N.A.	0.357
		K3	0.174	N.A.	0.302
		K4	0.189	0.234	0.347

[1]<RL: Below reporting limit, N/A: not available

Examples 9-13:

[0373] Examples (9-13) highlight the preparation of formulations that use a smaller amount of antibody and excipients than intended in the final formulations. However these formulations preserve the molar ratio of the pembrolizumab/stabilizer and pembrolizumab/surfactant of the final intended formulations. The anti-oxidant, buffer and metal chelator concentrations were tested at the final intended concentration. The pembrolizumab (5 mg/mL), PS80 (0.0016%) and stabilizer (e.g., 1.4% sucrose) concentrations were scaled down by a factor of 5 and studied as surrogate formulations for the more concentrated, final intended formulations. For example, Formulation 1A in Table 20 has the same molar ratios as a formulation comprising 25mg/mL pembrolizumab, 7% sucrose and 0.02% PS80. It is expected that the formulations disclosed in Examples 9-12 are representative of the intended final formulations and that the disclosed results suggest how the final higher concentration formulations would behave. It is understood that some parameters being studied, e.g. aggregation, may be impacted by the decrease in concentration due to a decreased likelihood of intermolecular interactions; however, to compensate, a more aggressive stability regimen was pursued (50 °C for 10 days) to induce and identify stability risk.

[0374] The concentration of anti-oxidant (e.g. methionine), buffer (e.g. histidine) and metal chelator (e.g. DTPA and EDTA) concentrations were not scaled down in a similar manner to the other excipients. Methionine is a functional excipient that is used to reduce the Met-105 oxidation by expunging oxidants (such as dissolved oxygen), thus maintaining the chemical stability of pembrolizumab. Similarly, DTPA is a functional excipient that is used to complex metal ion impurities which may otherwise trigger undesired protein degradation. Since it is more challenging to maintain chemical stability at lower pembrolizumab concentrations, the methionine and DTPA concentrations were held constant at 10 mM and 20 µM, respectively. It is expected that if a specific amount of methionine is effective in the low concentration formulations, it would most likely be as effective at preventing oxidation in the higher concentration formulations. L-Histidine and/or L-Histidine hydrochloride at 10 mM is expected to maintain buffering capacity at the intended pH of the formulations tested.

EXAMPLE 9

Evaluation of the Stability of Low Concentration Pembrolizumab Formulations in Combination with Methionine

[0375] An initial formulation study was performed to evaluate the stability of formulations comprising a low (5 mg/ml) concentration of pembrolizumab and to evaluate the impact of different formulation excipients. Throughout Examples 9-12, the arginine used was L-arginine or L-arginine·HCl, the glycine used was glycine and the proline used was L-proline.

[0376] Pembrolizumab drug substance in 10 mM Histidine pH 5.5 (41.2 mg/mL) was combined with polysorbate-80 (PS80) solution (~ 0.36 mg/mL) then QS to final volume with buffer to yield a protein (20 mg/mL)/PS80 (0.16 mg/mL) stock solution in 10mM histidine pH 5.5. Pembrolizumab formulations were prepared to 5 mg/mL target concentration by spiking the protein/PS80 stock solution with excipient stock solutions and respective buffer. All stock solutions used for formulations were filtered through Millapore Express® PLUS Stericup® 0.22 µm PES filters prior to use. Test formulations comprising a low concentration of pembrolizumab were prepared in a 96-well plate at a volume of 1 mL. Excipients were spiked into the protein/PS80 stock solution to achieve target levels of each excipient and brought to final volume using histidine buffer pH 5.5 (see Table 20). (2-Hydroxypropyl)-β-cyclodextrin (sold under the name CAVITRON™) and (sulfobutylether)-β-cyclodextrin (sold under the trade name CAPTISOL™) are denoted as HPBC and SBEC, respectively. The well plate was covered with a 96-well silicone sealing mat and then was vacuum sealed (2x) in moisture barrier bags to minimize potential evaporation. Samples were staged in 2-8 °C (as used herein and throughout

the Examples, the term "5 °C" is used interchangeably with "2-8 °C", which indicates 5 °C ± 3 °C (standard deviation)) and 50 °C environmental stability chambers.

Table 20. Low Concentration Pembrolizumab Formulations.

Form.[1]	Stabilizer	Anti-Oxidant	Form.[1]	Stabilizer	Anti-Oxidant
1A	1.4% sucrose	—	5B	0.4% glycine	10 mM Met
1B	1.4% sucrose	10 mM Met	6A	1.4% HPBC	—
2A	0.8% mannitol	—	6B	1.4% HPBC	10 mM Met
2B	0.8% mannitol	10 mM Met	7A	0.8% arginine	—
3A	1.4% trehalose	—	7B	0.8% arginine	10 mM Met
3B	1.4% trehalose	10 mM Met	8A	0.8% proline	—
4A	0.8% sorbitol	—	8B	0.8% proline	10 mM Met
4B	0.8% sorbitol	10 mM Met	9A	0.8% SBEC	—
5A	0.4% glycine	—	9B	0.8% SBEC	10 mM Met

[1]All formulations comprised 5 mg/mL pembrolizumab, 10 mM Histidine buffer and 0.004% PS80, in addition to the excipients listed.

[0377] Each of the test formulations were visually inspected for changes in coloration or precipitate formation (data not shown). Additionally, stability of the formulations was evaluated using turbidity (A350), UP-SEC (to assess purity) and HP-IEX (charge profile) after the10-day stability period. Formulations 9A and 9B comprising SBEC were visibly turbid upon removal from the stability chamber. On the contrary, formulations 6A and 6B, comprising HPBC, did not show any visible signs of turbidity. Formulations 9A and 9B were not tested further by UP-SEC and HP-IEX, only turbidity, as highlighted in Table 21. UP-SEC results demonstrate that there were no changes for any of the formulations that were stored at 5 °C during the 10-day time period with the exception of formulations comprising arginine (with or without methionine), where a slight decrease in % mAb was observed by UP-SEC (< 0.5%). All other formulations were considered stable at the 5°C storage condition. At 50 °C, more pronounced changes were observed via UP-SEC (a decrease in % mAb) and HP-IEX (a decrease in % main and a significant increase in % pre-main, data not shown) for each of the formulations over the time period tested. Surprisingly, the highest decrease in % mAb (with corresponding increase in % aggregates) by UP-SEC after 10 days was observed with formulations 7 A and 7B at 50 °C compared to the other formulations stored at 50 °C for 10 days, suggesting that these

formulations have decreased stability. Turbidity (A350) results for formulations 7A and 7B after 10 days at 50 °C corroborated the UP-SEC results indicating a decrease in stability of formulations 7A and 7B.

[0378] Cyclodextrins have been shown to stabilize protein formulations in the literature through maximizing both conformational and colloidal stability; however, cyclodextrins have been primarily studied with IgG1 proteins. The mechanism by which cyclodextrins impart this stabilization is the subject of much debate. As shown in Table 21, turbidity and UP-SEC measurements of formulations 6A and 6B (comprising HPBC) demonstrated stability that was on par with other stabilizers tested over 10 days 50 °C, unlike other cyclodextrin formulations tested (9A and 9B, comprising SBEC), which had high turbidity after 10 days at 50°C.

[0379] There were no appreciable differences in charge profile among any of the formulations (with the exclusion of 7A/B and 9A/B which were not tested) at 50 °C for the 10-day testing period (data not shown). The addition of methionine (10 mM) to the tested formulations had a negligible effect on the prevention of aggregation through the testing period.

Table 21. Formulations used for Example 9.

Form.	Stabilizer	Anti-Oxidant	% mAb (UP-SEC)		Turbidity (A350)
			10 days @ 5 °C	*10 days @ 50 °C*	*10 days @ 50 °C*
1A	1.4% sucrose	—	99.1	96.0	0.017
1B	1.4% sucrose	10 mM Met	99.1	96.1	0.015
2A	0.8% mannitol	—	99.1	96.0	0.014
2B	0.8% mannitol	10 mM Met	99.1	96.1	0.015
3A	1.4% trehalose	—	99.1	96.0	0.015
3B	1.4% trehalose	10 mM Met	99.1	96.1	0.017
4A	0.8 % sorbitol	—	99.1	95.9	0.017
4B	0.8 % sorbitol	10 mM Met	99.1	96.1	0.015
5A	0.4 % glycine	—	99.0	96.1	0.018
5B	0.4 % glycine	10 mM Met	99.1	96.2	0.021
6A	1.4% HPBC	—	99.1	95.7	0.019
6B	1.4% HPBC	10 mM Met	99.1	95.8	0.015
7A	0.8 % arginine	—	98.7	60.3	0.091
7B	0.8 % arginine	10 mM Met	98.6	65.3	0.068

8A	0.8 % proline	—	99.1	95.2	0.016
8B	0.8 % proline	10 mM Met	99.1	95.3	0.021
9A	0.8% SBEC	—	DNT	DNT	0.134
9B	0.8% SBEC	10 mM Met	DNT	DNT	0.134

[1]All formulations comprised 5 mg/mL pembrolizumab, 10 mM Histidine buffer and 0.004% PS80, in addition to the excipients listed.

EXAMPLE 10

Analysis of Low Concentration Pembrolizumab Formulations Comprising Methionine in Combination with Metal Chelators

[0380] In order to investigate the impact of metal chelators (DTPA and EDTA) on low concentration pembrolizumab formulations, a series of compositions were formulated and tested as described below. Pembrolizumab (20 mg/mL)/PS80 (0.16 mg/mL) stock solution in 10mM histidine pH 5.5 was prepared as described above in Example 9. Formulations 1 – 8 (C through F) were prepared in a 96-well plate by spiking stock solutions of the following excipients: sucrose (5% w/v), mannitol (5% w/v), trehalose (5% w/v), sorbitol (5% w/v), glycine (5% w/v), HPBC (5% w/v), arginine (5% w/v), proline (5% w/v), methionine (2% w/v), DTPA (0.01% w/v), and EDTA (0.01% w/v) into pembrolizumab /PS80 stock solution to achieve the target compositions (QS to 1 mL with histidine pH 5.5 buffer) listed in Table 22. All stock solutions used for formulations were filtered through Millapore Express® PLUS Stericup® 0.22 µm PES filters prior to use. The well plate was covered with a 96-well silicone sealing mat and then was vacuum sealed (2x) in moisture barrier bags to minimize potential evaporation. Samples were staged in 5 °C and 50 °C environmental stability chambers for time period of 10 days.

Table 22. Low Concentration Pembrolizumab Formulations Comprising Methionine in Combination with DTPA and EDTA.

Form.[1]	Stabilizer	Anti-Oxidant	Metal Chelator	Form.[1]	Stabilizer	Anti-Oxidant	Metal Chelator
1C	1.4% sucrose	—	DTPA	5E	0.4 % glycine	—	EDTA
1D	1.4% sucrose	10 mM Met	DTPA	5F	0.4 % glycine	10 mM Met	EDTA
1E	1.4% sucrose	—	EDTA	6C	1.4% HPBC	—	DTPA
1F	1.4% sucrose	10 mM Met	EDTA	6D	1.4% HPBC	10 mM Met	DTPA
2C	0.8% mannitol	—	DTPA	6E	1.4% HPBC	—	EDTA

Form.[1]	Stabilizer	Anti-Oxidant	Metal Chelator	Form.[1]	Stabilizer	Anti-Oxidant	Metal Chelator
2D	0.8% mannitol	10 mM Met	DTPA	6F	1.4% HPBC	10 mM Met	EDTA
2E	0.8% mannitol	—	EDTA	7C	0.8 % arginine	—	DTPA
2F	0.8% mannitol	10 mM Met	EDTA	7D	0.8 % arginine	10 mM Met	DTPA
3C	1.4% trehalose	—	DTPA	7E	0.8 % arginine	—	EDTA
3D	1.4% trehalose	10 mM Met	DTPA	7F	0.8 % arginine	10 mM Met	EDTA
3E	1.4% trehalose	—	EDTA	8C	0.8 % proline	—	DTPA
3F	1.4% trehalose	10 mM Met	EDTA	8D	0.8 % proline	10 mM Met	DTPA
4C	0.8 % sorbitol	—	DTPA	8E	0.8 % proline	—	EDTA
4D	0.8 % sorbitol	10 mM Met	DTPA	8F	0.8 % proline	10 mM Met	EDTA
4E	0.8 % sorbitol	—	EDTA	9C	0.8% SBEC	—	DTPA
4F	0.8 % sorbitol	10 mM Met	EDTA	9D	0.8% SBEC	10 mM Met	DTPA
5C	0.4 % glycine	—	DTPA	9E	0.8% SBEC	—	EDTA
5D	0.4 % glycine	10 mM Met	DTPA	9F	0.8% SBEC	10 mM Met	EDTA

[1]All formulations comprised 5 mg/mL pembrolizumab, 10 mM Histidine buffer and 0.004% PS80, in addition to the excipients listed.

[0381] Each of the test formulations was visually inspected for any change in color or precipitate over the course of the 10 day testing period (data not shown). Similar to results in Example 9, formulations comprising SBEC were visibly turbid once removed from the stability chamber after 10 days @ 50 °C. Again, turbidity measurements (data not shown) support the decreased stability of these formulations in comparison to other formulations tested. As a result, formulations 9C – 9F were not subjected to further testing. For the remaining formulations, results from turbidity and UP-SEC measurements were very similar to results listed in Table 21 (with the exclusion of formulations comprising arginine (7C – 7F)), suggesting little to no influence of the addition of a metal chelator on stability over 10 days at 50 °C. See Table 23. Again, formulations comprising arginine (7C-7F) showed the largest change in % mAb (monomer) and highest turbidity values (data not shown) over the stability time period. Even though formulations 7C – 7F showed a very appreciable difference in % mAb, the UP-SEC

results for 7D and 7F demonstrate the added benefit of incorporating a metal chelator in combination with methionine to inhibit aggregation. The combination of methionine and EDTA (7F) resulted in a slightly higher % mAb than the combination of methionine and DTPA (7D). There were no appreciable differences in charge profile among any of the formulations (with the exclusion of 7C-7F which were not tested) at 50 °C for the 10-day testing period (data not shown).

Table 23. Low Concentration Pembrolizumab Formulations Comprising Methionine in Combination with DTPA and EDTA.

Form.	Stabilizer	Anti-Oxidant	Metal Chelator	% mAb (UP-SEC)	
				10 d/ 5 °C	*10 d/ 50 °C*
1C	1.4% sucrose	—	DTPA	99.1	95.9
1D	1.4% sucrose	10 mM Met	DTPA	99.1	96.0
1E	1.4% sucrose	—	EDTA	99.1	95.9
1F	1.4% sucrose	10 mM Met	EDTA	99.1	96.0
2C	0.8% mannitol	—	DTPA	99.1	95.9
2D	0.8% mannitol	10 mM Met	DTPA	99.1	95.9
2E	0.8% mannitol	—	EDTA	99.0	95.9
2F	0.8% mannitol	10 mM Met	EDTA	99.1	95.9
3C	1.4% trehalose	—	DTPA	99.1	95.8
3D	1.4% trehalose	10 mM Met	DTPA	99.1	96.0
3E	1.4% trehalose	—	EDTA	99.1	96.0
3F	1.4% trehalose	10 mM Met	EDTA	99.1	96.0
4C	0.8 % sorbitol	—	DTPA	99.1	95.9
4D	0.8 % sorbitol	10 mM Met	DTPA	99.1	95.9
4E	0.8 % sorbitol	—	EDTA	99.1	96.0
4F	0.8 % sorbitol	10 mM Met	EDTA	--	--
5C	0.4 % glycine	—	DTPA	99.1	95.9
5D	0.4 % glycine	10 mM Met	DTPA	99.1	96.0
5E	0.4 % glycine	—	EDTA	99.1	96.0
5F	0.4 % glycine	10 mM Met	EDTA	99.1	96.1

6C	1.4% HPBC	—	DTPA	99.1	94.9
6D	1.4% HPBC	10 mM Met	DTPA	99.1	95.0
6E	1.4% HPBC	—	EDTA	99.1	94.9
6F	1.4% HPBC	10 mM Met	EDTA	99.1	95.0
7C	0.8 % arginine	—	DTPA	98.7	66.9
7D	0.8 % arginine	10 mM Met	DTPA	98.5	69.7
7E	0.8 % arginine	—	EDTA	98.7	66.6
7F	0.8 % arginine	10 mM Met	EDTA	98.5	70.1
8C	0.8 % proline	—	DTPA	99.1	95.1
8D	0.8 % proline	10 mM Met	DTPA	99.1	95.2
8E	0.8 % proline	—	EDTA	99.1	95.0
8F	0.8 % proline	10 mM Met	EDTA	99.1	95.0
9C	0.8% SBEC	—	DTPA	DNT[1]	
9D	0.8% SBEC	10 mM Met	DTPA		
9E	0.8% SBEC	—	EDTA		
9F	0.8% SBEC	10 mM Met	EDTA		

[1] Did not test.

EXAMPLE 11

Evaluation of the Effect of pH on the Stability of Low Concentration Pembrolizumab Formulations in Combination with Methionine

[0382] A further study was performed to evaluate the stability of formulations in histidine buffer at different pH values. In this study, histidine buffers at pH values of 4.5, 6.0 and 6.4 were evaluated and the impact on stability of pembrolizumab was evaluated.

[0383] For this study, pembrolizumab drug product formulations were prepared at a concentration of 5 mg/mL in a 96-well plate. Pembrolizumab (20 mg/mL)/PS80 (0.16 mg/mL) stock solutions in 10mM histidine at pH values of 4.5, 6.0 and 6.4 were prepared from pembrolizumab/PS80 stock solution pH 5.5 by adjusting the pH with dilute HCl or NaOH to the target pH. Excipient stock solutions were adjusted to the target pH in a similar manner and were filtered through Millapore Express® PLUS Stericup® 0.22 µm PES filters prior to use. The following excipient stock solutions were spiked into the pembrolizumab (20 mg/mL)/PS80 (0.16 mg/mL) stock solutions to achieve the target concentrations listed in Table 24: sucrose (5%

w/v), mannitol (5% w/v), trehalose (5% w/v), sorbitol (5% w/v), glycine (5% w/v), HPBC (5% w/v), arginine (5% w/v), proline (5% w/v), and methionine (2% w/v). The well plate was covered with a 96-well silicone sealing mat and then was vacuum sealed (2x) in moisture barrier bags to minimize potential evaporation. Samples were staged in 5 °C and 50 °C environmental stability chambers for time period of 10 days.

Table 24. Pembrolizumab Formulations Comprising Methionine at Various pH Values.

Form.[1]	Stabilizer	Anti-Oxidant	pH	Form.[1]	Stabilizer	Anti-Oxidant	pH
1G	1.4% sucrose	—	4.5	5G	0.4% glycine	—	4.5
1H	1.4% sucrose	10 mM Met	4.5	5H	0.4% glycine	10 mM Met	4.5
1J	1.4% sucrose	—	6.0	5J	0.4% glycine	—	6.0
1K	1.4% sucrose	10 mM Met	6.0	5K	0.4% glycine	10 mM Met	6.0
1L	1.4% sucrose	—	6.4	5L	0.4% glycine	—	6.4
1M	1.4% sucrose	10 mM Met	6.4	5M	0.4% glycine	10 mM Met	6.4
2G	0.8% mannitol	—	4.5	6G	1.4 % HPBC	—	4.5
2H	0.8% mannitol	10 mM Met	4.5	6H	1.4 % HPBC	10 mM Met	4.5
2J	0.8% mannitol	—	6.0	6J	1.4 % HPBC	—	6.0
2K	0.8% mannitol	10 mM Met	6.0	6K	1.4 % HPBC	10 mM Met	6.0
2L	0.8% mannitol	—	6.4	6L	1.4 % HPBC	—	6.4
2M	0.8% mannitol	10 mM Met	6.4	6M	1.4 % HPBC	10 mM Met	6.4
3G	1.4% trehalose	—	4.5	7G	0.8% arginine	—	4.5
3H	1.4% trehalose	10 mM Met	4.5	7H	0.8% arginine	10 mM Met	4.5
3J	1.4% trehalose	—	6.0	7J	0.8% arginine	—	6.0
3K	1.4% trehalose	10 mM Met	6.0	7K	0.8% arginine	10 mM Met	6.0
3L	1.4% trehalose	—	6.4	7L	0.8% arginine	—	6.4
3M	1.4% trehalose	10 mM Met	6.4	7M	0.8% arginine	10 mM Met	6.4
4G	0.8% sorbitol	—	4.5	8G	0.8% proline	—	4.5

4H	0.8% sorbitol	10 mM Met	4.5	8H	0.8% proline	10 mM Met	4.5
4J	0.8% sorbitol	—	6.0	8J	0.8% proline	—	6.0
4K	0.8% sorbitol	10 mM Met	6.0	8K	0.8% proline	10 mM Met	6.0
4L	0.8% sorbitol	—	6.4	8L	0.8% proline	—	6.4
4M	0.8% sorbitol	10 mM Met	6.4	8M	0.8% proline	10 mM Met	6.4

[1] All formulations comprised 5 mg/mL pembrolizumab, 10 mM Histidine buffer and 0.004% PS80, in addition to the formulation excipients listed in the Table.

[0384] The formulations were evaluated by visual observation, turbidity (A350), UP-SEC (purity), and HP-IEX (charge profile). After the 10 day test period at 50 °C, formulations comprising arginine at pH 4.5 (7G & 7H) were visibly turbid. All other formulations listed in Table 24 showed no visual signs of aggregation. Turbidity (A350) values were measured after 10 days and are shown in Table 25. The measured turbidity values for formulations at pH 6.0 were consistently lower than those measured at pH 4.5 and 6.4, suggesting increased stability at pH 6.0. A trend in increased turbidity was observed for all formulations at pH 6.4. Purity of the formulations was tested after 10 days at 50 °C by UP-SEC. All formulations at pH 4.5 showed a significant decrease in % mAb (data not shown) with a corresponding increase in % aggregates (HMW). For all formulations tested at the various pH values, the addition of methionine to the formulation resulted in less aggregation after 10 days at 50 °C, with the largest changes being observed in all formulations at pH 4.5. Surprisingly, formulations 5G and 5H were significantly better than the baseline formulation and showed the smallest % change in % mAb (and smallest subsequent increase in % aggregates) over the stability time period, suggesting relatively increased stability of these formulations over other formulations at pH 4.5.

[0385] Charge profile of formulations after 10 days at 50 °C was determined by HP-IEX (data not shown). All formulations at a respective pH showed similar charge profiles for each stabilizer tested. Formulations at pH 4.5 showed the lowest % acidic and % pre-main peaks after the stability time period, albeit with a corresponding significant increase in % basic variants (> 30%). The charge profiles of formulations at pH 6.0 were comparable to those in Example 9 (Histidine pH 5.5). Formulations at pH 6.4 showed charge profiles opposite to those at pH 4.5 where a significant change in % acidic variants (> 30%) was observed with only a small increase in % pre-main peak. The % main peak in all formulations was very similar for all formulations regardless of pH (41 – 43%). The addition of methionine to the formulations did not result in any significant change in charge profile.

Table 25. Low Concentration Pembrolizumab Formulations Comprising Methionine at Various pH Values.

Form.	Stabilizer	Anti-Oxidant	pH	% Aggregates (UP-SEC)		Turbidity (A350)
				10 days/ 5°C	10 days/ 50 °C	
1G	1.4% sucrose	—	4.5	2.76	54.57	0.021
1H	1.4% sucrose	10 mM Met	4.5	2.77	50.72	0.019
1J	1.4% sucrose	—	6.0	0.99	3.69	0.017
1K	1.4% sucrose	10 mM Met	6.0	0.90	3.21	0.015
1L	1.4% sucrose	—	6.4	4.09	6.14	0.029
1M	1.4% sucrose	10 mM Met	6.4	3.85	5.67	0.024
2G	0.8% mannitol	—	4.5	2.78	55.49	0.021
2H	0.8% mannitol	10 mM Met	4.5	2.76	52.06	0.018
2J	0.8% mannitol	—	6.0	1.02	3.38	0.014
2K	0.8% mannitol	10 mM Met	6.0	0.99	3.26	0.014
2L	0.8% mannitol	—	6.4	3.88	5.80	0.025
2M	0.8% mannitol	10 mM Met	6.4	3.74	5.61	0.022
3G	1.4% trehalose	—	4.5	2.75	54.87	0.028
3H	1.4% trehalose	10 mM Met	4.5	2.75	50.90	0.020
3J	1.4% trehalose	—	6.0	0.91	3.37	0.014
3K	1.4% trehalose	10 mM Met	6.0	0.89	3.20	0.014
3L	1.4% trehalose	—	6.4	3.79	5.79	0.022
3M	1.4% trehalose	10 mM Met	6.4	3.74	5.51	0.020
4G	0.8% sorbitol	—	4.5	2.77	55.48	0.023
4H	0.8% sorbitol	10 mM Met	4.5	2.76	51.85	0.018
4J	0.8% sorbitol	—	6.0	0.89	3.39	0.018
4K	0.8% sorbitol	10 mM Met	6.0	0.98	3.25	0.015
4L	0.8% sorbitol	—	6.4	3.71	5.64	0.023
4M	0.8% sorbitol	10 mM Met	6.4	3.67	5.49	0.020
5G	0.4% glycine	—	4.5	2.83	27.06	0.017
5H	0.4% glycine	10 mM Met	4.5	2.83	25.90	0.015

5J	0.4% glycine	—	6.0	1.00	3.53	0.016
5K	0.4% glycine	10 mM Met	6.0	1.02	3.31	0.014
5L	0.4% glycine	—	6.4	3.66	5.82	0.022
5M	0.4% glycine	10 mM Met	6.4	3.62	5.50	0.024
6G	1.4 % HPBC	—	4.5	2.73	60.52	0.024
6H	1.4 % HPBC	10 mM Met	4.5	2.74	56.97	0.020
6J	1.4 % HPBC	—	6.0	0.99	3.53	0.017
6K	1.4 % HPBC	10 mM Met	6.0	0.97	3.36	0.016
6L	1.4 % HPBC	—	6.4	3.82	5.90	0.029
6M	1.4 % HPBC	10 mM Met	6.4	3.91	5.76	0.029
7G	0.8% arginine	—	4.5	DNT[1]	DNT[1]	1.061
7H	0.8% arginine	10 mM Met	4.5	DNT[1]	DNT[1]	1.090
7J	0.8% arginine	—	6.0	0.94	6.36	0.019
7K	0.8% arginine	10 mM Met	6.0	0.89	6.03	0.020
7L	0.8% arginine	—	6.4	4.05	6.23	0.098
7M	0.8% arginine	10 mM Met	6.4	3.74	6.20	0.044
8G	0.8% proline	—	4.5	2.80	35.98	0.019
8H	0.8% proline	10 mM Met	4.5	2.80	34.40	0.015
8J	0.8% proline	—	6.0	1.00	3.50	0.016
8K	0.8% proline	10 mM Met	6.0	0.90	3.32	0.015
8L	0.8% proline	—	6.4	3.73	5.86	0.026
8M	0.8% proline	10 mM Met	6.4	3.73	5.61	0.022

[1]Did not test.

EXAMPLE 12

Evaluation of Pembrolizumab Formulations Comprising Methionine and DTPA at Various Concentrations

[0386] Previous studies suggested that the addition of methionine (anti-oxidant) and a metal chelator may have benefit in reducing aggregation (see Example 10). In order to investigate the impact of anti-oxidant and metal chelator concentration on suppressing the propensity for aggregation, a series of compositions were formulated and tested as described below. Pembrolizumab (20 mg/mL)/PS80 (0.16 mg/mL) stock solution in histidine pH 5.5 buffer was prepared as previously described in Example 9. Stock solutions (20 mg/mL) of the various

stabilizers (sucrose, mannitol, trehalose, sorbitol, glycine, HPBC, arginine, and proline) were spiked into the pembro/PS80 stock solution. Methionine was used as the anti-oxidant and DTPA was used as the metal chelator. As noted prior, all stock solutions used for formulations were filtered through Millapore Express® PLUS Stericup® 0.22 µm PES filters prior to use. Final formulations of the compositions listed in Table 26 were prepared by spiking stock solutions of methionine (20 mg/mL) and DTPA (0.1 mg/mL) into the pembro/PS80/stabilizer solution in a 96-well plate and then bringing to a final volume of 1 mL with histidine pH 5.5 buffer. The well plate was covered with a 96-well silicone sealing mat and then was vacuum sealed (2x) in moisture barrier bags to minimize potential evaporation. Samples were staged in 5 °C and 50 °C environmental stability chambers for time period of 10 days.

Table 26. Pembrolizumab Formulations Comprising Methionine and DTPA at Various Concentrations.

Form.[1]	Stabilizer	Met.[2] (mM)	DTPA (µM)	Form.[1]	Stabilizer	Met.[2] (mM)	DTPA (µM)
1N	1.4% sucrose	—	—	4R	0.8% sorbitol	10	20
1P	1.4% sucrose	5	10	4S	0.8% sorbitol	5	30
1Q	1.4% sucrose	15	10	4T	0.8% sorbitol	15	30
1R	1.4% sucrose	10	20	5N	0.4% glycine	—	—
1S	1.4% sucrose	5	30	5P	0.4% glycine	5	10
1T	1.4% sucrose	15	30	5Q	0.4% glycine	15	10
1U	1.4% sucrose	5	—	5R	0.4% glycine	10	20
1V	1.4% sucrose	10	—	5S	0.4% glycine	5	30
1W	1.4% sucrose	15	—	5T	0.4% glycine	15	30
1X	1.4% sucrose	—	10	6N	1.4 % HPBC	—	—
1Y	1.4% sucrose	—	20	6P	1.4 % HPBC	5	10
1Z	1.4% sucrose	—	30	6Q	1.4 % HPBC	15	10
2N	0.8% mannitol	—	—	6R	1.4 % HPBC	10	20
2P	0.8% mannitol	5	10	6S	1.4 % HPBC	5	30
2Q	0.8% mannitol	15	10	6T	1.4 % HPBC	15	30
2R	0.8% mannitol	10	20	7N	0.8% arginine	—	—
2S	0.8% mannitol	5	30	7P	0.8% arginine	5	10

2T	0.8% mannitol	15	30	7Q	0.8% arginine	15	10
3N	1.4% trehalose	—	—	7R	0.8% arginine	10	20
3P	1.4% trehalose	5	10	7S	0.8% arginine	5	30
3Q	1.4% trehalose	15	10	7T	0.8% arginine	15	30
3R	1.4% trehalose	10	20	7N	0.8% proline	—	—
3S	1.4% trehalose	5	30	7P	0.8% proline	5	10
3T	1.4% trehalose	15	30	7Q	0.8% proline	15	10
4N	0.8% sorbitol	—	—	7R	0.8% proline	10	20
4P	0.8% sorbitol	5	10	7S	0.8% proline	5	30
4Q	0.8% sorbitol	15	10	7T	0.8% proline	15	30

[1]All formulations comprised 5 mg/mL pembrolizumab, 10 mM Histidine buffer, pH 5.5, and 0.004% PS80 in addition to the excipients listed.
[2]Methionine

[0387] The formulations were evaluated by visual observation, turbidity (A350), UP-SEC (purity), HP-IEX (charge profile). After the 10 day test period at 50 °C, no formulations were visibly turbid or experienced a color change. Turbidity values for all formulations (with the exception of arginine formulations 7N – 7T) were very similar across the various formulations tested and closely resembled value shown in Example 9 (data not shown). From the turbidity data, the effect of the addition of different concentrations of methionine alone or in combination with different concentrations of DPTA, was not evident. Similar to the results shown in Examples 9 and 10, formulations comprising arginine showed the largest increase in % HMW species (Table 27) over the stability testing period, albeit formulations 7Q and 7T (15 mM methionine) showed slightly less % HMW species, suggesting potential increased stability of these formulations over others with lower concentrations of methionine. A similar trend was observed for all other formulations where the lowest % HMW species were observed in formulations having 15 mM methionine and at least 10 μM DTPA incorporated, although the difference was very small.

[0388] There were no appreciable differences in charge profile among any of the formulations (with the exclusion of 7C-7F which were not tested) at 50 °C for the 10-day testing period. However, there was a significant decrease in the % main peak (~ 53% → ~ 41%) and increase in the % acidic variants and % pre-main peak for all formulations when compared to the formulations stored at 5 °C for 10 days (data not shown).

Table 27. Pembrolizumab Formulations Comprising Methionine and DTPA at Various Concentrations.

Formulation	Stabilizer	Methionine (mM)	DTPA (μM)	% Aggregates (UP-SEC)	
				10 d/5 °C	*10 d/50 °C*
1N	1.4% sucrose	—	—	0.92	5.1
1P	1.4% sucrose	5	10	0.91	4.85
1Q	1.4% sucrose	15	10	0.92	4.73
1R	1.4% sucrose	10	20	0.91	4.8
1S	1.4% sucrose	5	30	0.92	4.75
1T	1.4% sucrose	15	30	0.92	4.54
1U	1.4% sucrose	5	—	0.86	4.64
1V	1.4% sucrose	10	—	0.92	4.55
1W	1.4% sucrose	15	—	0.92	4.48
1X	1.4% sucrose	—	10	0.92	4.8
1Y	1.4% sucrose	—	20	0.91	4.79
1Z	1.4% sucrose	—	30	0.87	4.82
2N	0.8% mannitol	—	—	0.86	5.37
2P	0.8% mannitol	5	10	0.92	5.14
2Q	0.8% mannitol	15	10	0.92	4.96
2R	0.8% mannitol	10	20	0.91	5.07
2S	0.8% mannitol	5	30	0.86	5.03
2T	0.8% mannitol	15	30	0.94	4.84
3N	1.4% trehalose	—	—	0.86	5.03
3P	1.4% trehalose	5	10	0.87	4.78
3Q	1.4% trehalose	15	10	0.92	4.64
3R	1.4% trehalose	10	20	0.87	4.70
3S	1.4% trehalose	5	30	0.86	4.69
3T	1.4% trehalose	15	30	0.87	4.53
4N	0.8% sorbitol	—	—	0.77	5.3
4P	0.8% sorbitol	5	10	0.93	5.1
4Q	0.8% sorbitol	15	10	0.85	4.9

4R	0.8% sorbitol	10	20	0.85	5.0
4S	0.8% sorbitol	5	30	0.91	4.94
4T	0.8% sorbitol	15	30	0.92	4.82
5N	0.4% glycine	—	—	0.9	5.12
5P	0.4% glycine	5	10	0.86	5.03
5Q	0.4% glycine	15	10	0.91	4.85
5R	0.4% glycine	10	20	0.93	4.96
5S	0.4% glycine	5	30	0.91	4.9
5T	0.4% glycine	15	30	0.89	4.75
6N	1.4 % HPBC	—	—	0.91	5.03
6P	1.4 % HPBC	5	10	0.91	5.08
6Q	1.4 % HPBC	15	10	0.92	4.85
6R	1.4 % HPBC	10	20	0.92	4.98
6S	1.4 % HPBC	5	30	0.91	5.13
6T	1.4 % HPBC	15	30	0.87	4.9
7N	0.8% arginine	—	—	1.32	30.89
7P	0.8% arginine	5	10	1.34	30.12
7Q	0.8% arginine	15	10	1.54	27.09
7R	0.8% arginine	10	20	1.54	28.89
7S	0.8% arginine	5	30	1.54	29.82
7T	0.8% arginine	15	30	1.53	27.39
7N	0.8% proline	—	—	0.93	5.21
7P	0.8% proline	5	10	0.86	4.93
7Q	0.8% proline	15	10	0.92	4.81
7R	0.8% proline	10	20	0.92	4.87
7S	0.8% proline	5	30	0.92	5.04
7T	0.8% proline	15	30	0.91	4.85

[0389] HP-HIC analysis was performed on select formulations shown in Table 27 in order to assess the impact of methionine and DTPA concentrations on stability and oxidation after 10 days at 50°C. Results for formulations 1N, 1Q and 1T indicate that the presence of 15 mM

methionine resulted in the smallest change in oxidation over the stability time period. Overall, the results shown in Table 28 demonstrated that the addition of methionine to formulations resulted in a reduced oxidation rate in a concentration dependent manner (formulations 1U – 1W). No additional benefit was observed upon addition of DTPA (formulations 1X – 1Z) as a chelator even in conjunction with the addition of methionine (formulations 1N – 1T).

Table 28. Pembrolizumab Formulations Comprising Methionine and DTPA at Various Concentrations.

Formulation	Stabilizer	Methionine (mM)	DTPA (μM)	Met-105 (HP-HIC)	
				10 d/5 °C	*10 d/50 °C*
1N	1.4% sucrose	—	—	8.45	23.50
1P	1.4% sucrose	5	10	6.87	11.36
1Q	1.4% sucrose	15	10	6.69	11.56
1R	1.4% sucrose	10	20	6.90	9.38
1S	1.4% sucrose	5	30	7.13	11.15
1T	1.4% sucrose	15	30	6.80	8.56
1U	1.4% sucrose	5	—	6.91	10.11
1V	1.4% sucrose	10	—	6.76	8.88
1W	1.4% sucrose	15	—	6.71	8.37
1X	1.4% sucrose	—	10	8.00	25.05
1Y	1.4% sucrose	—	20	8.43	24.94
1Z	1.4% sucrose	—	30	8.16	25.37

EXAMPLE 13

Evaluation of the Effect of pH on the Stability of Low Concentration Pembrolizumab Formulations in Combination with Methionine

[0390] An additional study was undertaken to evaluate the impact of histidine buffer on the stability of pembrolizumab formulations. In order to do so, formulations shown in Example 9 were prepared in water-for-injection (without pH adjustment) instead of 10 mM histidine pH 5.5. Pembrolizumab drug substance (~45 mg/mL) in 10 mM histidine pH 5.5 buffer was dialyzed with water-for-injection (WFI) to a final concentration of 15.5 mg/mL. Pembrolizumab (15.5 mg/mL)/PS80 (0.16 mg/mL) stock solution was prepared by addition of PS80 to pembrolizumab

solution (15.5 mg/mL) in WFI followed by filtration through a SteriFlip® 0.22 µm PVE filter unit. Formulations to be tested were prepared by spiking excipient stock solutions (prepared in WFI and filtered through 0.22 µm PVE filter) into pembrolizumab/PS80 stock solutions to yield concentrations shown in Table 29. Similar to the study in Examples 9 & 10, 10 mM methionine and either 20 µM DTPA or 50 µM EDTA was added to assess the ability to reduce aggregation over the stability testing period. Formulations were prepared in a 96-well plate with a final drug product volume of 1 mL. The well plate was sealed with a silicone sealing mat prior to vacuum sealing in moisture barrier bags (2 times). Formulations were staged at 5 °C and 50 °C for 10 days.

Table 29. Low Concentration Pembrolizumab Formulations Prepared in WFI.

Form.[1]	Stabilizer	Anti-Oxidant (10 mM)	Metal Chelator	Form.[1]	Stabilizer	Anti-Oxidant (10 mM)	Metal Chelator
1A'	1.4% sucrose	—	—	5A'	0.4% glycine	—	—
1B'	1.4% sucrose	Met	—	5B'	0.4% glycine	Met	—
1C'	1.4% sucrose	—	DTPA	5C'	0.4% glycine	—	DTPA
1D'	1.4% sucrose	Met	DTPA	5D'	0.4% glycine	Met	DTPA
1E'	1.4% sucrose	—	EDTA	5E'	0.4% glycine	—	EDTA
1F'	1.4% sucrose	Met	EDTA	5F'	0.4% glycine	Met	EDTA
2A'	0.8% mannitol	—	—	6A'	1.4% HPBC	—	—
2B'	0.8% mannitol	Met	—	6B'	1.4% HPBC	Met	—
2C'	0.8% mannitol	—	DTPA	6C'	1.4% HPBC	—	DTPA
2D'	0.8% mannitol	Met	DTPA	6D'	1.4% HPBC	Met	DTPA
2E'	0.8% mannitol	—	EDTA	6E'	1.4% HPBC	—	EDTA
2F'	0.8% mannitol	Met	EDTA	6F'	1.4% HPBC	Met	EDTA
3A'	1.4% trehalose	—	—	7A'	0.8% arginine	—	—
3B'	1.4% trehalose	Met	—	7B'	0.8% arginine	Met	—
3C'	1.4% trehalose	—	DTPA	7C'	0.8% arginine	—	DTPA

3D'	1.4% trehalose	Met	DTPA	7D'	0.8% arginine	Met	DTPA
3E'	1.4% trehalose	—	EDTA	7E'	0.8% arginine	—	EDTA
3F'	1.4% trehalose	Met	EDTA	7F'	0.8% arginine	Met	EDTA
4A'	0.8% sorbitol	—	—	8A'	0.8% proline	—	—
4B'	0.8% sorbitol	Met	—	8B'	0.8% proline	Met	—
4C'	0.8% sorbitol	—	DTPA	8C'	0.8% proline	—	DTPA
4D'	0.8% sorbitol	Met	DTPA	8D'	0.8% proline	Met	DTPA
4E'	0.8% sorbitol	—	EDTA	8E'	0.8% proline	—	EDTA
4F'	0.8% sorbitol	Met	EDTA	8F'	0.8% proline	Met	EDTA

[1] All formulations comprised 5 mg/mL pembrolizumab and 0.004% PS80 in addition to the excipients listed.

[0391] The prepared formulations were tested by visual appearance, differential scanning fluorimetry (thermal unfolding), turbidity, UP-SEC (purity), and HP-IEX (charge profile). No formulations exhibited a color change or were visibly turbid upon removing from stability conditions. The measured turbidity values were very similar across all formulations tested. In contrast to turbidity results measure for arginine formulations prepared in 10 mM histidine pH 5.5 buffer (7A – 7F, Examples 1 and 2), formulations prepared in WFI (7A' – 7F') showed significantly lower turbidity values after the stability testing period (data not shown).

[0392] In comparison to formulations prepared in Examples 9 and 10, analogous formulations prepared in WFI showed a moderate improvement in thermal unfolding behavior through a shift in Tm1 to higher temperature (Table 30). Exceptions to this statement are mannitol formulations 2E' (EDTA) and 2F' (Met + EDTA) which showed almost identical Tm1 values to those formulations prepared in Examples 9 and 10 (data not shown). Formulations 6A' – 6F' showed no thermal transitions presumably as a result of SYPRO™ dye preferentially binding to the cyclodextrin pocket. For all formulations tested, the presence of EDTA (50 μM) alone as the metal chelator resulted in lower Tm1 values than corresponding formulations with Met, Met + DTPA , DTPA, or Met + EDTA.

[0393] The change in pH of the unbuffered formulations was measured over the stability testing period to assess the self-buffering ability of the pembrolizumab formulations (see Table 30). Formulations 1-5F' (Met + EDTA) showed the smallest change in pH over 10 days at 50

°C. For Cavitron® (HPBC) formulations (6A' – 6F') the smallest change in pH was observed in formulation 6B' which utilized methionine, while the smallest change in pH observed for arginine formulations (7A'- 7F') was observed in formulation 7A' (no methionine or metal chelator).

Table 30. Pembrolizumab Formulations Prepared in WFI.

Form.	Stabilizer	Anti-Oxidant (10 mM)	Metal Chelator	DSF (thermal unfolding)	pH	
				Tm1 (°C)	10 days/ 5 °C	10 days/ 50 °C
1A'	1.4% sucrose	—	—	66.0	5.92	5.71
1B'	1.4% sucrose	Met	—	60.8	6.22	5.73
1C'	1.4% sucrose	—	DTPA	65.4	6.00	5.53
1D'	1.4% sucrose	Met	DTPA	58.6	6.02	5.52
1E'	1.4% sucrose	—	EDTA	60.8	6.22	5.77
1F'	1.4% sucrose	Met	EDTA	65.2	5.79	5.75
2A'	0.8% mannitol	—	—	66.8	6.16	5.42
2B'	0.8% mannitol	Met	—	65.6	6.15	5.61
2C'	0.8% mannitol	—	DTPA	65.2	6.06	5.52
2D'	0.8% mannitol	Met	DTPA	65.0	5.92	5.52
2E'	0.8% mannitol	—	EDTA	58.6	5.45	5.71
2F'	0.8% mannitol	Met	EDTA	58.6	5.59	5.72
3A'	1.4% trehalose	—	—	65.4	6.14	5.78
3B'	1.4% trehalose	Met	—	65.8	6.33	5.80
3C'	1.4% trehalose	—	DTPA	65.4	6.07	5.63
3D'	1.4% trehalose	Met	DTPA	65.0	5.97	5.64
3E'	1.4% trehalose	—	EDTA	61.4	5.84	5.79
3F'	1.4% trehalose	Met	EDTA	65.6	5.79	5.82
4A'	0.8% sorbitol	—	—	65.4	6.01	5.85
4B'	0.8% sorbitol	Met	—	65.4	6.29	5.85
4C'	0.8% sorbitol	—	DTPA	66.0	6.04	5.66
4D'	0.8% sorbitol	Met	DTPA	65.6	6.02	5.67

4E'	0.8% sorbitol	—	EDTA	61.2	5.78	5.80
4F'	0.8% sorbitol	Met	EDTA	65.6	5.71	5.81
5A'	0.4% glycine	—	—	66.6	6.25	5.91
5B'	0.4% glycine	Met	—	65.2	6.33	5.91
5C'	0.4% glycine	—	DTPA	65.2	6.10	5.76
5D'	0.4% glycine	Met	DTPA	66.2	6.07	5.75
5E'	0.4% glycine	—	EDTA	65.4	6.04	5.90
5F'	0.4% glycine	Met	EDTA	65.4	5.92	5.89
6A'	1.4% HPBC	—	—	—	6.17	5.82
6B'	1.4% HPBC	Met	—	—	6.20	5.90
6C'	1.4% HPBC	—	DTPA	—	6.17	5.68
6D'	1.4% HPBC	Met	DTPA	—	6.04	5.66
6E'	1.4% HPBC	—	EDTA	—	6.23	5.87
6F'	1.4% HPBC	Met	EDTA	—	6.24	5.87
7A'	0.8% arginine	—	—	64.2	6.02	5.92
7B'	0.8% arginine	Met	—	58.8	6.21	5.95
7C'	0.8% arginine	—	DTPA	58.6	6.10	5.81
7D'	0.8% arginine	Met	DTPA	63.4	6.03	5.78
7E'	0.8% arginine	—	EDTA	64.2	6.24	5.85
7F'	0.8% arginine	Met	EDTA	64.2	6.21	5.94
8A'	0.8% proline	—	—	61.6	6.29	5.87
8B'	0.8% proline	Met	—	59.2	6.28	5.90
8C'	0.8% proline	—	DTPA	65.8	6.14	5.78
8D'	0.8% proline	Met	DTPA	59.0	6.11	5.73
8E'	0.8% proline	—	EDTA	59.0	6.30	5.93
8F'	0.8% proline	Met	EDTA	65.0	6.29	5.92

[0394] The amount of aggregation of each of the formulations over a 10 day time period at 50 °C was also measured by UP-SEC. The % mAb and % aggregates (HMW species) for all formulations tested were very similar with the exception of formulations 7A' – 7F' (arginine formulations), which showed an increase in the % HMW species (~ 4%). From the UP-SEC

data there was no clear evidence that the addition of methionine (10 mM), DTPA (20 μM), EDTA (50 μM) or combinations thereof, significantly reduced aggregation.

[0395] Charge profiles of formulations after 10 days at 50 °C was determined by HP-IEX (data not shown). All formulations showed similar charge profiles for each stabilizer tested. A significant decrease in the % main peak (~ 53% → ~ 41%) and increase in the % acidic variants and % pre-main peak for all formulations was observed when compared to the formulations stored at 5 °C for 10 days (data not shown). Formulations prepared in WFI showed higher % acidic peaks (~28%) with comparable % pre-main peak and % basic variants to analogous formulations in Examples 9 and 10 after 10 days at 50 °C. The addition of methionine, DTPA, EDTA, or combinations thereof, to the formulations did not result in any significant change in charge profile.

EXAMPLE 14

Development of a High Concentration Lyophilized Drug Product Formulation Comprising Pembrolizumab

[0396] A summary of the design of experiments and results from all the drug product batches is provided in Table 32. All formulations contained histidine buffer (pH 5.5) and polysorbate 80 (PS 80) as a surfactant. Various test formulations were manufactured using different cryoprotectants, stabilizers, etc., with varied concentrations of pembrolizumab and excipients. The following pembrolizumab drug substance batches were used to formulate the test formulations for the studies:

- 204 mg/mL pembrolizumab in 10 mM Histidine buffer, pH 5.5
- 288 mg/mL pembrolizumab in 3% Arginine.HCl, 10 mM Histidine buffer, pH 5.5

[0397] The lyophilization processes used for the studies were conducted using a model LYOSTAR 3 (SP Scientific) as described in Table 31.

[0398] Batch 0021: Batch 0021 was manufactured starting with 103 mg/mL pembrolizumab formulated in sucrose. A volume of 2.30 mL was filled in 2R vials, 6R vials and 10R vials. A 55 hour lyophilization cycle was used ("lyo cycle A," see Table 31). Post-lyophilization, the residual moisture, syringeable volume, and expansion volume were measured. Generally a range of reconstitution times 17 – 28 minutes were observed.

[0399] Batch 0022: Batch 0022 was manufactured starting with 48 – 103 mg/mL pembrolizumab formulated in various combinations of sucrose, mannitol and arginine hydrochloride (Arg.HCl). A volume of 2.30 – 4.97 mL was filled in 2R vials, 6R vials, 10R vials and 10R vials. A longer primary drying extended by 5 hours was adopted. Thus, the

lyophilization cycle used was similar to lyophilization cycle A, extended to 60 hours ("lyo cycle B" see Table 31). Generally, reconstitution times ranged from 4 to 23 minutes. The residual moisture was from 0.24 – 0.26%.

[0400] Batch 0024: Batch 0024 was manufactured starting with 104 – 200 mg/mL pembrolizumab formulated in various combinations of sucrose and arginine hydrochloride (Arg.HCl). Drug substance used was 288 mg/mL pembrolizumab in 3% Arg, 10 mM His pH 5.5. A volume of 1.24 – 2.30 mL was filled in 2R vials. For the lyophilization process, one shelf was fully loaded with 7% sucrose vials. The secondary drying time was reduced from 8 hours to 6 hours. Thus, the lyophilization cycle used had a 2 hour shorter secondary drying time compared to lyophilization cycle A ("lyo cycle C" see Table 31). Generally, reconstitution times ranged from 37 to 42 minutes. There were some difficulties in dissolving the lyophilization cake, which were not improved by the introduction of a centrifugation step. The residual moisture measured was 0.27%.

[0401] Batch 0025: Batch 0025 was formulated with 25 mg/mL pembrolizumab formulated in sucrose. A volume of 10.66 mL was filled in 15R vials. A conservative version of lyophilization cycle A was adopted (approx. 136 hours, ("lyo cycle D" see Table 31). Among other changes, a longer primary drying step was used. Generally, reconstitution times ranged from 2 minutes, 20 sec to 4 minutes, 40 seconds. The residual moisture was from 0.4 – 0.5%.

[0402] Batch 0027: Batch 0027 was formulated with 25 mg/mL and 35 mg/mL pembrolizumab in sucrose. A volume of 6.8 – 9.5 mL was filled in 15R vials. A conservative version of lyophilization cycle A was adopted (~ 136 hours, "lyo cycle E" see Table 31) with a longer primary drying step comprised of a two-step drying process (- 20°C and -10°C). Vials were reconstituted with a lower volume (1.0 mL) of water. Generally, reconstitution times ranged from 4 minutes, 20 seconds to 6 minutes, 15 seconds. The residual moisture was from 0.14 – 0.17%. The rate of the syringe out of the reconstitution was extremely slow and difficult with a 3-mL syringe fitted with a 27G ½" needle.

[0403] Batch 0028: Batch 0028 was formulated with (1) 25 mg/mL or 35 mg/mL pembrolizumab in sucrose, (volume of 6.78 – 9.6 mL, filled in 15R or 20R vials) or (2) 35 mg/mL pembrolizumab in arginine (volume 6.78 mL filled in 15R vials). Lyophilization cycle A was used without changes (approx. 55 hours). These vials were reconstituted with 1.2 mL water. Generally, reconstitution times ranged from 5 minutes, 10 seconds to 6 minutes, 15 seconds. The residual moisture was from 0.60 – 0.85%. 3-mL syringes fitted with 27G ½" needles were easier to fill and empty with the Arginine-containing reconstituted solution as compared to the sucrose formulations, which was assumed to be a result of viscosity.

[0404] This example evaluated lyophilized formulations that were made with starting solutions comprising 200 mg pembrolizumab at protein concentrations between 48 mg/mL – 200 mg/mL. All formulations were lyophilized to yield a white cake. Following lyophilization, the cakes were reconstituted with SWFI and the reconstituted solutions were evaluated for tonicity, viscosity and reconstitution time. Lyo cakes were reconstituted with lesser water than the fill volume to achieve an approximate concentration of 167 mg/mL (i.e. 200 mg/vial). The lyo cakes manufactured with high concentration pre-lyo solutions (> 100 mg/mL) were generally more compact in nature.

[0405] Reconstitution times for the different formulations varied from 2 to 42 minutes (see Table 32). In general, reconstitution times were longer with increasing protein concentration of pre-lyo solution. Results of the analysis of the reconstituted solution indicate that arginine hydrochloride had similar effect in reducing the reconstitution time as the excipients tested, but may help lower viscosity of the reconstituted solution. The impact of other excipients (e.g., sucrose, mannitol) and lyophilization process parameters on the reconstitution times were found to be negligible.

Table 31. Lyophilization Cycles Used for Example 14

Batch No. / Lyo Cycle	Freezing	Primary Drying	Secondary Drying
0021 Cycle A	Load 5°C Ramp to -10°C, 20m Hold at -10°C, 1h Ramp to -50°C, 2h 40m Hold at -50°C, 1h Ramp to -10°C, 1h 20m Hold at -10°C, 3h Ramp to -50°C, 2h 40m Hold at -50°C, 1h	Pressure set to 113 mTorr Ramp to -15°C, 45m Hold at -15°C, 24h Ramp to -5°C, 5h	Pressure set to 113 mTorr Ramp to 30°C, 1h 10m Hold at 30°C, 8h Ramp to 5°C, 30m Backfill with nitrogen
0022 Cycle B	Load 5°C Ramp to -10°C, 20m Hold at -10°C, 1h Ramp to -50°C, 2h 40m Hold at -50°C, 1h Ramp to -10°C, 1h 20m Hold at -10°C, 3h Ramp to -50°C, 2h 40m Hold at -50°C, 1h	Pressure set to 113 mTorr Ramp to -15°C, 45m Hold at -15°C, 29h Ramp to -5°C, 5h	Pressure set to 113 mTorr Ramp to 30°C, 1h 10m Hold at 30°C, 8h Ramp to 5°C, 30m Backfill with nitrogen
0024 Cycle C	Load 5°C Ramp to -10°C, 20m Hold at -10°C, 1h Ramp to -50°C, 2h 40m Hold at -50°C, 1h	Pressure set to 113 mTorr Ramp to -15°C, 45m Hold at -15°C, 29h Ramp to -5°C, 5h	Pressure set to 113 mTorr Ramp to 30°C, 1h 10m Hold at 30°C, 6h Ramp to 5°C, 30m

Batch No. / Lyo Cycle	Freezing	Primary Drying	Secondary Drying
	Ramp to -10°C, 1h 20m Hold at -10°C, 3h Ramp to -50°C, 2h 40m Hold at -50°C, 1h		Backfill with nitrogen
0025 Cycle D	Load 5°C Ramp to -10°C, 20m Hold at -10°C, 1h Ramp to -50°C, 2h 40m Hold at -50°C, 1h Ramp to -10°C, 1h 20m Hold at -10°C, 3h Ramp to -50°C, 2h 40m Hold at -50°C, 1h	Pressure set to 113 mTorr Ramp to -20°C, 2h Hold at -20°C, 103h Ramp to -5°C, 7h 30m	Pressure set to 113 mTorr Ramp to 30°C, 1h 10m Hold at 30°C, 8h Ramp to 5°C, 30m Backfill with nitrogen
0027 Cycle E	Load 5°C Ramp to -10°C, 20m Hold at -10°C, 1h Ramp to -50°C, 2h 40m Hold at -50°C, 1h Ramp to -10°C, 1h 20m Hold at -10°C, 3h Ramp to -50°C, 2h 40m Hold at -50°C, 1h	Pressure set to 113 mTorr Ramp to -20°C, 5h Hold at -20°C, 60h Ramp to -15°C, 3h Hold at -15°C, 31h Ramp to -5°C, 9h	Pressure set to 113 mTorr Ramp to 30°C, 6h Hold at 30°C, 8h Ramp to 5°C, 30m Backfill with nitrogen
0028 Cycle A	Load 5°C Ramp to -10°C, 20m Hold at -10°C, 1h Ramp to -50°C, 2h 40m Hold at -50°C, 1h Ramp to -10°C, 1h 20m Hold at -10°C, 3h Ramp to -50°C, 2h 40m Hold at -50°C, 1h	Pressure set to 113 mTorr Ramp to -15°C, 45m Hold at -15°C, 24h Ramp to -5°C, 5h	Pressure set to 113 mTorr Ramp to 30°C, 1h 10m Hold at 30°C, 8h Ramp to 5°C, 30m Backfill with nitrogen

Table 32. Results Summary for Lyophilization Experiments

Batch #	Experiment	Formulation (pre-lyo)	Fill (mL)/vial(s)	Reconstituted Formulation	Properties (% moisture, reconstitution data, etc.)		
0021	103 mg/mL with sucrose	6.18 mM his pH 5.5, 4.32% suc, 0.01% PS 80	Fill 2.3 mL/ 2R, 6R, 10R vials	166.7 mg/mL pembro, 10 mM his pH 5.5, 7% suc, 0.02% PS 80	6R: 0.10%; 1.0mL water – 21m (170 mg/mL)	10R: 0.11%; 1.0mL water – 17m	2R: 0.13%; 1.0mL water – 28m
0022 A	103 mg/mL with Mannitol/ Sucrose	6.2 mM His, 1.04% Suc, 2.6% mannitol, 0.12% PS80	2.3 mL in 2R and 6R vials	166.7 mg/mL pembro, 4.2% Mannitol, 1.68% Suc, 10 mM His, 0.02% PS80	23 m with 1.1 mL water		
0022 B	75 mg/mL with Sucrose	4.5 mM His, 3.15%	3.2 mL in 6R, 10R vials	166.7 mg/mL pembro, 10 mM	15 m with 1.1 mL water		

Batch #	Experiment	Formulation (pre-lyo)	Fill (mL)/vial(s)	Reconstituted Formulation	Properties (% moisture, reconstitution data, etc.)		
		Suc, 0.014% PS 80		His, 7% Suc, 0.03% PS 80			
0022 C	55.3 mg/mL with Sucrose	2.32% Suc, 3.32 mM His, 0.01% PS 80	4.34 mL in 10R, 15R vials	166.7 mg/mL pembro, 7% Suc, 10 mM His, 0.03% PS-80	4 m with 1.1 mL water (131.6 mg/mL)	Moisture 0.21% (15 mL vial)	
0022 D	48.33 mg/mL with Suc/Arg	1% Arg, 1.83% Suc, 3.32 mM His, 0.01% PS-80	4.97 mL in 10R, 15R vials	166.7 mg/mL pembro, 3% Arg, 5.5% Suc, 10 mM His, 0.03% PS-80	5 m with 1.1 mL water in 10R vial (142.9 mg/mL)	4 m with 1.1 mL water in 15R vial (158.8 mg/mL)	Moisture 0.24% (10 mL vial), 0.26% (15 mL vial)
0022 E	55.3 mg/mL with Arg	1% Arg, 3.32 mM His, 0.01% PS 80	4.34 mL in 15R vials	166.7 mg/mL pembro, 3% Arg, 10 mM His, 0.03% PS-80	10 m with 1.1 mL water (173 mg/mL)		
0024 A	104 mg/mL with Suc/Arg	3.13% Suc, 1.25% Arg.HCl, 0.01% PS-80 in 6.26 mM His	2.3 mL in 2R vials	166.7 mg/mL pembro, 5% Suc, 2% Arg, 0.02% PS-80 in 10 mM His	40 m with 1.2 mL water, 169.4 mg/mL; with 0.9% saline > 50 m	Centrifuge reconst: 45 m, no foaming (x 1000 - 3000 g)	Could not be dissolved in methanol
0024 B	104 mg/mL with Suc/Arg	2.32% Suc, 1.25% Arg.HCl, 0.01% PS-80 in 6.26 mM His	2.3 mL in 2R vials	166.7 mg/mL pembro 3.7% Suc, 2% Arg, 0.02% PS 80, 10 mM His	37 m with 1.2 mL water, 165.3 mg/mL	Centrifuge reconst: 35 m, no foaming (x 1000 - 3000 g)	Moisture 0.27%
0024 C	200 mg/mL with Suc/Arg	3.7% Suc, 2.08% Arg.HCl, 0.02% PS-80 in 10 mM His	1.24 mL in 2R vials	166.7 mg/mL pembro, 3.7% Suc, 2% Arg, 0.02% PS 80, 8.3 mM His	42 m with 1.2 mL water, 173.7 mg/mL	Centrifuge reconst: 45 m, no foaming (x 3000 g)	Could not be dissolved in methanol
0025 A	25 mg/mL with Sucrose	1.05% Suc, 1.5 mM His, 0.003% PS-80	10.66 mL in 15R vial	166.7 mg/mL pembro, 7% Suc, 0.02% PS 80,10 mM His	4 m 40 s with 1.2 mL water; 183 mg/mL	Moisture 0.5%	
0025 B	25 mg/mL with Sucrose	2.10% Suc, 1.5 mM His, 0.003% PS-80	10.66 mL in 15R vial	166.7 mg/mL pembro, 14% Suc, 0.02% PS 80, 10 mM His	2 m 20 s with 1.2 mL water; 173 mg/mL	Moisture 0.4%	
0027 A	35 mg/mL with Sucrose	1.47% Suc, 2.1 mM His, 0.004% PS-80	6.8 mL in 15R vials	166.7 mg/mL pembro, 7% Suc, 0.02% PS 80,10 mM His	6 m 15 s with 1.0 mL water (189 mg/mL)	Moisture 0.17%	1.1 mL solution syringed out; rate – very slow with 3-mL

Batch #	Experiment	Formulation (pre-lyo)	Fill (mL)/vial(s)	Reconstituted Formulation	Properties (% moisture, reconstitution data, etc.)		
							syringe fitted with a 27G ½" needle
0027 B	25 mg/mL with Suc	1.05% Suc, 1.5 mM His, 0.003% PS-80	9.5 mL in 15R and 20R vials	166.7 mg/mL pembro, 7% Suc, 0.02% PS 80,10 mM His	4 m 20 s with 1.0 mL water (194 mg/mL)	Moisture 0.16% (15R vial); 0.14% (20R vial)	1.1 mL solution syringed out; rate – very slow with 3-mL syringe fitted with a 27G ½" needle
0028 A	35 mg/mL with Suc	1.454% Suc, 2.07 mM His, 0.004% PS-80	6.78 mL in 15R vials	166.7 mg/mL pembro, 7% Suc, 0.02% PS-80 in 10 mM His	5m 20s with 1.2 mL water (166 mg/mL)	Moisture 0.60%	Vol of DP syringed out, 3mL syr+27G 0.5" needle (mL) = 1.3 mL (Label vol = 1.2 mL)
0028 B	25 mg/mL with Suc	1.04% Suc, 1.48 mM His, 0.003% PS-80	9.60 mL in 20R vials	166.7 mg/mL pembro, 7% Suc, 0.02% PS-80 in 10 mM His	6m 15s with 1.2 mL water (165 mg/mL)	Moisture 0.85%	Vol of DP syringed out, 3mL syr+27G 0.5" needle (mL) = 1.3 mL (Label vol = 1.2 mL)
0028 C	35 mg/mL with Arg.HCl	0.623% Arg, 2.07 mM His, 0.0042% PS-80	6.78 mL in 15R vials	166.7 mg/mL pembro, 3% Arg, 0.02% PS-80 in 10 mM His	5m 10s with 1.2 mL water (169 mg/mL)	Moisture 0.81%	Vol of DP syringed out, 3mL syr+27G 0.5" needle (mL) = 1.3 mL (Label vol = 1.2 mL); easier to fill in the syringe

WHAT IS CLAIMED IS:

1. An anti-human programmed death receptor 1 (PD-1) antibody formulation, comprising:

a) about 5 mg/mL to about 200 mg/mL of an anti-human PD-1 antibody;

b) about 5 mM to about 20 mM acetate or citrate buffer;

c) a stabilizer selected from the group consisting of:

i) about 6 % to about 8 % weight/volume (w/v) sucrose, trehalose or (2-hydroxypropyl)-β-cyclodextrin;

ii) about 3 % to about 5 % w/v mannitol, sorbitol, L-arginine, a pharmaceutically acceptable salt of L-arginine, L-proline, or a pharmaceutically acceptable salt of L-proline; and

iii) about 1.8 % to about 2.2 % w/v glycine, or a pharmaceutically acceptable salt thereof;

d) about 0.01 % to about 0.10 % non-ionic surfactant;

wherein the non-ionic surfactant is polysorbate 80, polysorbate 20, or poloxamer 188, and

wherein the anti-human PD-1 antibody is pembrolizumab.

2. The anti-human PD-1 antibody formulation of claim 1, wherein the formulation has a pH between 5.0 and 6.0.

3. The anti-human PD-1 antibody formulation of claim 1, wherein the buffer is acetate.

4. The anti-human PD-1 antibody formulation of claim 1, wherein the buffer is citrate.

5. The anti-human PD-1 antibody formulation of claim 1, further comprising about 1 % to about 3 % w/v L-arginine, or a pharmaceutically acceptable salt thereof.

6. The anti-human PD-1 antibody formulation of claim 1, wherein the stabilizer is about 6 % to about 8 % weight/volume (w/v) sucrose.

7. The anti-human PD-1 antibody formulation of claim 1, wherein the stabilizer is about 6 % to about 8 % weight/volume (w/v) trehalose.

8. The anti-human PD-1 antibody formulation of claim 1, wherein the stabilizer is about 6 % to about 8 % weight/volume (w/v) (2- hydroxypropyl)-β-cyclodextrin.

9. The anti-human PD-1 antibody formulation of claim 1, wherein the stabilizer is about 3 % to about 5 % w/v mannitol.

10. The anti-human PD-1 antibody formulation of claim 1, wherein the stabilizer is 3 % to about 5 % w/v sorbitol.

11. The anti-human PD-1 antibody formulation of claim 1, wherein the stabilizer is 3 % to about 5 % w/v L-arginine or a pharmaceutically acceptable salt of L-arginine.

12. The anti-human PD-1 antibody formulation of claim 1, wherein the stabilizer is 3 % to about 5 % w/v L-proline, or a pharmaceutically acceptable salt of L-proline.

13. The anti-human PD-1 antibody formulation of claim 1, wherein the stabilizer is about 1.8 % to about 2.2 % w/v glycine, or a pharmaceutically acceptable salt thereof.

14. The anti-human PD-1 antibody formulation of claim 1, wherein the non-ionic surfactant is polysorbate 80.

15. The anti-human PD-1 antibody formulation of claim 1, wherein the non-ionic surfactant is polysorbate 20.

16. The anti-human PD-1 antibody formulation of claim 1, wherein the non-ionic surfactant is poloxamer 188.

17. The anti-human PD-1 antibody formulation of claim 1, wherein the formulation further comprises about 1 mM to about 20 mM anti-oxidant.

18. The anti-human PD-1 antibody formulation of claim 17, wherein the anti-oxidant is L-methionine, or a pharmaceutically acceptable salt thereof.

19. The anti-human PD-1 antibody formulation of claim 18, wherein the L-methionine is L-methionine HCl.

20. The anti-human PD-1 antibody formulation of claim 1, wherein the formulation is a liquid formulation.

21. The anti-human PD-1 antibody formulation of claim 1, wherein the concentration of pembrolizumab is about 25 mg/mL to about 100 mg/mL.

22. The anti-human PD-1 antibody formulation of claim 1, wherein the concentration of pembrolizumab is about 25 mg/mL.

23. The anti-human PD-1 antibody formulation of claim 1, wherein the concentration of pembrolizumab is about 165 mg/mL to about 170 mg/mL.

24. A method of treating cancer in a human patient in need thereof, the method comprising administering to the human patient an effective amount of an anti-human PD-1 antibody formulation comprising:

a) about 5 mg/mL to about 200 mg/mL of an anti-human PD-1 antibody;

b) about 5 mM to about 20 mM acetate or citrate buffer;

c) a stabilizer selected from the group consisting of:

i) about 6 % to about 8 % weight/volume (w/v) sucrose, trehalose or (2-hydroxypropyl)-β-cyclodextrin;

ii) about 3 % to about 5 % w/v mannitol, sorbitol, L-arginine, a pharmaceutically acceptable salt of L-arginine, L-proline, or a pharmaceutically acceptable salt of L-proline; and

iii) about 1.8 % to about 2.2 % w/v glycine, or a pharmaceutically acceptable salt thereof;

d) about 0.01 % to about 0.10 % non-ionic surfactant;

wherein the non-ionic surfactant is polysorbate 80, polysorbate 20, or poloxamer 188, and

wherein the anti-human PD-1 antibody is pembrolizumab.

25. The method of claim 24, wherein the concentration of pembrolizumab is about 25 mg/mL.

26. The method of claim 24, wherein the concentration of pembrolizumab is about 165 mg/mL to about 170 mg/mL.

27. The method of claim 24, wherein the formulation is administered by subcutaneous administration.

28. The method of claim 24, wherein the cancer is selected from the group consisting of: melanoma, lung cancer, head and neck cancer, bladder cancer, breast cancer, gastrointestinal cancer, multiple myeloma, hepatocellular cancer, lymphoma, renal cancer, mesothelioma, ovarian cancer, esophageal cancer, anal cancer, biliary tract cancer, colorectal cancer, cervical cancer, thyroid cancer, salivary cancer, prostate cancer (e.g. hormone refractory prostate adenocarcinoma), pancreatic cancer, colon cancer, esophageal cancer, liver cancer, thyroid cancer, glioblastoma, glioma, and other neoplastic malignancies.

29. The anti-human PD-1 antibody formulation of claim 24, wherein the buffer is acetate.

30. The anti-human PD-1 antibody formulation of claim 24, wherein the buffer is citrate.

ABSTRACT OF THE DISCLOSURE

The invention relates to stable formulations of antibodies against human programmed death receptor PD-1, or antigen binding fragments thereof. In some embodiments the formulations of the invention comprise between 5-200 mg/mL anti- PD-1 antibody, or antigen binding fragment thereof. The invention further provides methods for treating various cancers with stable formulations of the invention. In some embodiments of the methods of the invention, the formulations are administered to a subject by intravenous or subcutaneous administration.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (11-23)

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

First Named Inventor:	Manoj K. SHARMA	Nonprovisional Application Number (if known):	24439-US-CNT-4
Title of Invention:	STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF		

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

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

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

3. The applicable box is checked below:

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

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via USPTO patent electronic filing system.

---OR---

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

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

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

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

Signature /Patrick Rehfuss, Reg. No. 75,367/	Date 09/19/2025
Name (Print/Typed) Patrick Rehfuss	Practitioner Registration Number 75,367

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

☑ *Total of 1 forms are submitted.

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9) the Office of Personnel Management (OPM) for personnel research purposes; and

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PTO/SB/08a (01-25)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Application Number	
Filing Date	
First Named Inventor	Manoj K. SHARMA
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	24439-US-CNT-4

U.S. PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Inventor of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT		
	Application Number	
	Filing Date	
	First Named Inventor	Manoj K. SHARMA
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	24439-US-CNT-4

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	38	3176181	EP	A1	2017-06-07	Akeso Biopharma Inc.		☐
	39	3117837	EP	A1	2017-06-18	Bayer Healthcare LLC		☐
	40	2691112	EP	B1	2018-05-23	Merck Sharp & Dohme Corp.		☐

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	41	3357508	EP	A1	2018-08-08	Suzhou Suncadia Biopharmaceuticals Co., Ltd. et al		☐
	42	3636752	EP	A1	2020-04-15	Alteogen, Inc.		☐
	43	3785701	EP	A1	2021-03-03	Alteogen, Inc.		☐
	44	2005502589	JP	A	2005-01-27	Shenoy, Bhami		☐
	45	2005536285	JP	A	2005-12-02	PHARMACIA		☐
	46	2006502116	JP	A	2006-01-19	MEDAREX INC.		☐
	47	2006249081	JP	A	2006-09-21	PHARMACIA & UPJOHN CO LLC		☐
	48	2010507670	JP	A	2010-03-11	Borhani, David W		☐
	49	2013517309	JP	A	2013-05-16	RAVURI, SATYA KRISHNA KISHORE		☐
	50	2013518896	JP	A	2013-05-23	Schultheiss, Nathan C et al.		☐
	51	2013543505	JP	A	2013-12-05	REGENERON PHARMACEUTICALS INC.		☐

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	52	2014515017	JP	A	2014-06-26	Sharma, Manoj K		☐
	53	2014525915	JP	A	2014-10-02	REGENERON PHARMACEUTICALS INC.		☐
	54	2015528464	JP	A	2015-09-28	BAYER HEALTHCARE		☐
	55	2015528465	JP	A	2015-09-28	BAYER HEALTHCARE		☐
	56	2016525117	JP	A	2016-08-22	GENENTECH INC.		☐
	57	2016531849	JP	A	2016-10-13	BRISTOL-MYERS SQUIBB CO.		☐
	58	2017501167	JP	A	2017-01-12	Cheung, Jeanne et al.		☐
	59	2017532059	JP	A	2017-11-02	MERCK & CO. INC.		☐
	60	2018510142	JP	A	2018-04-12	Reichert, Paul et al.		☐
	61	2018513159	JP	A	2018-05-24	BRISTOL-MYERS SQUIBB CO.		☐
	62	2023109942	JP	A	2023-08-08	MERCK SHARP & DOHME LLC		☐

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	63	7467438	JP	B2	2024-04-10	Merck Sharp & Dohme LLC		☐
	64	20100054780	KR	A	2010-05-25	Organon NV		☐
	65	20140026434	KR	A	2014-03-05	MERCK SHARP & DOHME CORP.		☐
	66	20170041272	KR	A	2017-04-14	MERCK SHARP & DOHME CORP.		☐
	67	20180069056	KR	A	2018-06-22	MERCK SHARP & DOHME CORP.		☐
	68	2494107	RU	C2	2006-05-02	Ono Farmas JuTikal Ko., Ltd.		☐
	69	2348615	RU	C2	2009-03-10	AVENTIS FARMA S.A.		☐
	70	2560701	RU	C2	2015-08-20	ABBVIE BIOTECHNOLOGY LTD.		☐
	71	2015123476	RU	A	2015-10-20	MERCK SHARP & DOHME CORP.		☐
	72	2589691	RU	C2	2016-07-10	OBSHSHESTVO S OGRANICHENNOJ OTVETSTVENNOSTYU "PROM		☐
	73	2589691	RU	C2	2016-07-10	OBSHSHESTVO S OGRANICHENNOJ OTVETSTVENNOSTYU "PROM		☐

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	74	201806974	TW	A	2018-03-01	BOEHRINGER INGELHEIM INTERNATIONAL GMBH		☐
	75	1989011297	WO	A1	1989-11-30	Centocor, Inc.		☐
	76	1992004381	WO	A1	1992-03-19	Scotgen Limited		☐
	77	1994006448	WO	A1	1994-03-31	The Scripps Research Institute		☐
	78	199704801	WO	A1	1997-02-13	Genetech, Inc.		☐
	79	2000053631	WO	A1	2000-09-14	Schering Corporation		☐
	80	2001030393	WO	A2	2001-03-03	Ludwig Institute for Cancer Research		☐
	81	2001018051	WO	A2	2001-03-15	Schering Corporation		☐
	82	2002072636	WO	A2	2002-09-19	Altus Biologics Inc.		☐
	83	2002102303	WO	A2	2002-12-27	MEDIMMUNE, INC.		☐
	84	03009817	WO	A2	2003-02-06	Protein Design Labs, Inc.		☐

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	85	2003009817	WO	A1	2003-02-06	Protein Design Labs Inc.		☐
	86	2003039485	WO	A2	2003-05-15	Protein Design Labs		☐
	87	2003086310	WO	A2	2003-10-23	Univ. Ramot		☐
	88	2004007520	WO	A2	2004-01-22	MEDAREX INC et al.		☐
	89	2004018312	WO	A1	2004-03-04	PHARMACIA CORPORATION		☐
	90	2004024068	WO	A2	2004-03-25	Genentech		☐
	91	2004055164	WO	A2	2004-07-01	Abgenix Inc.		☐
	92	2004056875	WO	A1	2004-07-08	Wyeth & Cambridge Antibody Technology		☐
	93	2004071439	WO	A2	2004-08-26	Elan Pharmaceuticals, Inc.		☐
	94	2004071517	WO	A2	2004-08-26	Schering Corporation		☐
	95	2004081190	WO	A2	2004-09-23	Schering Corporation		☐

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	96	2005013972	WO	A1	2005-02-17	AVENTIS PHARMA S.A.		☐
	97	2005120571	WO	A2	2005-12-22	Ramot at Tel Aviv University Ltd.		☐
	98	2006044908	WO	A2	2006-04-27	GENETECH, INC.		☐
	99	2006121168	WO	A1	2006-11-16	Ono Pharmaceutical Co., Ltd.		☐
	100	2006133486	WO	A1	2006-12-21	The MacFarlane Burnet Institute For Medical Resear		☐
	101	2007019232	WO	A2	2007-02-15	Immunogen, Inc.		☐
	102	2007024846	WO	A2	2007-03-01	Eli Lilly and Company		☐
	103	2007076524	WO	A2	2007-07-05	Centocor, Inc.		☐
	104	2007092772	WO	A2	2007-08-16	Medimmune, Inc.		☐
	105	2007110339	WO	A1	2007-10-04	F. Hoffmann-La Roche AG		☐
	106	2007124299	WO	A2	2007-11-01	NOVARTIS AG et al.		☐

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	107	2007147019	WO	A2	2007-12-21	Zymogenetics, Inc.		☐
	108	2008057240	WO	A2	2008-05-15	Abbott Biotechnology LTD.		☐
	109	2006096491	WO	A9	2008-05-29	PHARMACIA & UPJOHN COMPANY LLC et al.		☐
	110	2008076321	WO	A1	2008-06-26	Schering Corporation		☐
	111	2008079246	WO	A2	2008-07-03	MEDAREX INC et al.		☐
	112	2008079290	WO	A2	2008-07-03	Amgen Inc.		☐
	113	2008086395	WO	A2	2008-07-17	Wyeth		☐
	114	2008103432	WO	A1	2008-08-28	Schering Corporation		☐
	115	2008103473	WO	A1	2008-08-28	Schering Corporation		☐
	116	2008121301	WO	A1	2008-10-09	BORHANI DAVID W		☐
	117	2008153610	WO	A2	2008-12-18	Schering Corporation		☐

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	118	2008156712	WO	A1	2008-12-24	N.V. ORGANON		☐
	119	2008157409	WO	A1	2008-12-24	ELAN PHARMACEUTICAL, INC.		☐
	120	2009009407	WO	A1	2009-01-15	Smithkline Beecham Corp.		☐
	121	2009043933	WO	A1	2009-04-09	Glaxo Group Limited		☐
	122	2009084659	WO	A1	2009-07-09	CHUGAI SEIYAKU KABUSHIKI KAISHA et al.		☐
	123	2009101611	WO	A1	2009-08-20	Curetech Ltd.		☐
	124	2009120684	WO	A1	2009-10-01	Medimmune, LLC		☐
	125	2009126688	WO	A2	2009-10-15	Genentech, Inc.		☐
	126	2010032220	WO	A1	2010-03-25	Pfizer Inc.		☐
	127	2010062372	WO	A2	2010-06-03	President and Fellows of Harvard College		☐
	128	2010069858	WO	A1	2010-06-24	Ono Pharmaceutical Co., Ltd.		☐

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	129	2010102241	WO	A1	2010-09-10	Genentech, Inc.		☐
	130	2010129469	WO	A1	2010-11-11	ABBOTT BIOTECH LTD et al.		☐
	131	2010148337	WO	A1	2010-12-23	WYETH LLC		☐
	132	2010148337	WO	A1	2010-12-23	WYETH LLC		☐
	133	2011012637	WO	A2	2011-02-03	HOFFMANN LA ROCHE		☐
	134	2011012637	WO	A2	2011-02-03	Hoffman-LaRoche		☐
	135	2011017070	WO	A1	2011-02-10	Merck Sharp & Dohme Corp.		☐
	136	2011024862	WO	A1	2011-03-03	Sanyo Chemical Industries, Ltd.		☐
	137	2011029892	WO	A2	2011-03-17	F. HOFFMANN-LA ROCHE AG		☐
	138	2011034822	WO	A1	2011-03-24	Shenoy, Bhami		☐
	139	2011056772	WO	A1	2011-05-12	Schering Corporation		☐

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	140	2011080209	WO	A2	2011-07-07	HOFFMANN LA ROCHE et al.		☐
	141	2011089062	WO	A2	2011-07-28	F. HOFFMANN-LA ROCHE AG		☐
	142	2011097372	WO	A2	2011-08-11	APTUIT LAURUS PRIVATE LIMITED		☐
	143	2011116090	WO	A1	2011-09-22	Abbott Research B.V.		☐
	144	2011139718	WO	A1	2011-11-10	GENENTECH, INC.		☐
	145	2012010799	WO	A1	2012-01-26	LFB-Biotechnologies		☒
	146	2012010799	WO	A1	2012-01-26	LFB-Biotechnologies		☐
	147	2012018538	WO	A2	2012-02-09	Schering Corporation		☐
	148	2012047954	WO	A1	2012-04-12	REGENERON PHARMACEUTICALS, INC.		☐
	149	2012076670	WO	A2	2012-06-14	NOVARTIS AG		☐
	150	2012135035	WO	A1	2012-10-04	Amgen, Inc.		☐

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	151	2012135408	WO	A1	2012-10-04	MERCK SHARP & DOHME CORP..		☐
	152	2012165917	WO	A1	2012-12-06	LG Life Sciences Ltd.		☐
	153	2013016648	WO	A2	2013-01-31	REGENERON PHARMACEUTICALS, INC.		☐
	154	2013063468	WO	A1	2013-05-02	Massachusetts Institute of Technology		☐
	155	2013151999	WO	A1	2013-10-10	President and Fellows of Harvard College		☐
	156	2013167720	WO	A1	2013-11-14	NOVARTIS AG		☐
	157	2014004436	WO	A2	2014-01-03	Merck Sharp & Dohme Corp.		☐
	158	2014036071	WO	A1	2014-03-06	BAYER HEALTHCARE LLC		☐
	159	2014036076	WO	A1	2014-03-06	BAYER HEALTHCARE LLC		☐
	160	2015009856	WO	A2	2015-01-22	Genentech, Inc.		☐
	161	2015011199	WO	A1	2015-01-29	Novaliq GMBH		☐

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	162	2015038777	WO	A1	2015-03-19	Arsia Therapeutics, Inc.		☐
	163	2015038782	WO	A1	2015-03-19	Arsia Therapeutics, Inc.		☐
	164	2015038811	WO	A2	2015-03-19	Arsia Therapeutics, Inc.		☐
	165	2015038818	WO	A2	2015-03-19	Arsia Therapeutics, Inc.		☐
	166	2015042246	WO	A1	2015-03-26	Bristol Myers Squibb Co.		☐
	167	2015048520	WO	A1	2015-04-02	GENENTECH, INC.;F. HOFFMANN-LA ROCHE AG		☐
	168	2015095423	WO	A2	2015-06-25	GENENTECH, INC. et al.		☐
	169	2015143343	WO	A2	2015-09-24	THE BRIGHAM AND WOMEN'S HOSPITAL, INC.		☐
	170	2016011264	WO	A1	2016-01-21	Genentech, Inc. and Hoffman-La AGRoche		☒
	171	2016015675	WO	A1	2016-02-04	Akeso Biopharma, Inc.	Equivalent=US20170216433	☐
	172	2016024228	WO	A1	2016-02-18	Acerta Pharma B.V.		☐

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	173	2016028656	WO	A1	2016-02-25	Merck Sharp & Dohme Corp.		☐
	174	2016028672	WO	A1	2016-02-25	MERCK SHARP & DOHME CORP.		☐
	175	2016035006	WO	A1	2016-03-10	DR. REDDY'S LABORATORIES LIMITED		☐
	176	2016035006	WO	A1	2016-03-10	DR. REDDY'S LABORATORIES LIMITED		☐
	177	2016040238	WO	A1	2016-03-17	CELGENE CORPORATION		☐
	178	2016070051	WO	A2	2016-05-06	ONCOMED PHARMACEUTICALS, INC.		☐
	179	2016100882	WO	A1	2016-06-23	NOVARTIS AG		☐
	180	2016106302	WO	A1	2016-06-30	Bristol-Myers Squibb		☒
	181	2016118654	WO	A1	2016-07-28	IMMUNEXCITE, INC.		☐
	182	2016137850	WO	A1	2016-09-01	Merck Sharp & Dohme Corp.		☐
	183	2016140717	WO	A1	2016-09-09	MERCK SHARP & DOHME CORP. et al.		☐

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	184	2016153839	WO	A1	2016-09-29	MERCK SHARP & DOHME et al.		☐
	185	2016168133	WO	A1	2016-10-20	MERCK SHARP & DOHME CORP.		☐
	186	2016168716	WO	A1	2016-10-20	Bristol-Myers Squibb Company		☐
	187	2016176504	WO	A1	2016-11-03	Bristol-Myers Squibb Company		☐
	188	2016196173	WO	A1	2016-12-08	MERCK SHARP & DOHME CORP. et al.		☐
	189	2016200782	WO	A1	2016-12-15	Macrogenics, Inc.		☐
	190	2017009813	WO	A1	2017-01-19	LAURUS LABS PRIVATE LIMITED		☐
	191	2017015560	WO	A2	2017-01-26	SORRENTO THERAPEUTICS, INC.		☐
	192	2017021526	WO	A1	2017-02-09	AMGEN RESEARCH (MUNICH) GMBH		☐
	193	2017025498	WO	A1	2017-02-16	PIERIS PHARMACEUTICALS GMBH		☐
	194	2017030823	WO	A2	2017-02-23	Merck Sharp & Dohme Corp.		☐

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	195	2017037203	WO	A1	2017-03-09	IMMUTEP S.A.S.		☐
	196	2017040790	WO	A1	2017-03-09	Agenus Inc.		☐
	197	2017040864	WO	A1	2017-03-09	FIRST WAVE BIOPHARMA		☐
	198	2017048824	WO	A1	2017-03-23	COMPASS THERAPEUTICS LLC		☐
	199	2017053748	WO	A2	2017-03-30	GENENTECH, INC.		☒
	200	2017054646	WO	A1	2017-04-06	Jiangsu Hengrui Medicine Co.		☐
	201	2017055547	WO	A1	2017-04-06	SYMPHOGEN A/S		☐
	202	2017059095	WO	A1	2017-04-06	Potenza Therapeutics, Inc.		☐
	203	2017075124	WO	A1	2017-05-04	Merck Sharp & Dohme Corp.		☐
	204	2017079150	WO	A1	2017-05-11	JANSSEN BIOTECH, INC.		☐
	205	2017089895	WO	A1	2017-06-01	Legochem Biosciences, Inc.		☐

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	206	2017112621	WO	A1	2017-06-29	Merck Sharp & Dohme Corp.		☐
	207	2017131496	WO	A1	2017-08-03	HANMI PHARM. CO., LTD.		☐
	208	2017198741	WO	A1	2017-11-23	Boehringer Ingelheim Int'l GMBH		☐
	209	2018091729	WO	A2	2018-05-24	ZAKLADY FARMACEUTYCZNE POLPHARMA SA		☐
	210	2018116198	WO	A1	2018-06-28	SERUM INSTITUTE OF INDIA PRIVATE LIMITED		☐
	211	2018158332	WO	A1	2018-09-07	MEDIMMUNE LIMITED		☐
	212	2018160722	WO	A1	2018-09-07	MEDIMMUNE LIMITED		☐
	213	2018183928	WO	A1	2018-10-04	BRISTOL MYERS SQUIBB CO		☐
	214	2018187057	WO	A1	2018-10-11	REGENERON PHARMACEUTICALS, INC.		☐
	215	2018204343	WO	A1	2018-11-08	Merck Sharp & Dohme Corp.		☐
	216	2018204368	WO	A1	2018-11-08	MERCK SHARP & DOHME CORP. et al.		☐

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	217	2018204374	WO	A1	2018-11-08	Merck Sharp & Dohme Corp.		☐
	218	2018204405	WO	A1	2018-11-08	MERCK SHARP & DOHME CORP.		☐
	219	2018222718	WO	A1	2018-12-06	BRISTOL-MYERS SQUIBB COMPANY		☐
	220	2018222722	WO	A2	2018-12-06	BRISTOL-MYERS SQUIBB COMPANY		☐
	221	2020022791	WO	A1	2020-01-30	ALTEOGEN, INC		☐
	222	2020028011	WO	A1	2020-02-06	SHIRE-NPS PHARMACEUTICALS INC.		☐
	223	2020081408	WO	A1	2020-04-23	MERCK SHARP & DOHME CORP.		☐
	224	2020096917	WO	A1	2020-05-14	MERCK SHARP & DOHME CORP.		☐
	225	2020097141	WO	A1	2020-05-14	MERCK SHARP & DOHME CORP. et al.		☐
	226	2020197230	WO	A1	2020-10-01	ALTEOGEN INC.		☐
	227	2021118930	WO	A2	2021-06-17	GENENTECH INC		☐

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	2	ACCESSION NUMBER: 2013:400660 (Year: 2013), 1 page	☐
	3	ACCESSION NUMBER: 2017:1215621 (Year: 2017), 2 pages	☐
	4	AGARKHED, MEERA ET AL., Effect of Polysorbate 80 Concentration on Thermal and Photostability of a Monoclonal Antibody, AAPS Pharm Sci Tech, 14(1), 1-9, 2013	☐
	5	AHAMED, TANGIR, Phase Behavior of an Intact Monoclonal Antibody, Biochemical Journal, 93, 610-619, 2007	☐
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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached timing statement under 37 CFR 1.97(e).

☐ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☒ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and the IDS Auto-Load Instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☐ No IDS size fee is required under 37 CFR 1.17(v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

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SIGNATURE

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Patrick Rehfuss, Reg. No. 75,367/	Date (YYYY-MM-DD)	2025-09-19
Name/Print	Patrick Rehfuss	Registration Number	75,367

PC.1.19.25

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This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you 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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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.

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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: MERCK SHARP & DOHME LLC

Application No./Patent No.: _____ Filed/Issue Date: _____

Titled: STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

MERCK SHARP & DOHME LLC, a Limited Liability Company, subsidiary of Merck & Co., Inc.

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Manoj K. Sharma et al. To: Merck Sharp & Dohme Corp.

   The document was recorded in the United States Patent and Trademark Office at

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This collection of information is required by 37 CFR 3.73(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.**

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☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Cynthia A. Francisco/	March 7, 2023
Signature	Date
Cynthia A. Francisco	Executive Director, Asset Management
Printed or Typed Name	Title or Registration Number

Attorney Docket No.: 24439

WORLDWIDE ASSIGNMENT

WHEREAS, I/WE,
(1) Manoj K. Sharma, located at Littleton, MA,
(2) Wendy Benjamin, located at North Brunswick, NJ,
(3) Sarita Mittal, located at Bridgewater, NJ,
(4) Ashwin Basarkar, located at Keasbey, NJ,
(5) Chakravarthy Nachu Narasimhan, located at Scotch Plains, NJ,
(6) Ramesh S. Kashi, located at Warren, NJ,
(7) Mohammed Shameem, located in Nanuet, NY,
(8) Soumendu Bhattacharya, located in East Windsor, NJ,
(9) William P. Forrest, Jr., located in Middletown, NJ

(hereinafter ASSIGNOR(S)), is/are the inventor(s) of the invention described in an application for Patents having the Attorney Docket Number indicated above and the following Title of the Invention:

STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

and/or in the following application(s):

U.S. Provisional Application No. 62/500,238 filed on May 2, 2017;
U.S. Application No. 16/609612 having a filing date of October 30, 2019; and
PCT International Application No. PCT/US2018/030459 having a filing date of May 1, 2018.

WHEREAS I/WE covenant that the rights and property herein conveyed are free and clear of any encumbrance, and that I/we have the full right to convey the same as herein expressed.

WHEREAS, Merck Sharp & Dohme Corp., a corporation organized under the laws of the State of New Jersey, having an office at 126 East Lincoln Avenue, Rahway, New Jersey 07065, and its successors, assigns and legal representatives (hereinafter **ASSIGNEE**), is desirous of obtaining the entire right, title and interest in, to and under the invention disclosed in said application or applications;

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, I/we, said ASSIGNOR(S), do each hereby sell, assign and transfer or confirm the grant and assignment to said **ASSIGNEE** my/our entire right, title and interest in all countries of the world in and to my/our invention described in said application for Patents, in and to the right to file patent applications in the name of **ASSIGNEE**, its designee, or in any or all of our names, at its election, on the aforesaid invention in all countries of the world, together with all rights of priority in the aforesaid countries deriving from the above-identified application for Patents under the International Convention for the Protection of Industrial Property, under the Inter-American Convention relating to Inventions, Patents, Designs and Industrial Models and under any other international arrangement relating to patents or intellectual property, in and to any and all Letters Patent that are granted from the aforesaid application for Patents, in and to any applications claiming priority benefits to a provisional patent application or other applications filed on said invention, and in and to any continuations, divisions, reexaminations, reissues, renewals and extensions thereof of any of said Letters Patent, the same to be held and enjoyed by said **ASSIGNEE**, to the full ends of the terms for which all Letters Patent therefore may be granted, as fully and entirely as the same would have been held and enjoyed by us if this assignment and sale had not been made.

AND I/WE HEREBY covenant and agree that we will at any time, upon the request and at the expense of **ASSIGNEE**, without further compensation or charge to said **ASSIGNEE**, execute and deliver any and all documents that may be necessary or desirable to perfect the title to the foregoing invention, patent applications, and Letters Patent and continuations, divisions, reexaminations, reissues, renewals and extensions thereof in the name of **ASSIGNEE**, including the execution and procurement of any and all further documents evidencing this assignment and sale as may be necessary or desirable for recording the same in the Patent Office of any country concerned, and will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein.

I/WE HEREBY authorize **ASSIGNEE** to insert in this instrument the Application Number(s) and the filing date(s) of said application for Patents when officially notified thereof.

This document may be executed in any number of counterparts, each of which so executed shall be deemed to be an original, but all such components shall together constitute but one and the same document.

Attorney Docket No.: 24439

Executed this 01 day of Aug, 2018

Manoj K. Sharma

ACKNOWLEDGEMENT

Commonwealth of Massachusetts

County Name, ss. Middlesex

On this 1 day of August, 2018, before me, the undersigned notary public, personally appeared **Manoj K. Sharma** proved to me through satisfactory evidence of identification, which was Massachusetts License, to be the person whose name is signed on the preceding document, and acknowledged to me that he/she signed it voluntarily for its stated purpose.

JEANNE B. SILL
Notary Public
COMMONWEALTH OF MASSACHUSETTS
My Commission Expires
February 7, 2025

Jeanne B Sill
Notary Public: Jeanne B. Sill
My Commission Expires: February 7, 2025

Executed this ____ day of _____, 2018

Wendy Benjamin

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____, 2018, personally appeared before me **Wendy Benjamin** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Notary Public

Computer Generated Template "Assignment-Merck Sharp & Dohme. Single Assignee Worldwide" (Assignment) Merck Sharp & Dohme Corp. 11/04/2010

Executed this _____ day of _____ , 2018

_____
Sarita Mittal

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____ , 2018, personally appeared before me **Sarita Mittal** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of _____ , 2018

_____
Ashwin Basarkar

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of _____)

On this _____ day of _____ , 2018, personally appeared before me **Ashwin Basarkar** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Attorney Docket No.: 24439

Executed this _____ day of _____ , 2018

_____
Chakravarthy Nachu Narasimhan

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____ , 2018, personally appeared before me **Chakravarthy Nachu Narasimhan** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of _____ , 2018

_____
Ramesh S. Kashi

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of _____)

On this _____ day of _____ , 2018, personally appeared before me **Ramesh S. Kashi** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of _____ , 2018

_____
Mohammed Shameem

ACKNOWLEDGEMENT

State of New York)
) s.s.:
County of _____)

On this _____ day of _____ , 2018, personally appeared before me **Mohammed Shameem** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of _____ , 2018

_____
Soumendu Bhattacharya

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____ , 2018, personally appeared before me **Soumendu Bhattacharya** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of _____ , 2018

_____
William P. Forrest, Jr.

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____ , 2018, personally appeared before me **William P. Forrest, Jr.** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Attorney Docket No.: 24439

WORLDWIDE ASSIGNMENT

WHEREAS, I/WE,
(1) Manoj K. Sharma, located at Littleton, MA,
(2) Wendy Benjamin, located at North Brunswick, NJ,
(3) Sarita Mittal, located at Bridgewater, NJ,
(4) Ashwin Basarkar, located at Keasbey, NJ,
(5) Chakravarthy Nachu Narasimhan, located at Scotch Plains, NJ,
(6) Ramesh S. Kashi, located at Warren, NJ,
(7) Mohammed Shameem, located in Nanuet, NY,
(8) Soumendu Bhattacharya, located in East Windsor, NJ,
(9) William P. Forrest, Jr., located in Middletown, NJ

(hereinafter ASSIGNOR(S)), is/are the inventor(s) of the invention described in an application for Patents having the Attorney Docket Number indicated above and the following Title of the Invention:

STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

and/or in the following application(s):

U.S. Provisional Application No. 62/500,238 filed on May 2, 2017;
U.S. Application No. 16/609612 having a filing date of October 30, 2019; and
PCT International Application No. PCT/US2018/030459 having a filing date of May 1, 2018.

WHEREAS I/WE covenant that the rights and property herein conveyed are free and clear of any encumbrance, and that I/we have the full right to convey the same as herein expressed.

WHEREAS, Merck Sharp & Dohme Corp., a corporation organized under the laws of the State of New Jersey, having an office at 126 East Lincoln Avenue, Rahway, New Jersey 07065, and its successors, assigns and legal representatives (hereinafter **ASSIGNEE**), is desirous of obtaining the entire right, title and interest in, to and under the invention disclosed in said application or applications;

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, I/we, said ASSIGNOR(S), do each hereby sell, assign and transfer or confirm the grant and assignment to said **ASSIGNEE** my/our entire right, title and interest in all countries of the world in and to my/our invention described in said application for Patents, in and to the right to file patent applications in the name of **ASSIGNEE**, its designee, or in any or all of our names, at its election, on the aforesaid invention in all countries of the world, together with all rights of priority in the aforesaid countries deriving from the above-identified application for Patents under the International Convention for the Protection of Industrial Property, under the Inter-American Convention relating to Inventions, Patents, Designs and Industrial Models and under any other international arrangement relating to patents or intellectual property, in and to any and all Letters Patent that are granted from the aforesaid application for Patents, in and to any applications claiming priority benefits to a provisional patent application or other applications filed on said invention, and in and to any continuations, divisions, reexaminations, reissues, renewals and extensions thereof of any of said Letters Patent, the same to be held and enjoyed by said **ASSIGNEE**, to the full ends of the terms for which all Letters Patent therefore may be granted, as fully and entirely as the same would have been held and enjoyed by us if this assignment and sale had not been made.

AND I/WE HEREBY covenant and agree that we will at any time, upon the request and at the expense of **ASSIGNEE**, without further compensation or charge to said **ASSIGNEE**, execute and deliver any and all documents that may be necessary or desirable to perfect the title to the foregoing invention, patent applications, and Letters Patent and continuations, divisions, reexaminations, reissues, renewals and extensions thereof in the name of **ASSIGNEE**, including the execution and procurement of any and all further documents evidencing this assignment and sale as may be necessary or desirable for recording the same in the Patent Office of any country concerned, and will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein.

I/WE HEREBY authorize **ASSIGNEE** to insert in this instrument the Application Number(s) and the filing date(s) of said application for Patents when officially notified thereof.

This document may be executed in any number of counterparts, each of which so executed shall be deemed to be an original, but all such components shall together constitute but one and the same document.

Executed this ____ day of _____, 2018

_____
Manoj K. Sharma

ACKNOWLEDGEMENT

Commonwealth of Massachusetts

County Name, ss. _____

On this _____ day of _____, 2018, before me, the undersigned notary public, personally appeared **Manoj K. Sharma** proved to me through satisfactory evidence of identification, which was _____, to be the person whose name is signed on the preceding document, and acknowledged to me that he/she signed it voluntarily for its stated purpose.

_____
Notary Public:
My Commission Expires: _____

Executed this 2nd day of July, 2018

_____
Wendy Benjamin

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this 3rd day of July, 2018, personally appeared before me **Wendy Benjamin** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

DINA A. KUSTER
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires 8/7/2020

Computer Generated Template "Assignment-Merck Sharp & Dohme, Single Assignee Worldwide" (Assignment) Merck Sharp & Dohme Corp. 11/04/2010

Attorney Docket No.: 24439

Executed this 2ND day of July, 2018

Sarita Mittal

Sarita Mittal

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this 2nd day of July, 2018, personally appeared before me **Sarita Mittal** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Dina A Kuster
Notary Public

DINA A. KUSTER
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires 8/7/2020

Executed this ____ day of _____, 2018

_____
Ashwin Basarkar

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of _____)

On this _____ day of _____, 2018, personally appeared before me **Ashwin Basarkar** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this 23 day of July, 2018

Chakravarthy Nachu Narasimhan

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this 23 day of July, 2018, personally appeared before me **Chakravarthy Nachu Narasimhan** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Dina A Kuster
Notary Public

DINA A. KUSTER
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires 8/7/2020

Executed this _____ day of _____, 2018

Ramesh S. Kashi

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of _____)

On this _____ day of _____, 2018, personally appeared before me **Ramesh S. Kashi** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Notary Public

Executed this _____ day of _____ , 2018

_____
Mohammed Shameem

ACKNOWLEDGEMENT

State of New York)
) s.s.:
County of _____)

On this _____ day of _____ , 2018, personally appeared before me **Mohammed Shameem** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this 2 day of JULY , 2018

_____
Soumendu Bhattacharya

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this 2 day of July , 2018, personally appeared before me **Soumendu Bhattacharya** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

DINA A. KUSTER
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires 8/7/2021

Attorney Docket No.: 24439

Executed this 9 day of July, 2018

William P. Forrest, Jr.

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this 9 day of July, 2018, personally appeared before me **William P. Forrest, Jr.** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Notary Public

DINA A. KUSTER
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires 8/7/2020

Computer Generated Template "Assignment-Merck Sharp & Dohme, Single Assignee Worldwide" (Assignment) Merck Sharp & Dohme Corp. 11/04/2016

Attorney Docket No.: 24439

WORLDWIDE ASSIGNMENT

WHEREAS, I/WE,
(1) Manoj K. Sharma, located at Littleton, MA,
(2) Wendy Benjamin, located at North Brunswick, NJ,
(3) Sarita Mittal, located at Bridgewater, NJ,
(4) Ashwin Basarkar, located at Keasbey, NJ,
(5) Chakravarthy Nachu Narasimhan, located at Scotch Plains, NJ,
(6) Ramesh S. Kashi, located at Warren, NJ,
(7) Mohammed Shameem, located in Nanuet, NY,
(8) Soumendu Bhattacharya, located in East Windsor, NJ,
(9) William P. Forrest, Jr., located in Middletown, NJ

(hereinafter ASSIGNOR(S)), is/are the inventor(s) of the invention described in an application for Patents having the Attorney Docket Number indicated above and the following Title of the Invention:

STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

and/or in the following application(s):

U.S. Provisional Application No. 62/500,238 filed on May 2, 2017;
U.S. Application No. 16/609612 having a filing date of October 30, 2019; and
PCT International Application No. PCT/US2018/030459 having a filing date of May 1, 2018.

WHEREAS I/WE covenant that the rights and property herein conveyed are free and clear of any encumbrance, and that I/we have the full right to convey the same as herein expressed.

WHEREAS, Merck Sharp & Dohme Corp., a corporation organized under the laws of the State of New Jersey, having an office at 126 East Lincoln Avenue, Rahway, New Jersey 07065, and its successors, assigns and legal representatives (hereinafter **ASSIGNEE**), is desirous of obtaining the entire right, title and interest in, to and under the invention disclosed in said application or applications;

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, I/we, said ASSIGNOR(S), do each hereby sell, assign and transfer or confirm the grant and assignment to said **ASSIGNEE** my/our entire right, title and interest in all countries of the world in and to my/our invention described in said application for Patents, in and to the right to file patent applications in the name of **ASSIGNEE**, its designee, or in any or all of our names, at its election, on the aforesaid invention in all countries of the world, together with all rights of priority in the aforesaid countries deriving from the above-identified application for Patents under the International Convention for the Protection of Industrial Property, under the Inter-American Convention relating to Inventions, Patents, Designs and Industrial Models and under any other international arrangement relating to patents or intellectual property, in and to any and all Letters Patent that are granted from the aforesaid application for Patents, in and to any applications claiming priority benefits to a provisional patent application or other applications filed on said invention, and in and to any continuations, divisions, reexaminations, reissues, renewals and extensions thereof of any of said Letters Patent, the same to be held and enjoyed by said **ASSIGNEE**, to the full ends of the terms for which all Letters Patent therefore may be granted, as fully and entirely as the same would have been held and enjoyed by us if this assignment and sale had not been made.

AND I/WE HEREBY covenant and agree that we will at any time, upon the request and at the expense of **ASSIGNEE**, without further compensation or charge to said **ASSIGNEE**, execute and deliver any and all documents that may be necessary or desirable to perfect the title to the foregoing invention, patent applications, and Letters Patent and continuations, divisions, reexaminations, reissues, renewals and extensions thereof in the name of **ASSIGNEE**, including the execution and procurement of any and all further documents evidencing this assignment and sale as may be necessary or desirable for recording the same in the Patent Office of any country concerned, and will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein.

I/WE HEREBY authorize **ASSIGNEE** to insert in this instrument the Application Number(s) and the filing date(s) of said application for Patents when officially notified thereof.

This document may be executed in any number of counterparts, each of which so executed shall be deemed to be an original, but all such components shall together constitute but one and the same document.

Executed this _____ day of _____ , 2018

_____
Manoj K. Sharma

ACKNOWLEDGEMENT

Commonwealth of Massachusetts

County Name, ss. _____

On this _____ day of _____, 2018, before me, the undersigned notary public, personally appeared **Manoj K. Sharma** proved to me through satisfactory evidence of identification, which was _____, to be the person whose name is signed on the preceding document, and acknowledged to me that he/she signed it voluntarily for its stated purpose.

_____
Notary Public:
My Commission Expires: _____

Executed this _____ day of _____ , 2018

_____
Wendy Benjamin

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____ , 2018, personally appeared before me **Wendy Benjamin** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Attorney Docket No.: 24439

Executed this 7 day of JULY, 2018

Sarita Mittal

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____, 2018, personally appeared before me **Sarita Mittal** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Notary Public

Executed this 7th day of JULY, 2018

Ashwin Basarkar

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Middlesex)

On this 7 day of JULY, 2018, personally appeared before me **Ashwin Basarkar** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Notary Public

ASHOKKUMAR MUTREJA
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires 7/31/2022

Computer Generated Template "Assignment-Merck Sharp & Dohme, Single Assignee Worldwide" (Assignment) Merck Sharp & Dohme Corp. 11/04/2013

Attorney Docket No.: 24439

Executed this _____ day of _____ , 2018

_____
Chakravarthy Nachu Narasimhan

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____ , 2018, personally appeared before me **Chakravarthy Nachu Narasimhan** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of _____ , 2018

_____
Ramesh S. Kashi

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of _____)

On this _____ day of _____ , 2018, personally appeared before me **Ramesh S. Kashi** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Attorney Docket No.: 24439

Executed this ____ day of _____ , 2018

_____
Mohammed Shameem

ACKNOWLEDGEMENT

State of New York)
) s.s.:
County of _____)

On this _____ day of _____ , 2018, personally appeared before me **Mohammed Shameem** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this ____ day of _____ , 2018

_____
Soumendu Bhattacharya

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____ , 2018, personally appeared before me **Soumendu Bhattacharya** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Attorney Docket No.: 24439

Executed this _____ day of _____ , 2018

_____
William P. Forrest, Jr.

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____ , 2018, personally appeared before me **William P. Forrest, Jr.** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Attorney Docket No.: 24439

WORLDWIDE ASSIGNMENT

WHEREAS, I/WE,
(1) Manoj K. Sharma, located at Littleton, MA,
(2) Wendy Benjamin, located at North Brunswick, NJ,
(3) Sarita Mittal, located at Bridgewater, NJ,
(4) Ashwin Basarkar, located at Keasbey, NJ,
(5) Chakravarthy Nachu Narasimhan, located at Scotch Plains, NJ,
(6) Ramesh S. Kashi, located at Warren, NJ,
(7) Mohammed Shameem, located in Nanuet, NY,
(8) Soumendu Bhattacharya, located in East Windsor, NJ,
(9) William P. Forrest, Jr., located in Middletown, NJ

(hereinafter ASSIGNOR(S)), is/are the inventor(s) of the invention described in an application for Patents having the Attorney Docket Number indicated above and the following Title of the Invention:

STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

and/or in the following application(s):

U.S. Provisional Application No. 62/500,238 filed on May 2, 2017;
U.S. Application No. 16/609612 having a filing date of October 30, 2019; and
PCT International Application No. PCT/US2018/030459 having a filing date of May 1, 2018.

WHEREAS I/WE covenant that the rights and property herein conveyed are free and clear of any encumbrance, and that I/we have the full right to convey the same as herein expressed.

WHEREAS, Merck Sharp & Dohme Corp., a corporation organized under the laws of the State of New Jersey, having an office at 126 East Lincoln Avenue, Rahway, New Jersey 07065, and its successors, assigns and legal representatives (hereinafter **ASSIGNEE**), is desirous of obtaining the entire right, title and interest in, to and under the invention disclosed in said application or applications;

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, I/we, said ASSIGNOR(S), do each hereby sell, assign and transfer or confirm the grant and assignment to said **ASSIGNEE** my/our entire right, title and interest in all countries of the world in and to my/our invention described in said application for Patents, in and to the right to file patent applications in the name of **ASSIGNEE**, its designee, or in any or all of our names, at its election, on the aforesaid invention in all countries of the world, together with all rights of priority in the aforesaid countries deriving from the above-identified application for Patents under the International Convention for the Protection of Industrial Property, under the Inter-American Convention relating to Inventions, Patents, Designs and Industrial Models and under any other international arrangement relating to patents or intellectual property, in and to any and all Letters Patent that are granted from the aforesaid application for Patents, in and to any applications claiming priority benefits to a provisional patent application or other applications filed on said invention, and in and to any continuations, divisions, reexaminations, reissues, renewals and extensions thereof of any of said Letters Patent, the same to be held and enjoyed by said **ASSIGNEE**, to the full ends of the terms for which all Letters Patent therefore may be granted, as fully and entirely as the same would have been held and enjoyed by us if this assignment and sale had not been made.

AND I/WE HEREBY covenant and agree that we will at any time, upon the request and at the expense of **ASSIGNEE**, without further compensation or charge to said **ASSIGNEE**, execute and deliver any and all documents that may be necessary or desirable to perfect the title to the foregoing invention, patent applications, and Letters Patent and continuations, divisions, reexaminations, reissues, renewals and extensions thereof in the name of **ASSIGNEE**, including the execution and procurement of any and all further documents evidencing this assignment and sale as may be necessary or desirable for recording the same in the Patent Office of any country concerned, and will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein.

I/WE HEREBY authorize **ASSIGNEE** to insert in this instrument the Application Number(s) and the filing date(s) of said application for Patents when officially notified thereof.

This document may be executed in any number of counterparts, each of which so executed shall be deemed to be an original, but all such components shall together constitute but one and the same document.

Attorney Docket No.: 24439

Executed this ____ day of _____ , 2018

_____
Manoj K. Sharma

ACKNOWLEDGEMENT

Commonwealth of Massachusetts

County Name, ss. _____

On this _____ day of _____, 2018, before me, the undersigned notary public, personally appeared **Manoj K. Sharma** proved to me through satisfactory evidence of identification, which was _____, to be the person whose name is signed on the preceding document, and acknowledged to me that he/she signed it voluntarily for its stated purpose.

_____
Notary Public:
My Commission Expires: _____

Executed this ____ day of _____ , 2018

_____
Wendy Benjamin

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____ , 2018, personally appeared before me **Wendy Benjamin** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Computer Generated Template "Assignment-Merck Sharp & Dohme. Single Assignee Worldwide" (Assignment) Merck Sharp & Dohme Corp. 11/04/2010

Attorney Docket No.: 24439

Executed this ____ day of _____ , 2018

_____
Sarita Mittal

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____ , 2018, personally appeared before me **Sarita Mittal** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this ____ day of _____ , 2018

_____
Ashwin Basarkar

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of _____)

On this _____ day of _____ , 2018, personally appeared before me **Ashwin Basarkar** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Computer Generated Template "Assignment-Merck Sharp & Dohme. Single Assignee Worldwide" (Assignment) Merck Sharp & Dohme Corp. 11/04/2010

Attorney Docket No.: 24439

Executed this _____ day of _____, 2018

_____
Chakravarthy Nachu Narasimhan

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____, 2018, personally appeared before me **Chakravarthy Nachu Narasimhan** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of _____, 2018

_____
Ramesh S. Kashi

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of _____)

On this _____ day of _____, 2018, personally appeared before me **Ramesh S. Kashi** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Computer Generated Template "Assignment-Merck Sharp & Dohme, Single Assignee Worldwide" (Assignment) Merck Sharp & Dohme Corp. 11/04/2010

Attorney Docket No.: 24439

Executed this 11 day of July, 2018

Mohammed Shameem

ACKNOWLEDGEMENT

State of New York)
) s.s.:
County of Westchester)

On this 11 day of July, 2018, personally appeared before me **Mohammed Shameem** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

BARBARA J. REILLY
Notary Public, State of New York
No. 01RE6070570
Qualified in Westchester County
My Commission Expires March 4, 2021

Notary Public

Executed this ____ day of _____, 2018

Soumendu Bhattacharya

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____, 2018, personally appeared before me **Soumendu Bhattacharya** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Notary Public

Computer Generated Template "Assignment-Merck Sharp & Dohme. Single Assignee Worldwide" (Assignment) Merck Sharp & Dohme Corp. 11/04/2010

Attorney Docket No.: 24439

Executed this _____ day of _____, 2018

_____
William P. Forrest, Jr.

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____, 2018, personally appeared before me **William P. Forrest, Jr.** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Computer Generated Template "Assignment-Merck Sharp & Dohme, Single Assignee Worldwide" (Assignment) Merck Sharp & Dohme Corp. 11/04/2010

Attorney Docket No.: 24439

WORLDWIDE ASSIGNMENT

WHEREAS, I/WE,
(1) Manoj K. Sharma, located at Littleton, MA,
(2) Wendy Benjamin, located at North Brunswick, NJ,
(3) Sarita Mittal, located at Bridgewater, NJ,
(4) Ashwin Basarkar, located at Keasbey, NJ,
(5) Chakravarthy Nachu Narasimhan, located at Scotch Plains, NJ,
(6) Ramesh S. Kashi, located at Warren, NJ,
(7) Mohammed Shameem, located in Nanuet, NY,
(8) Soumendu Bhattacharya, located in East Windsor, NJ,
(9) William P. Forrest, Jr., located in Middletown, NJ

(hereinafter ASSIGNOR(S)), is/are the inventor(s) of the invention described in an application for Patents having the Attorney Docket Number indicated above and the following Title of the Invention:

STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

and/or in the following application(s):

U.S. Provisional Application No. 62/500,238 filed on May 2, 2017;
U.S. Application No. 16/609612 having a filing date of October 30, 2019; and
PCT International Application No. PCT/US2018/030459 having a filing date of May 1, 2018.

WHEREAS I/WE covenant that the rights and property herein conveyed are free and clear of any encumbrance, and that I/we have the full right to convey the same as herein expressed.

WHEREAS, Merck Sharp & Dohme Corp., a corporation organized under the laws of the State of New Jersey, having an office at 126 East Lincoln Avenue, Rahway, New Jersey 07065, and its successors, assigns and legal representatives (hereinafter **ASSIGNEE**), is desirous of obtaining the entire right, title and interest in, to and under the invention disclosed in said application or applications;

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, I/we, said ASSIGNOR(S), do each hereby sell, assign and transfer or confirm the grant and assignment to said **ASSIGNEE** my/our entire right, title and interest in all countries of the world in and to my/our invention described in said application for Patents, in and to the right to file patent applications in the name of **ASSIGNEE**, its designee, or in any or all of our names, at its election, on the aforesaid invention in all countries of the world, together with all rights of priority in the aforesaid countries deriving from the above-identified application for Patents under the International Convention for the Protection of Industrial Property, under the Inter-American Convention relating to Inventions, Patents, Designs and Industrial Models and under any other international arrangement relating to patents or intellectual property, in and to any and all Letters Patent that are granted from the aforesaid application for Patents, in and to any applications claiming priority benefits to a provisional patent application or other applications filed on said invention, and in and to any continuations, divisions, reexaminations, reissues, renewals and extensions thereof of any of said Letters Patent, the same to be held and enjoyed by said **ASSIGNEE**, to the full ends of the terms for which all Letters Patent therefore may be granted, as fully and entirely as the same would have been held and enjoyed by us if this assignment and sale had not been made.

AND I/WE HEREBY covenant and agree that we will at any time, upon the request and at the expense of **ASSIGNEE**, without further compensation or charge to said **ASSIGNEE**, execute and deliver any and all documents that may be necessary or desirable to perfect the title to the foregoing invention, patent applications, and Letters Patent and continuations, divisions, reexaminations, reissues, renewals and extensions thereof in the name of **ASSIGNEE**, including the execution and procurement of any and all further documents evidencing this assignment and sale as may be necessary or desirable for recording the same in the Patent Office of any country concerned, and will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein.

I/WE HEREBY authorize **ASSIGNEE** to insert in this instrument the Application Number(s) and the filing date(s) of said application for Patents when officially notified thereof.

This document may be executed in any number of counterparts, each of which so executed shall be deemed to be an original, but all such components shall together constitute but one and the same document.

Executed this _____ day of _____ , 2018

_____
Manoj K. Sharma

ACKNOWLEDGEMENT

Commonwealth of Massachusetts

County Name, ss. _____

On this _____ day of _____, 2018, before me, the undersigned notary public, personally appeared **Manoj K. Sharma** proved to me through satisfactory evidence of identification, which was _____, to be the person whose name is signed on the preceding document, and acknowledged to me that he/she signed it voluntarily for its stated purpose.

_____
Notary Public:
My Commission Expires: _____

Executed this _____ day of _____ , 2018

_____
Wendy Benjamin

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____ , 2018, personally appeared before me **Wendy Benjamin** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Attorney Docket No.: 24439

Executed this _____ day of _____ , 2018

_____
Sarita Mittal

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____ , 2018, personally appeared before me **Sarita Mittal** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of _____ , 2018

_____
Ashwin Basarkar

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of _____)

On this _____ day of _____ , 2018, personally appeared before me **Ashwin Basarkar** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this ____ day of _____, 2018

_____
Chakravarthy Nachu Narasimhan

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____, 2018, personally appeared before me **Chakravarthy Nachu Narasimhan** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this 2nd day of JULY, 2018

Ramesh S. Kashi

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of _____)

On this 2nd day of July, 2018, personally appeared before me **Ramesh S. Kashi** to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

STEVEN O'LOUGHLIN
NOTARY PUBLIC OF NEW JERSEY
Comm. # 50082101
My Commission Expires 1/4/2022

Executed this ____ day of _____ , 2018

_____
Mohammed Shameem

ACKNOWLEDGEMENT

State of New York)
) s.s.:
County of _____)

On this _____ day of _____ , 2018, personally appeared before me **Mohammed Shameem** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this ____ day of _____ , 2018

_____
Soumendu Bhattacharya

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____ , 2018, personally appeared before me **Soumendu Bhattacharya** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Attorney Docket No.: 24439

Executed this _____ day of _____ , 2018

_____
William P. Forrest, Jr.

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this _____ day of _____ , 2018, personally appeared before me **William P. Forrest, Jr.** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

WORLDWIDE ASSIGNMENT

WHEREAS, I,

Yogita Krishnamachari, located in Scotch Plains, NJ

am an inventor(s) along with

(1) Manoj K. Sharma, located at Littleton, MA,
(2) Wendy Benjamin, located at North Brunswick, NJ,
(3) Sarita Mittal, located at Bridgewater, NJ,
(4) Ashwin Basarkar, located at Keasbey, NJ,
(5) Chakravarthy Nachu Narasimhan, located at Scotch Plains, NJ,
(6) Ramesh S. Kashi, located at Warren, NJ,
(7) Mohammed Shameem, located in Nanuet, NY,
(8) Soumendu Bhattacharya, located in East Windsor, NJ, and
(9) William P. Forrest, Jr., located in Middletown, NJ,

of the invention described in an application for Patents having the Attorney Docket Number indicated above and the following Title of the Invention:

STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

and/or in the following application(s):

U.S. Provisional Application No. 62/500,238 filed on May 2, 2017;
U.S. Application No. 16/609612 having a filing date of October 30, 2019; and
PCT International Application No. PCT/US18/030459 having a filing date of May 1, 2018.

WHEREAS I covenant that the rights and property herein conveyed are free and clear of any encumbrance, and that I have the full right to convey the same as herein expressed.

WHEREAS, Merck Sharp & Dohme Corp., a corporation organized under the laws of the State of New Jersey, having an office at 126 East Lincoln Avenue, Rahway, New Jersey 07065, and its successors, assigns and legal representatives (hereinafter **ASSIGNEE**), is desirous of obtaining the entire right, title and interest in, to and under the invention disclosed in said application or applications;

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, I do hereby sell, assign and transfer or confirm the grant and assignment to said **ASSIGNEE** my entire right, title and interest in all countries of the world in and to the invention described in said application for Patents, in and to the right to file patent applications in the name of **ASSIGNEE**, its designee, or in any or all of our names, at its election, on the aforesaid invention in all countries of the world, together with all rights of priority in the aforesaid countries deriving from the above-identified application for Patents under the International Convention for the Protection of Industrial Property, under the Inter-American Convention relating to Inventions, Patents, Designs and Industrial Models and under any other international arrangement relating to patents or intellectual property, in and to any and all Letters Patent that are granted from the aforesaid application for Patents, in and to any applications claiming priority benefits to a provisional patent application or other applications filed on said invention, and in and to any continuations, divisions, reexaminations, reissues, renewals and extensions thereof of any of said Letters Patent, the same to be held and enjoyed by said **ASSIGNEE**, to the full ends of the terms for which all Letters Patent therefore may be granted, as fully and entirely as the same would have been held and enjoyed by me/us if this assignment and sale had not been made.

AND I HEREBY covenant and agree that I will at any time, upon the request and at the expense of **ASSIGNEE**, without further compensation or charge to said **ASSIGNEE**, execute and deliver any and all documents that may be necessary or desirable to perfect the title to the foregoing invention, patent applications, and Letters Patent and continuations, divisions, reexaminations, reissues, renewals and extensions thereof in the name of **ASSIGNEE**, including the execution and procurement of any and all further documents evidencing this assignment and sale as may be necessary or desirable for recording the same in the Patent Office of any country concerned, and will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein.

I HEREBY authorize **ASSIGNEE** to insert in this instrument the Application Number(s) and the filing date(s) of said application for Patents when officially notified thereof.

This document may be executed in any number of counterparts, each of which so executed shall be deemed to be an original, but all such components shall together constitute but one and the same document.

Executed this 22 day of OCTOBER, 2019

Yogita Krishnamachari

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this 22 day of October, 2019, personally appeared before me **Yogita Krishnamachari** to me known, and known by me to be the same person(s) described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Notary Public

DINA A. KUSTER
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires 8/7/2020

STATE OF NEW JERSEY
DEPARTMENT OF TREASURY
FILING CERTIFICATION (CERTIFIED COPY)

MERCK SHARP & DOHME LLC
0600468333

I, the Treasurer of the State of New Jersey, do hereby certify, that the above named business did file and record in this department a Certificate of Merger on April 12th, 2022 and that the attached is a true copy of this document as the same is taken from and compared with the original(s) filed in this office and now remaining on file and of record.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed my Official Seal at Trenton, this 18th dav of April. 2022

Elizabeth Maher Muoio
State Treasurer

Certificate Number: 143726201
Verify this certificate online at
https://www.njportal.com/DOR/businessrecords/Validate.aspx

FILED
APR 12 2022
STATE TREASURER

CERTIFICATE OF MERGER
FOR THE MERGER OF
MERCK SHARP & DOHME CORP.
(ID: 7954401000)
WITH AND INTO
MERCK SHARP & DOHME LLC
(ID: 0600468333)

Pursuant to Section 74 of N.J. Stat. § 42:2C, the New Jersey Revised Uniform Limited Liability Company Act and Section 10 of N.J. Stat. § 14A, the New Jersey Business Corporation Act

Merck Sharp & Dohme LLC, a New Jersey limited liability company (the "***LLC***"), does hereby certify to the following facts relating to the merger (the "***Merger***") of Merck Sharp & Dohme Corp., a New Jersey corporation (the "***Corporation***"), with and into the LLC, with the LLC remaining as the surviving entity of the Merger (the "***Surviving Entity***"):

FIRST: The type of this filing is Merger.

SECOND: The name of the Surviving Entity of the Merger shall be Merck Sharp & Dohme LLC, which shall continue its existence as the surviving limited liability company under the name Merck Sharp & Dohme LLC.

THIRD: The address of the Surviving Entity is 126 East Lincoln Ave., P.O. Box 2000, Rahway, New Jersey 07065.

FOURTH: The Corporation's name is Merck Sharp & Dohme Corp. and it is incorporated pursuant to the New Jersey Business Corporation Act (the "***NJBCA***"). The LLC's name is Merck Sharp & Dohme LLC, and it is formed pursuant to the New Jersey Revised Uniform Limited Liability Company Act (the "***RULLCA***"). The Corporation and the LLC are the constituent corporations in the Merger.

FIFTH: A Plan and Agreement of Merger has been approved, adopted, executed and acknowledged by the Corporation and by the LLC in accordance with Section 75 of the RULLCA and Section 10 of the NJBCA.

SIXTH: The Plan and Agreement of Merger is on file at the place of business of the Surviving Entity. A copy of the executed Plan and Agreement of Merger will be furnished by the Surviving Entity to any member or any person having an interest in the Merger.

SEVENTH: This Certificate of Merger shall be effective at 12:01 a.m., Eastern Time, on May 1, 2022, in accordance with Section 76 of the RULLCA and Section 10 of the NJBCA.

[SIGNATURE PAGE NEXT]

IN WITNESS WHEREOF, each of Merck Sharp & Dohme LLC and Merck Sharp & Dohme Corp. has caused this Certificate of Merger to be executed in its company name by its authorized representative as of the 7th day of April, 2022.

MERCK SHARP & DOHME LLC

By: 

Name: Rita Karachun

Title: President

MERCK SHARP & DOHME CORP.

By:

Name: Jerome Mychalowych

Title: Vice President

IN WITNESS WHEREOF, each of Merck Sharp & Dohme LLC and Merck Sharp & Dohme Corp. has caused this Certificate of Merger to be executed in its company name by its authorized representative as of the 7th day of April, 2022.

MERCK SHARP & DOHME LLC

By:

_____

Name: Rita Karachun

Title: President

MERCK SHARP & DOHME CORP.

By:

_____

Name: Jerome Mychalowych

Title: Vice President

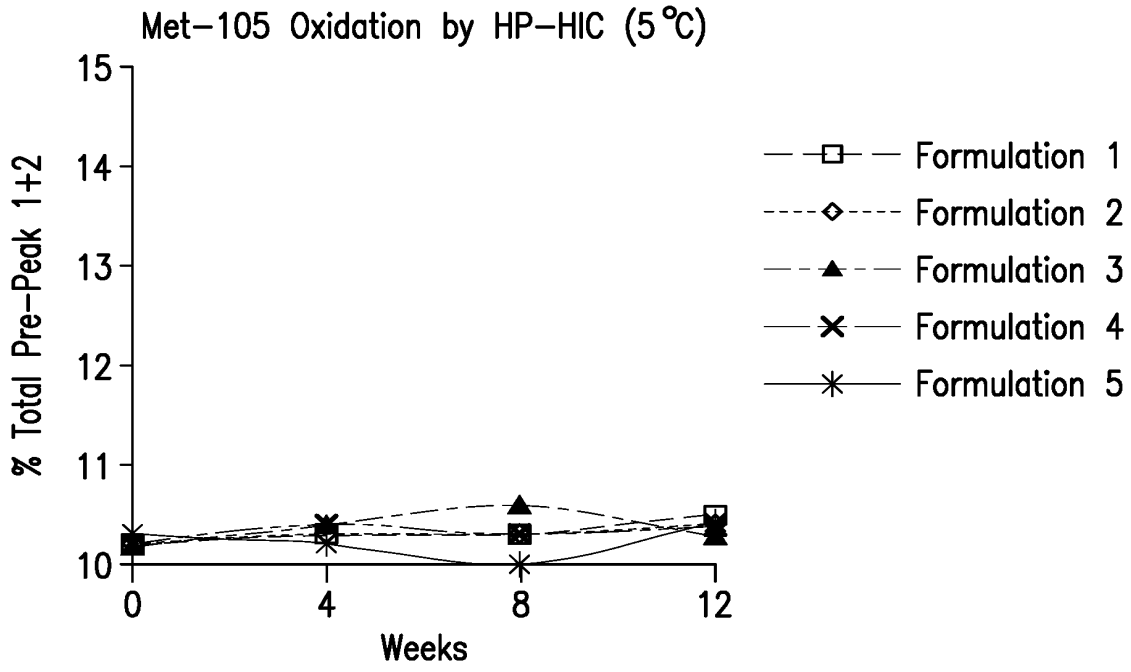

Met−105 Oxidation by HP−HIC (5 °C)
% Total Pre−Peak 1+2
15
14
13
12
11
10
0
4
8
12
Weeks
Formulation 1
Formulation 2
Formulation 3
Formulation 4
Formulation 5

FIG. 1A

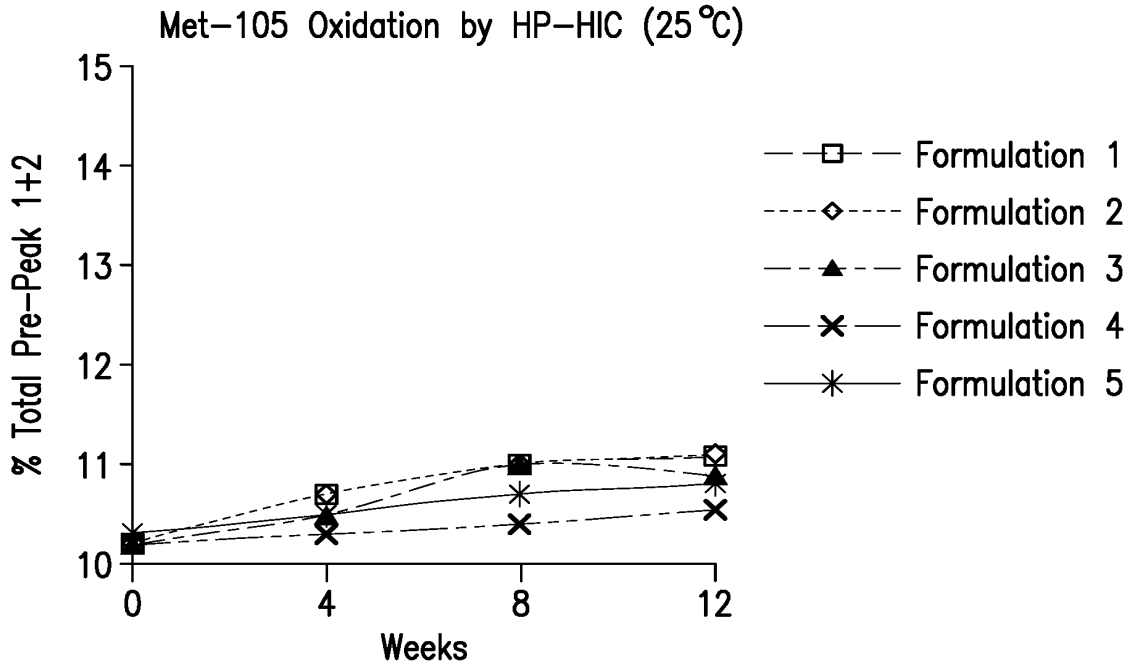

Met−105 Oxidation by HP−HIC (25 °C)
% Total Pre−Peak 1+2
15
14
13
12
11
10
0
4
8
12
Weeks
Formulation 1
Formulation 2
Formulation 3
Formulation 4
Formulation 5

FIG. 1B

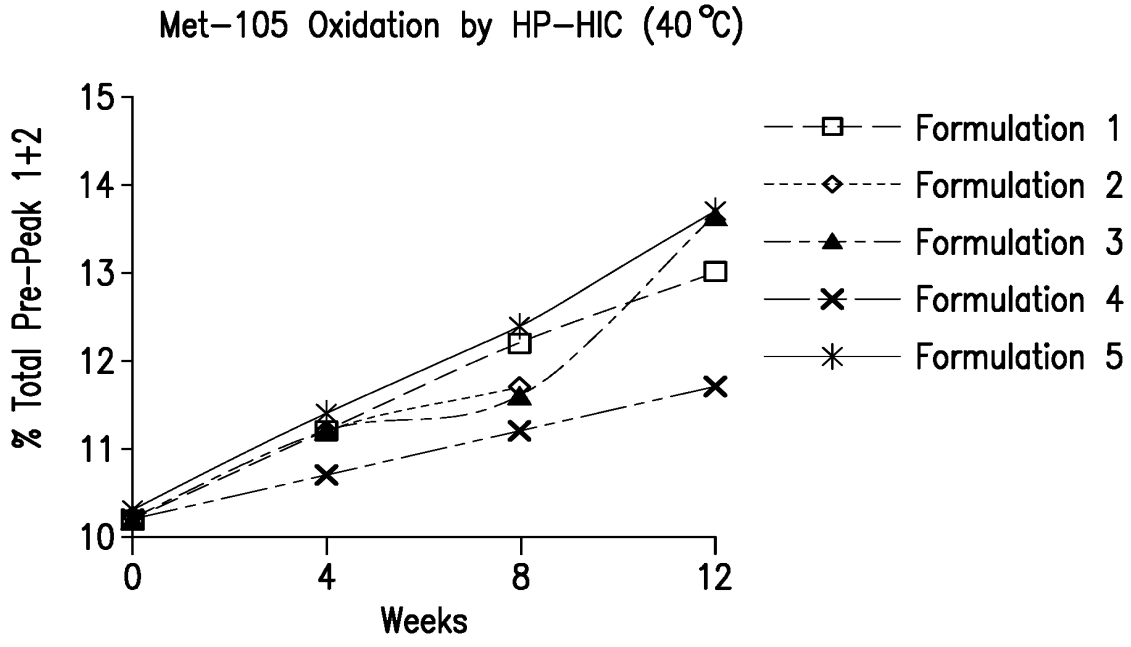

Met−105 Oxidation by HP−HIC (40 °C)
% Total Pre−Peak 1+2
15
14
13
12
11
10
0
4
8
12
Weeks
Formulation 1
Formulation 2
Formulation 3
Formulation 4
Formulation 5

FIG.1C

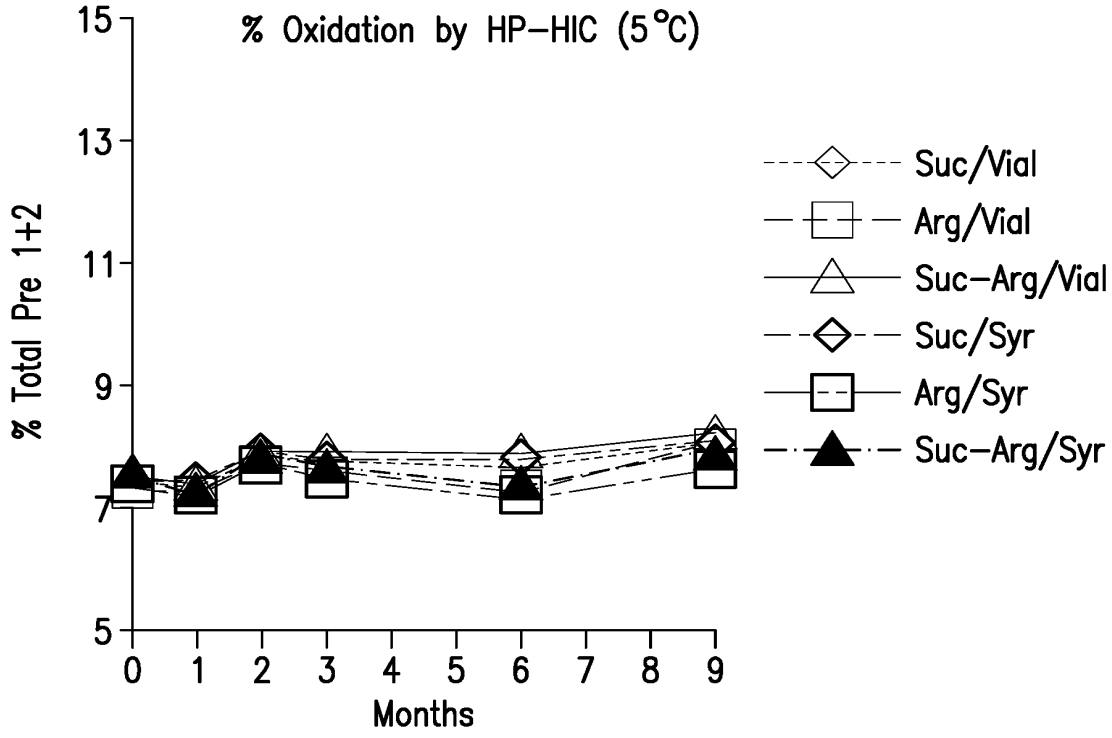

% Oxidation by HP-HIC (5°C)
% Total Pre 1+2
15
13
11
9
7
5
0
1
2
3
4
5
6
7
8
9
Months
Suc/Vial
Arg/Vial
Suc-Arg/Vial
Suc/Syr
Arg/Syr
Suc-Arg/Syr

FIG.2A

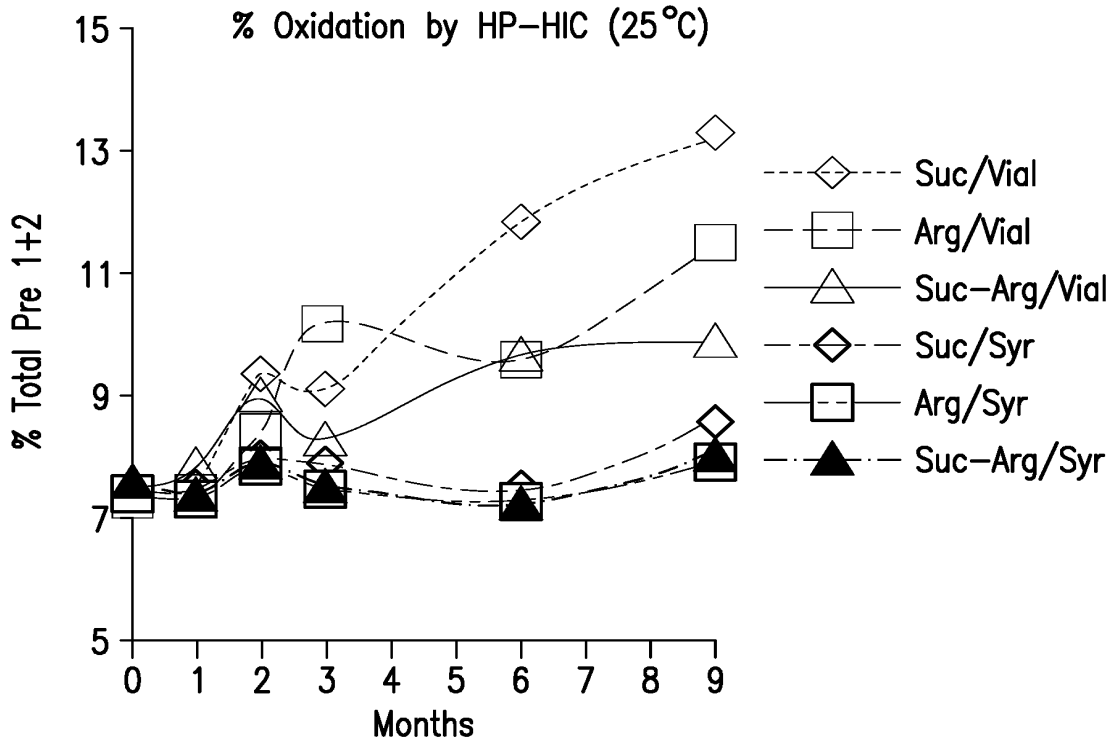

% Oxidation by HP-HIC (25°C)
% Total Pre 1+2
15
13
11
9
7
5
0
1
2
3
4
5
6
7
8
9
Months
Suc/Vial
Arg/Vial
Suc-Arg/Vial
Suc/Syr
Arg/Syr
Suc-Arg/Syr

FIG.2B

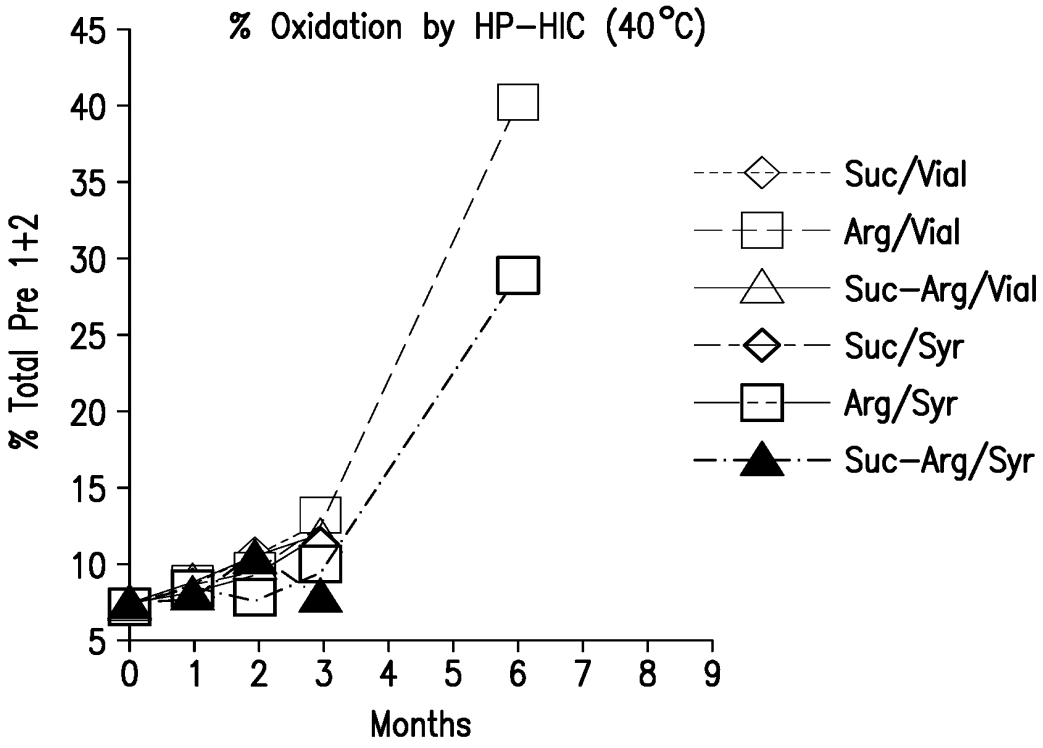

% Oxidation by HP-HIC (40°C)
% Total Pre 1+2
45
40
35
30
25
20
15
10
5
0
1
2
3
4
5
6
7
8
9
Months
Suc/Vial
Arg/Vial
Suc-Arg/Vial
Suc/Syr
Arg/Syr
Suc-Arg/Syr

FIG.2C

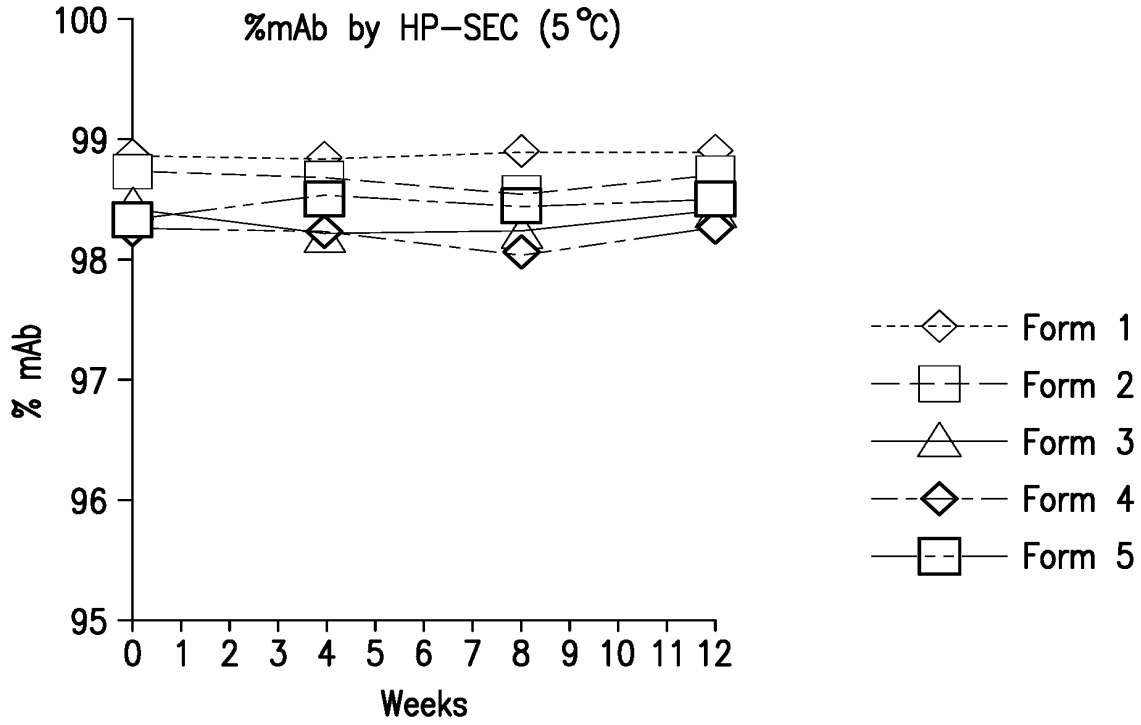

%mAb by HP-SEC (5°C)
100
99
98
97
96
95
% mAb
0 1 2 3 4 5 6 7 8 9 10 11 12
Weeks
Form 1
Form 2
Form 3
Form 4
Form 5

FIG.3A

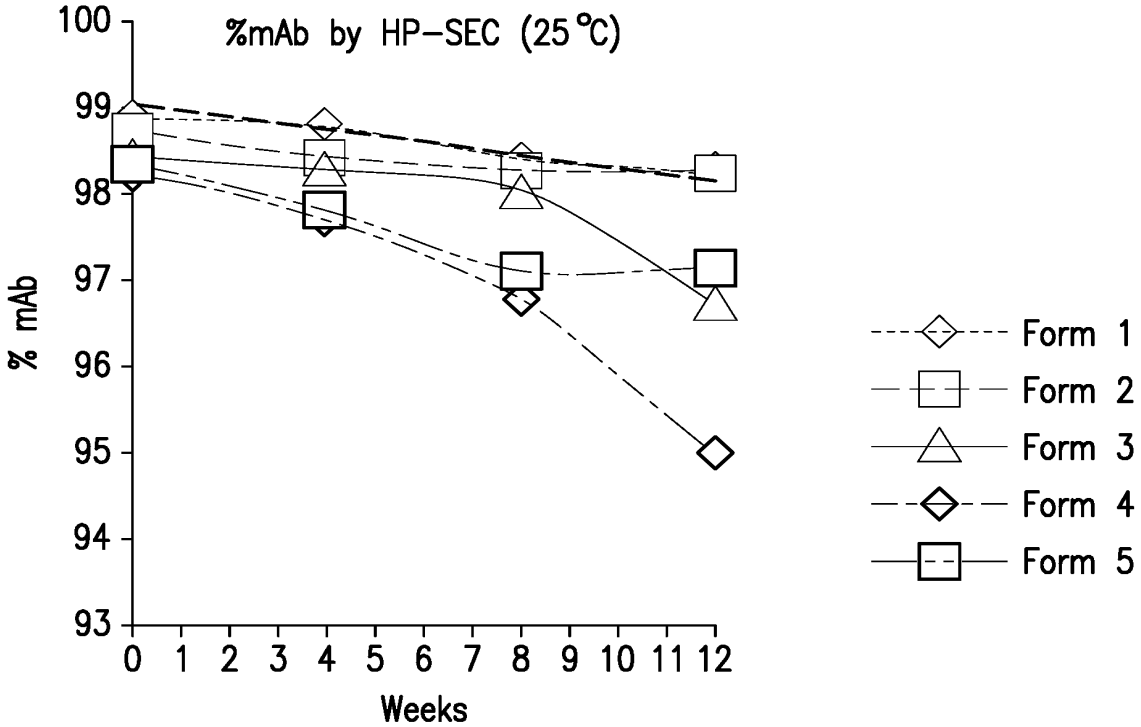

%mAb by HP-SEC (25°C)
100
99
98
97
96
95
94
93
% mAb
0 1 2 3 4 5 6 7 8 9 10 11 12
Weeks
Form 1
Form 2
Form 3
Form 4
Form 5

FIG.3B

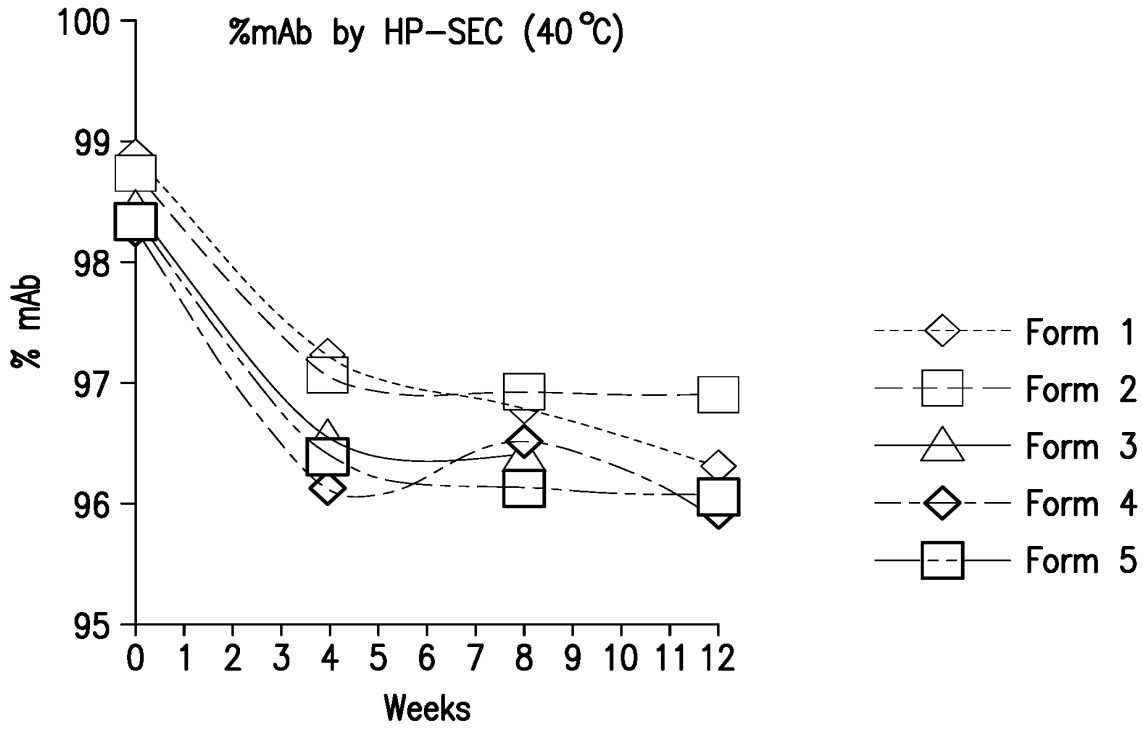

%mAb by HP-SEC (40°C)
100
99
98
97
96
95
% mAb
0 1 2 3 4 5 6 7 8 9 10 11 12
Weeks
Form 1
Form 2
Form 3
Form 4
Form 5

FIG.3C

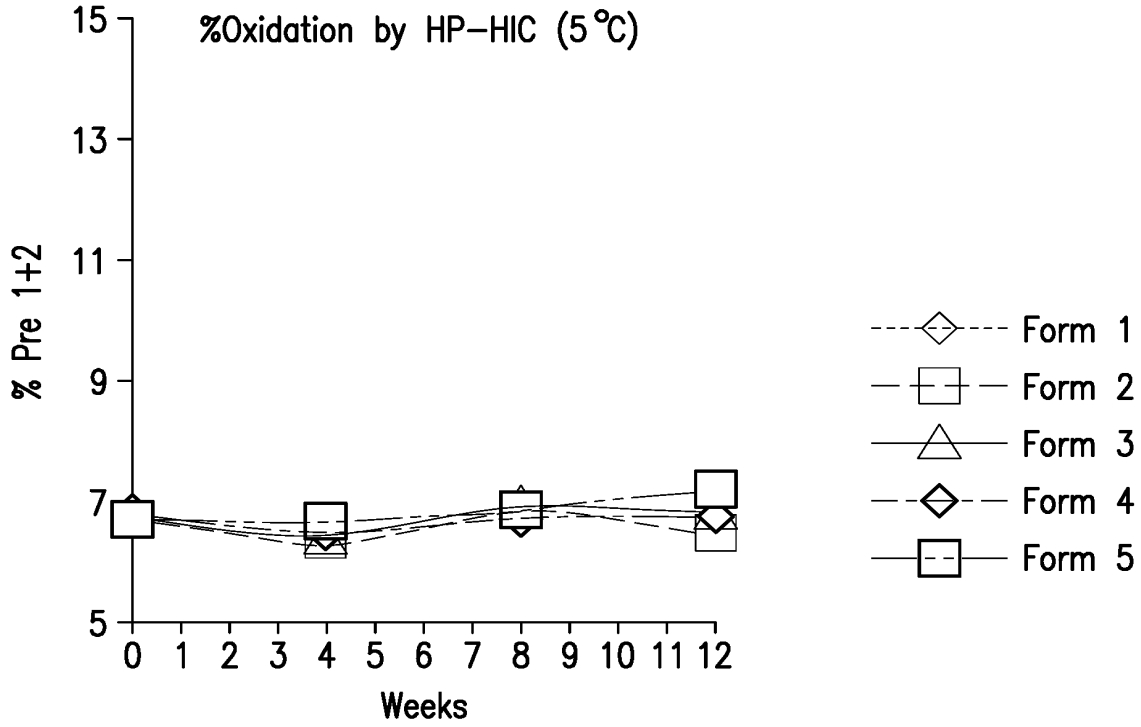

%Oxidation by HP-HIC (5 °C)
% Pre 1+2
15
13
11
9
7
5
0 1 2 3 4 5 6 7 8 9 10 11 12
Weeks
Form 1
Form 2
Form 3
Form 4
Form 5

FIG.4A

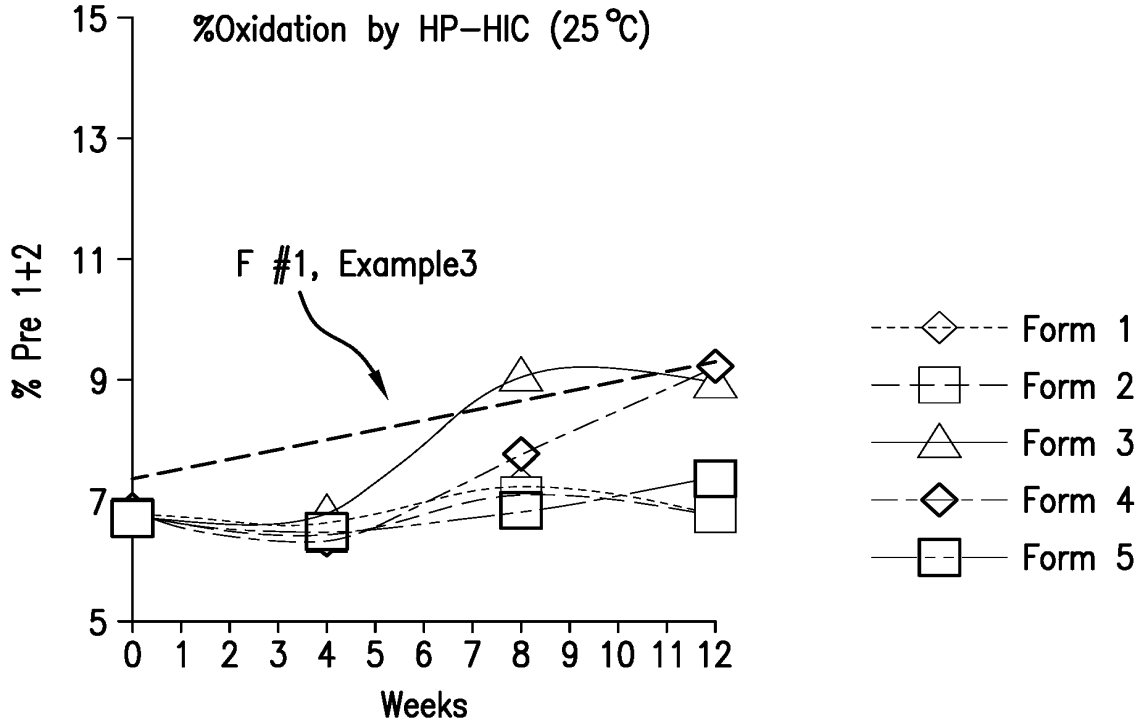

%Oxidation by HP-HIC (25 °C)
F #1, Example3
% Pre 1+2
15
13
11
9
7
5
0 1 2 3 4 5 6 7 8 9 10 11 12
Weeks
Form 1
Form 2
Form 3
Form 4
Form 5

FIG.4B

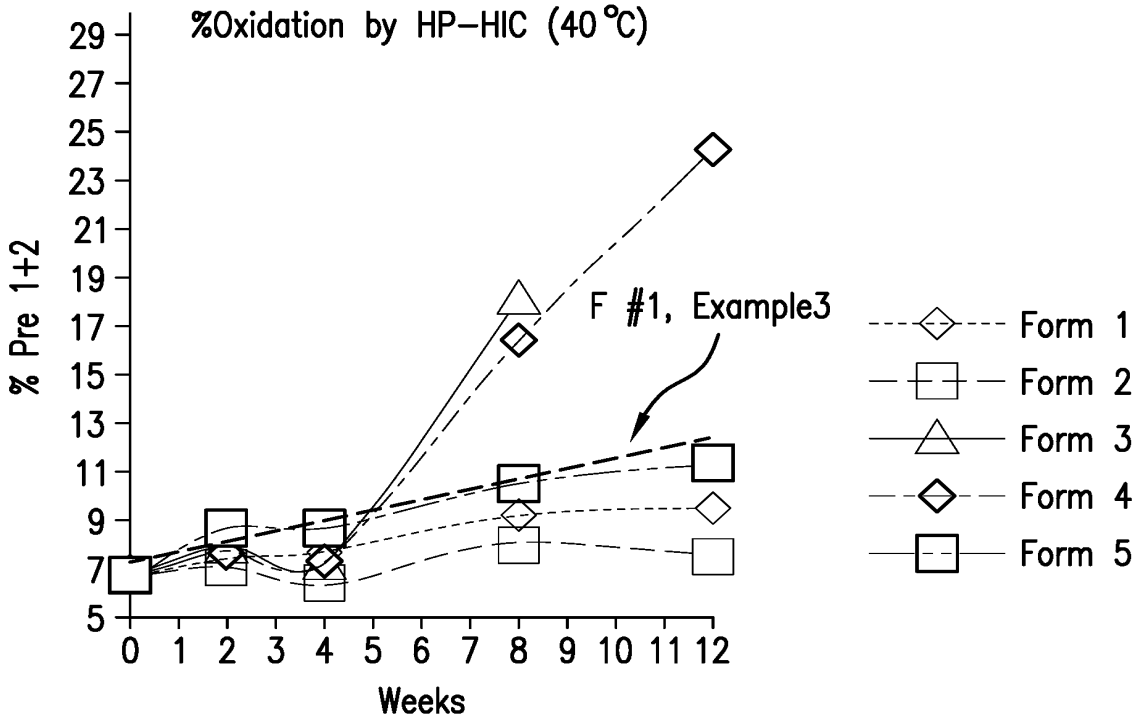

%Oxidation by HP-HIC (40 °C)
% Pre 1+2
29
27
25
23
21
19
17
15
13
11
9
7
5
0 1 2 3 4 5 6 7 8 9 10 11 12
Weeks
F #1, Example3
Form 1
Form 2
Form 3
Form 4
Form 5

FIG.4C

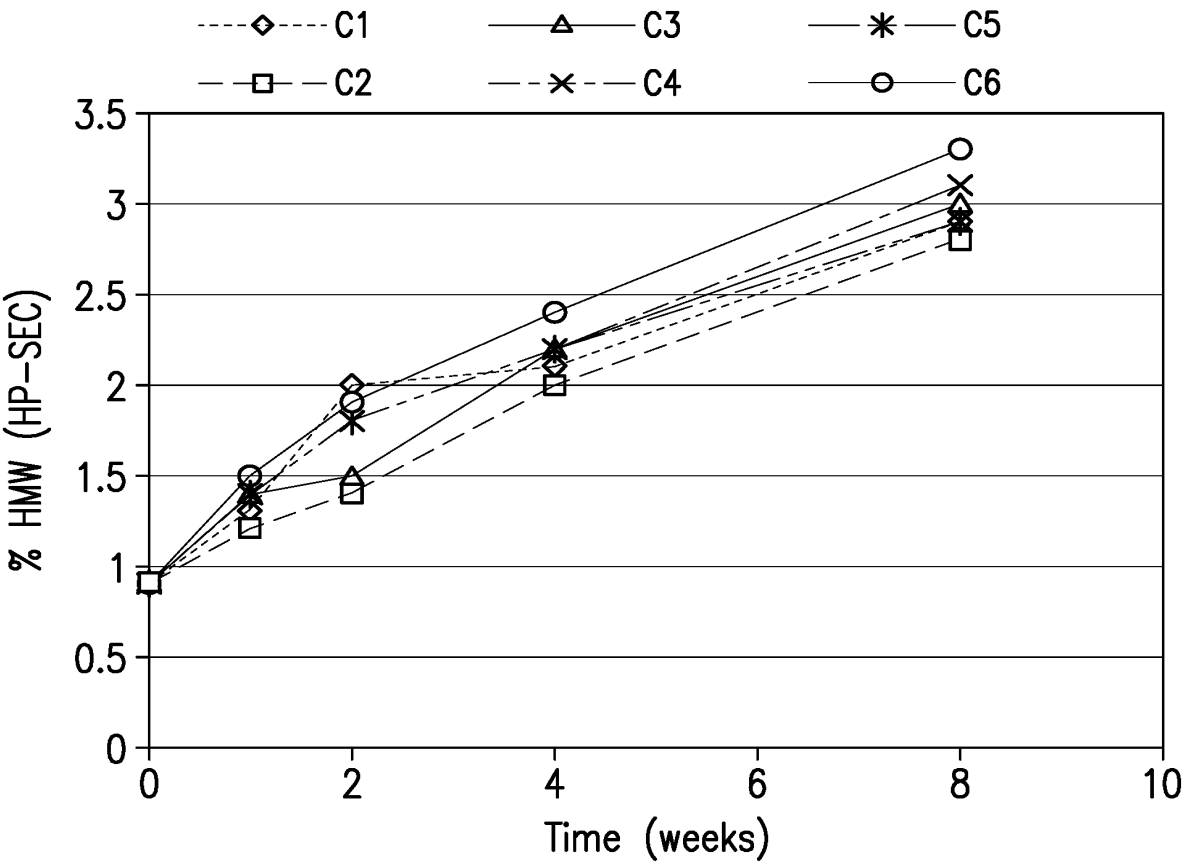


FIG.5

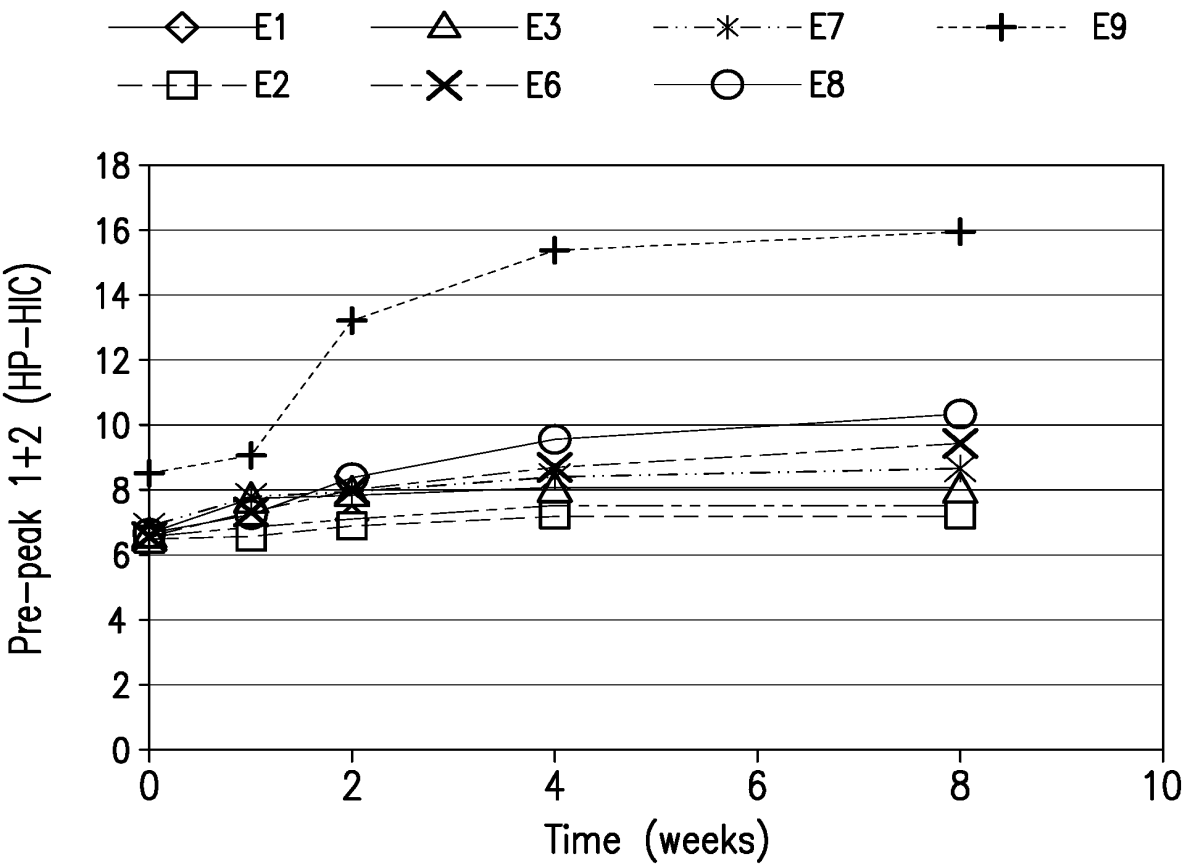

E1
E3
E7
E9
E2
E6
E8
Pre-peak 1+2 (HP-HIC)
18
16
14
12
10
8
6
4
2
0
0
2
4
6
8
10
Time (weeks)

FIG.6

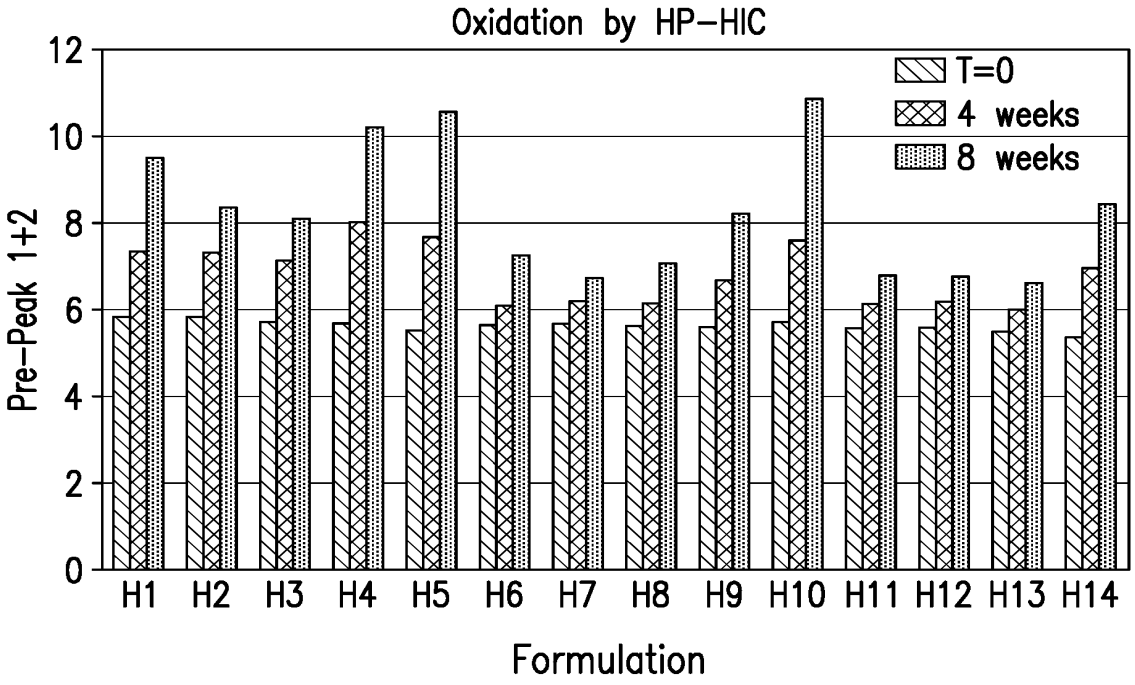

Oxidation by HP-HIC
T=0
4 weeks
8 weeks
Pre-Peak 1+2
0
2
4
6
8
10
12
H1
H2
H3
H4
H5
H6
H7
H8
H9
H10
H11
H12
H13
H14
Formulation

FIG.7

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/346,638	**10/01/2025 09:01:01 AM Z ET**	**24439-US-CNT-4**

Title of Invention

STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	6069	FILED BY	Christine Kanellidis
PATENT CENTER #	72490912	FILING DATE	-
CUSTOMER #	210	FIRST NAMED INVENTOR	Manoj K. Sharma
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Patrick Rehfuss

Documents

TOTAL DOCUMENTS: 10

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
24439USCNT4-ADS-26SEP2025.pdf	11	Application Data Sheet	2175 KB
24439USCNT4-TRACK1_REQ-DDSEP2025.pdf	2	Track One Request	215 KB
24439USCNT4-TRANLET-26SEP2025.pdf	3	Transmittal Letter	97 KB
24439USCNT4-DRW.pdf	11	Drawings-only black and white line drawings	136 KB
24439USCNT4-SPEC-17SEP2025-APP.TEXT.docx	110	Application body structured text document	209 KB

Warning: One or more paragraphs appear to have been formatted with line spacing of

'At least' a certain value. This may cause a difference in the page count when the app.txt is split into sections (Specification, Claims, Abstract). Please review and correct if necessary. Text decorations have been removed. Bookmarks were found and have been removed. One or more pages are missing page numbering. Page numbering will be automatically applied after submission.

MERCKLLC-POA-05SEP2025.pdf	3	Power of Attorney	1006 KB
24439USCNT4-IDS-26SEP2025.pdf	77	Information Disclosure Statement (IDS) Form (SB08)	1307 KB
24439USPCT-OATH-11DEC2019.pdf	10	Oath or Declaration filed	4994 KB
24439USCNT-373C-07MAR2023.pdf	38	Miscellaneous Incoming Letter	16367 KB
24439-US-CNT.xml	-	Sequence Listing Supp (XML File)	42 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
24439USCNT4-ADS-26SEP2025.pdf	86F8BAB01B39D219F7F7FDD0BF311219FFDE46DD670A74B8BDAB9B4CD1E86E0EA139D1F3BB578A9AEE85B13F75B02E1EFE955AC74D5D5232D780AC4E6E2E32D1
24439USCNT4-TRACK1_REQ-DDSEP2025.pdf	9652200582AEF576F0F9F8653D88DC1B807D209C4358E52440F78D5010E0D03CE51AC7840F9D9F92CA5AD7E96B9F787CF284DC62A2575F5BAAE400C5B1608A0F
24439USCNT4-TRANLET-26SEP2025.pdf	E5C3F512A74EF649154B3E1F56560DE06759093D8D20F4DFCB6812B371C4693E3908FD0C07B0A4F38AC602CAAE1DF0D5B1E35AEA52BFE8A29D1943E75B4EF7E1
24439USCNT4-DRW.pdf	F91A65E0EF4B4FB7198BBEFB39E3FCA9B8D0A64D16C87DC025C8CCBAD1C563933175DA8CAC7C6DD8069E3A858EB5C65CF3C2515DFCB1D2FC3DDFCFBE0612A99C
24439USCNT4-SPEC-17SEP2025-APP.TEXT.docx	D9270772C265DF2B0EBCECFE5862548057E497EFFCB20B5FE7A47B225FE4ED4AA91E901C39EFE55950032DED215332747961604E0102C29C23BCCD53D4FF20F7
MERCKLLC-POA-05SEP2025.pdf	D3B80D604AE0F39150E12CDE5C102B2A91DE6853B42645E61FE1266728CB19EFCC975F08EAEA785C7E8451CC3BE8183A8118B5E73C01AC541B37D30E9137A7A2
24439USCNT4-IDS-26SEP2025.pdf	13EC3FA6604FD9757F70A339ACC6B8A1DDD9934A85E01B63F3E30B2571991C119621EA8A66725EC10E4FDA5CAF9DAE15

	BD5F130C3D4679BE0F4B60A5A827251D
24439USPCT-OATH-11DEC2019.pdf	E4C4B4CC7A2D169BFCF3554F6D4D4B9E2AC819524384F47AB51986832DF40A9C7BD40EC758E7F1BCD12A964CFF9A2286143EB88071A8EEED357586A5E2748E68
24439USCNT-373C-07MAR2023.pdf	532E620C64F0C7BBA52473811C26B32323841A54C642DE1328DBB5417CE2AC63339EBC7CAFE7A31F14374053B3D821540157C74134A411359C9D15D44E3AF814
24439-US-CNT.xml	9BE0019827FE2E0180B57200A0FA1156B4AD9D5A0DA2299C59373099490D5840404B91F434A2B51C38C078998F731A53B5263D99E5EC8FAFE24FBA00241C0D35

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/346,638	**10/01/2025 09:01:01 AM Z ET**	**24439-US-CNT-4**

Title of Invention

STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

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CONFIRMATION #	6069	FILED BY	Christine Kanellidis
PATENT CENTER #	72490912	AUTHORIZED BY	Patrick Rehfuss
CUSTOMER #	210	FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Manoj K. Sharma

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 132755	**E202501020477912**	**Christine Kanellidis**

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
132755	**37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees)**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1055	FILING AN APPLICATION OR PRESENTATION OF BENEFIT CLAIM MORE THAN SIX YEARS AFTER EARLIEST BENEFIT DATE	2700.00	1	2700.00
1011	BASIC FILING FEE - UTILITY (PAPER FILING ALSO REQUIRES NON-ELECTRONIC FILING FEE UNDER 1.16(T))	350.00	1	350.00
1111	UTILITY PATENT APPL. SEARCH FEE	770.00	1	770.00

1311	PATENT APPL. EXAMINATION FEE	880.00	1	880.00
1817	REQUEST FOR PRIORITIZED EXAMINATION	4515.00	1	4515.00
1830	PROCESSING FEE, EXCEPT IN PROVISIONAL APPLICATIONS	150.00	1	150.00
1834	FILING AN INFORMATION DISCLOSURE STATEMENT THAT CAUSES THE CUMULATIVE NUMBER OF APPLICANT-PROVIDED ITEMS OF INFORMATION TO EXCEED 200	800.00	1	800.00
1202	EACH CLAIM IN EXCESS OF 20	200.00	10	2000.00
			TOTAL AMOUNT:	**¤12,165.00**

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New International Application Filed with the USPTO as a Receiving Office

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 19/346,638

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	350
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	770
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	880
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10			OR	x 200 =	2000
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x =	0
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
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	4000

APPLICATION AS AMENDED - PART II

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

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
19/346,638	10/01/2025		4000	24439-US-CNT-4	30	2

CONFIRMATION NO. 6069

210
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RAHWAY, NJ 07065-0907

FILING RECEIPT

OC00000009622914 2

Date Mailed: 10/21/2025

Receipt is acknowledged of this non-provisional utility 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 FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

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Inventor(s)

Manoj K. Sharma, Littleton, MA;
Wendy Benjamin, North Brunswick, NJ;
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William P. Forrest, Jr., Middletown, NJ;
Yogita Krishnamachari, Scotch Plains, NJ;

Applicant(s)

Merck Sharp & Dohme LLC, Rahway, NJ;

Assignment For Published Patent Application

Merck Sharp & Dohme LLC, Rahway, NJ

Power of Attorney: The patent practitioners associated with Customer Number 210

Domestic Applications for which benefit is claimed

This application is a CON of 18/182,135 03/10/2023
which is a CON of 16/609,612 10/30/2019 PAT 11,633,476
which is a 371 of PCT/US18/30459 05/01/2018
which claims benefit of 62/500,238 05/02/2017

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

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If Required, Foreign Filing License Granted: 10/20/2025

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 19/346,638**

Projected Publication Date: 01/29/2026

Non-Publication Request: No

Early Publication Request: No
Title

STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

Preliminary Class

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

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/346,638	10/01/2025	Manoj K. Sharma	24439-US-CNT-4	6069

210 7590 11/03/2025

MERCK
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER
CENTRAL, DOCKET

ART UNIT	PAPER NUMBER
OPAP	

NOTIFICATION DATE	DELIVERY MODE
11/03/2025	ELECTRONIC

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

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lori_schepisi@merck.com
merck_pair@firsttofile.com

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 19/346,638	**Applicant(s)** Sharma et al.	
	Examiner JoAnne L Burke	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 01 October 2025 IS **GRANTED** .

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

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

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

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

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

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

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

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

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to JoAnne Burke at (571) 272-458. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/JOANNE L BURKE/ Lead Paralegal Specialist, OPET	

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
19/346,638	10/01/2025	Manoj K. Sharma	24439-US-CNT-4

CONFIRMATION NO. 6069

210
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PUBLICATION NOTICE

OC000000100781430

Date Mailed: 01/29/2026

Title:STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

Publication No.US-2026-0027205-A1
Publication Date:01/29/2026

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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
19/346,638	10/01/2025	Manoj K. Sharma	24439-US-CNT-4	6069

210 7590 02/02/2026

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EXAMINER	
BALLARD, KIMBERLY	

ART UNIT	PAPER NUMBER
1675	

NOTIFICATION DATE	DELIVERY MODE
02/02/2026	ELECTRONIC

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lori_schepisi@merck.com
merck_pair@firsttofile.com

Office Action Summary	Application No. 19/346,638	Applicant(s) Sharma et al.	
	Examiner Kimberly A Ballard	Art Unit 1675	AIA (First Inventor to File) Status Yes

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

Period for Reply

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

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

Status

1)☑ Responsive to communication(s) filed on 01 October 2025.

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

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

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

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

Disposition of Claims*

5) ☑ Claim(s) 1-30 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-30 is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Status of Application, Amendments and/or Claims

1. Claims **1-30** are pending and under examination in the present office action.

Information Disclosure Statement

2. The information disclosure statement (IDS) filed October 1, 2025 has been considered and the references therein are of record.

Claim Objections

3. Claim **28** is objected to because of the following informalities: claim 28 repeats the term “esophageal cancer” twice within the listing of cancer types. Appropriate correction is required.

Claim Rejections - 35 USC § 112

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.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim **28** is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

Regarding claim 28, the "for example” phrase in line 5, “(e.g. hormone refractory prostate adenocarcinoma)”, renders the claim indefinite because it is unclear whether

the limitation(s) following the phrase are part of the claimed invention or else definitively limit the term "prostate cancer". See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 103

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, 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.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claim(s) **1-4, 6, 14** and **20-30** is/are rejected under 35 U.S.C. 103 as being unpatentable over **Sharma et al**. (US 9,220,776 B2) as evidenced by Wang et al. (*Oncoimmunology*, 2021, 10(1):1896643) (both listed on 10/01/2025 IDS).

Sharma et al. disclose stable formulations comprising an antibody directed against human programmed death receptor PD-1 (i.e., an anti-human PD-1 antibody) or antigen binding fragments thereof and methods for treating various cancers using these stable formulation of anti-human PD-1 antibodies (see col. 3, lines 24-30). Sharma teaches that the PD-1 blocking antibody is h409A11 (see col. 4 lines 49-50). As evidenced by Wang et al., the h409A11 humanized anti-PD-1 antibody is alternatively called pembrolizumab or MK3475 (see figure legend for Figure 2D at p. 7). See also col. 4 lines 56-59 of Sharma describing a method of treating cancer in a mammalian subject in need thereof, comprising administering an effective amount of any of the disclosed antibody formulations, and col. 6 lines 47-49 teaching that desirable subjects include human patients with cancer. Thus, Sharma discloses antibody formulations comprising

the anti-human PD-1 antibody pembrolizumab and their use in the treatment of cancer in a human patient, as in **claims 1** and **24**.

In particular, a liquid formulation is taught to include: (a) 25-100 mg/mL antibody, or antigen binding fragment thereof (i.e., *about 5 mg/mL to about 200 mg/mL antibody or antigen binding fragment thereof*; **claims 1a** and **24a**; *about 25 mg/ml to about 100 mg/ml*; **claim 21**); (b) about 10 mM histidine buffer (*about 5 mM to about 20 mM buffer*; **claims 1b** and **24b**); (c) about 70 mg/ml sucrose, which is 7% w/v sucrose (*about 6% to about 8% w/v sucrose*; **claims 1ci, 6** and **24 ci**); (d) about 0.2 mg/mL polysorbate 80, which is 0.02% of a non-ionic surfactant (about 0.01% to about 0.10% non-ionic surfactant; **claims 1d, 14** and **24d**); and (e) at pH 5.0 to 6.0 (*the formulation has a pH between 5.0 and 6.0*; **claim 2**). See column 4, lines 1-7 and 15-16 of Sharma. An exemplary liquid antibody formulation comprising 10 mM histidine buffer, pH 5.5, 7% sucrose, 0.02% polysorbate 80, and 25 mg/ml h409A11 (i.e., pembrolizumab) is provided, for instance, at col. 20 lines 16-18.

Thus, the patent's teachings are directly on point to elements **a, c** and **d** of present **claims 1** and **24**, the concentration of buffer in **claims 1b** and **24b**, the pH of **claim 2**, the stabilizer of **claim 6**, the surfactant of **claim 14**, and the liquid formulation of **claim 20**.

Reconstituted liquid formulations may comprise antibody at a concentration of about 25 mg/ml (or about 10, 15, 20, 25, 30, 40, 50, 60, 75, 80, 90 or 100 mg/ml), or higher concentrations such as 150 mg/ml or 200 mg/ml (col. 19 lines 1-4), which teach and suggest antibody concentration limitations of present **claims 21** (*about 25 mg/ml to about 100 mg/ml*), **claims 22** and **25** (*about 25 mg/ml*), and **claim 23** and **26** (*about 165 mg/ml to about 170 mg/ml*).

Regarding **claim 28** reciting different forms of cancer to be treated according to the presently claimed methods, Sharma discloses that the anti-human PD-1 antibody formulations are used in therapeutic methods for the treatment of: melanoma, myeloma, renal cancer, prostate cancer (e.g., hormone refractory prostate adenocarcinoma), bladder cancer, pancreatic cancer, breast cancer, colon cancer, lung cancer, squamous cell carcinoma of the head and neck, liver cancer, ovarian cancer, cervical cancer, thyroid cancer, glioblastoma, glioma, leukemia, lymphoma, and other neoplastic

malignancies such as melanoma, colorectal, liver, kidney, stomach, esophageal, breast, pancreas, and ovarian cancer (col. 6 lines 51-67; col. 7 lines 7-20). Additional cancers that are disclosed as being beneficially treated include nasopharyngeal cancer, cervical, vulval, anal, penile and oral cancers (col. 7 lines 30-38).

And regarding **claim 27**, Sharma teaches that the antibody formulations can be given by subcutaneous administration (col. 3, lines 16-19; col. 15 lines 51-53; and col. 20 lines 53-55).

Finally, at col. 13, lines 1-14, Sharma discloses that the term "buffer" encompasses those agents which maintain the solution pH in an acceptable range prior to lyophilization. Examples of buffers will control the pH within the range of about 5.0 to about 6.0 are taught to include succinate, gluconate, histidine, citrate and other organic acid buffers. Sharma indicates that histidine, acetate and citrate buffers in the range of 5.0-6.0 were explored for suitability in the antibody formulation, wherein histidine and acetate were noted to perform better than the citrate system.

Thus, while not preferred embodiments, the disclosure of acetate and citrate as suitable buffers nonetheless meets the limitations of present **claims 1b, 3-4** and **24b**. A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied,* 493 U.S. 975 (1989). See also *Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of filing to have substituted acetate or citrate buffer for histidine buffer in the exemplary formulation and thereby arrive at the presently claimed invention. Sharma teaches that each of these buffers (citrate, acetate and histidine) is capable of maintaining the desired pH of the antibody formulation in the range of 5.0-6.0, and thus recognizes the functional equivalency of the buffering agents. Again, while histidine is indicated as a preferred embodiment, this in no way negates or teaches away from the use of either acetate or citrate as a buffer in a liquid antibody formulation as claimed. Thus, the substitution of histidine with either acetate or citrate as a buffering agent would have been obvious and predictable. This is because the artisan has good reason

to pursue the known options within his or her technical grasp to obtain predictable results. Such would amount to the simple substitution of equivalent elements (i.e., one buffer for another) to achieve a predictable outcome.

6. Claim(s) **1-6, 14** and **20-30** is/are rejected under 35 U.S.C. 103 as being unpatentable over **Sharma et al**. (US 9,220,776 B2) as evidenced by Wang et al. (*Oncoimmunology*, 2021, 10(1):1896643) as applied to claims 1-4, 6, 14 and 20-30 above, and in view of **Wang et al**. (*Mol. Pharmaceutics*, 2015, 12, 4478-4487; hereinafter "Wang 2015") and **Barry et al**. (US 2009/0060906 A1) (all references listed on 10/01/2025 IDS).

The reasons why the teachings of **Sharma et al**. render obvious the invention of claims 1-4, 6, 14 and 20-30 is discussed above. As indicated above, Sharma teaches that the antibody formulation may additionally include amino acids such as arginine (col. 13 lines 24-25 of Sharma).

However, the reference does not teach that the formulation further comprises from about 1% to about 3% w/v L-arginine, or a pharmaceutically acceptable salt thereof, as in **claim 5**.

Wang 2015 teaches that antibody formulations comprising high concentrations of antibody can benefit from the addition of amino acid excipients or the salt forms to reduced viscosity and improve stability (see abstract). In particular, Wang teaches that the excipient arginine hydrochloride (ArgHCl) can lower the viscosity of antibody formulations (see Fig. 2) without causing detectable antibody aggregation, conformational changes, or decreased storage stability (see Conclusion at p. 4485).

Consistent with the teachings of Wang 2015, **Barry et al**. teach stable antibody formulations that include about 0.01% to about 5% arginine, with specific embodiments containing, for example, 1.0%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5% or 5% arginine (see [0005] and [0080]). In particular, an exemplary formulation can contain 100 mg/mL antibody, 10 mM histidine, 5% sucrose, 0.01% Tween 80 (polysorbate 80), 2% arginine and has a pH of 6.0 (see [0064]). Such teachings are directly on point to limitations regarding L-Arg in **claim 3**.

As such, it would have been obvious to one of ordinary skill in the art to have included L-arginine, as taught by Wang 2015 and Barry et al. as part of an anti-PD-1 antibody formulation so as to arrive at the presently claimed invention. The artisan would have been motivated to have included L-Arg so as to reduce viscosity of the composition and thereby reduce the risk of antibody aggregation. Given the well-established knowledge related to the inclusion of arginine in antibody formulations, the artisan would have had a reasonable expectation that including either L-Arg in the formulation would predictably improve the resultant antibody formation.

7. Claim(s) **1-4, 6-7, 9-15** and **17-30** is/are rejected under 35 U.S.C. 103 as being unpatentable over **Sharma et al**. (US 9,220,776 B2) as evidenced by Wang et al. (*Oncoimmunology*, 2021, 10(1):1896643) as applied to claims 1-4, 6, 14 and 20-30 above, and in view of **Li et al**. (WO 2017/054646 A1[1]; Pub April 6, 2017 with priority to earlier filing date) and **Luisi et al**. (US 2006/0210557 A1) (all references listed on 10/01/2025 IDS).

The reasons why the teachings of **Sharma et al**. render obvious the invention of claims 1-4, 6, 14 and 20-30 is discussed above. Additionally, Sharma indicates that greater stability of antibody formulations is desirable, particularly for long-term storage (col. 12 lines 65-66). Sharma indicates that agents that provide stability (i.e., stabilizers) to antibody formulations include bulking agents such as mannitol, glycine and sucrose (col. 12 lines 59-62); cryoprotectants (including sugars such as sucrose, glucose, trehalose and lactose; surfactants such as polysorbates; amino acids such as glycine, arginine and serine; col. 13 lines 17-25); and lyoprotectants such as polyols or sugars such as sucrose and trehalose (col. 13 lines 32-41).

Therefore, Sharma teaches and suggests an antibody formulation comprising pembrolizumab, a buffer (i.e., acetate or citrate), a stabilizer or "bulking agent" (i.e., sucrose, trehalose, mannitol or glycine; see col. 12 lines 59-66), and a non-ionic surfactant (i.e., polysorbate 80). However, Sharma does not teach the presently recited

[1] This document is in Chinese; however, US 2018/0339045 A1 is the English language equivalent of the WO document (PCT/CN2016/098982) and therefore reference and citations within this rejection will be made with respect to the '045 publication.

agents and their concentrations/percentages of trehalose (about 6-8% w/v), mannitol, sorbitol, L-arginine or L-proline (about 3-5% w/v), or glycine (about 1.8-2.2% w/v), as in **claims 1, 7, 9-13** and **24**, or that the surfactant may be polysorbate 20 (**claim 15**). And although Sharma teaches that the antibody formulation may also comprise amino acids such as glycine, arginine or serine, Sharma does not teach that the composition may further comprise about 1 mM to about 20 mM of an anti-oxidant (**claim 14**), wherein the anti-oxidant is L-methionine (**claim 15**) or L-methionine HCl (**claim 16**).

Li et al. teach stable pharmaceutical formulations comprising an anti-PD-1 antibody, a buffer, at least one stabilizer, and a surfactant ([0005]-[0006]). Li defines the term stabilizer to include lyoprotectants, which include saccharides, polyols and amino acids ([0060]). In particular, lyoprotectants can be selected from saccharides such as sucrose and trehalose ([0017], [0058], [0060]), aminosaccharides, polyols such as mannitol and sorbitol, and amino acids such as arginine and glycine, and mixtures thereof ([0060]). In addition to saccharides, amino acids and polyols, stabilizers are also taught to include surfactants, anti-oxidants, preservatives, cyclodextrins, salts and chelators ([0049]). Preferred stabilizers are suggested to include sucrose, trehalose and sorbitol ([0049] and [0017]). Li further discloses that the term “amino acid” includes, among others, arginine, glycine, methionine and proline ([0059]), and can be used in an amount of about 5 mM to about 500 mM, particularly about 5 to about 200 mM, and more particularly in about 100 mM to about 150 mM ([0049]).

Note that 3-5% w/v L-arginine is equivalent to about 172 mM to 287 mM, 3-5% w/v L-proline is equivalent to about 261 mM to 434 mM, and 1.8-2.2% w/v glycine is equivalent to about 240 mM to 293 mM. Thus, the range of 5 mM to 500 mM taught by Li encompasses all of the presently recited ranges for L-arginine, L-proline and glycine.

Further, Li teaches that the stabilizer can be present in the formulation in an amount from 30 mg/ml to 100 mg/ml (i.e., 3% w/v to 10% w/v), preferably from 60 mg/ml to 90 mg/ml (i.e., 6% w/v to 9% w/v/) ([0049]) or more preferably 85 to 95 mg/ml ([0017]) (i.e., 8.5% w/v to 9.5% w/v). Examples of formulations having 60 mg/ml (6% w/v) trehalose are given, for instance, at [0026]-[0028]. Taken together, such teachings provide for a stabilizer that may be: 6-8% w/v trehalose (**claims 1ci, 7** and **24ci**), 3-5%

w/v mannitol, sorbitol, L-arginine or L-proline (**claims 1cii, 9-12** and **24cii**), or 1.8-2.2% w/v glycine (**claims 1ciii, 13** and **24ciii**).

Regarding **claims 14-15**, Li teaches that the surfactant can be polysorbate 20 (PS20), polysorbate 80 (PS80), or poloxamer (Pluronic) (0055], [0018] and [0026]-[0028]).

Finally, Li teaches that the addition of an antioxidant to an anti-PD-1 antibody formulation can prevent oxidation of the active pharmaceutical agent. Suitable antioxidants can include, among others, methionine ([0057]).

Consistent with the teachings of Li et al., **Luisi et al**. teach stabilized liquid formulations for maintaining the stability of polypeptides, including therapeutic antibodies, wherein the formulations include an antioxidant in a sufficient amount as to inhibit by-product formation, such as the formation of high molecular weight polypeptide aggregates, low molecular weight polypeptide degradation fragments, and mixtures thereof (see abstract). A stabilized formulation comprising a therapeutically active antibody is taught to include a tonicity agent, such as about 2% w/v to about 6% w/v mannitol ([0026]), a buffering agent or amino acid ([0122]-[0123]), and an antioxidant such as 10 mM methionine ([0021], [0026], [0082]-[0083]), as well as a surfactant such as 0.01% to 0.1% PS80 ([0027], [0040]), and having a pH of about 5 to 7, and in particular about 6 ([0027]).

Luisi teaches that in addition to mannitol, sucrose, trehalose and glycine are taught as alternative, acceptable tonicity agents (see [0126]). Such tonicity agents may be present in the formulation at about 2% to about 6% w/v, or about 3% to about 5% w/v ([0127]). Again, such teachings provide for recited limitations pertaining to the stabilizer in present **claims 1, 6-7, 9, 13,** and **24**. The anti-oxidant may include L-methionine or an analog thereof (see [0015], [0020] and [0130]), and is present at a concentration of about 0.1 mM to about 20 mM, such as specifically about 5 mM, 6 mM, 7 mM, 8 mM, 9 mM, 10 mM, 11 mM, 12 mM, 13 mM, 14 mM, 15 mM, or about 12 mM to about 17 mM ([0131]), which addresses the limitations of present **claims 17-19**.

It would have been obvious to one of ordinary skill in the art at the time of filing to have substituted the stabilizer sucrose as taught by Sharma for one or more of trehalose, mannitol, sorbitol, L-arginine, L-proline or glycine as taught by Li and Luisi

and thereby arrive at the presently claimed antibody formulation. This is because the artisan has good reason to pursue the known options within his or her technical grasp to achieve predictable results. In the instant case, this would amount to the simple substitution of functionally equivalent elements (i.e., stabilizers, lyoprotectants, tonicity agents) to arrive at a predictable outcome. In fact, Sharma even suggests that agents such as trehalose can be used in place of sucrose, and therefore it would have been obvious to have substituted the art-recognized equivalent stabilizer/tonicity agents according to the concentrations of Li and Luisi with a reasonable expectation of success.

Further, it would have been obvious to one of ordinary skill in the art at the time of filing to have included an anti-oxidant such as L-methionine, as taught by Luisi, in the antibody formulation of Sharma and thereby arrive at the presently claimed invention. Given the teachings of Li and Luisi, the skilled artisan would have recognized that the addition of antioxidants in an antibody formulation helps to prevent oxidation of the therapeutic polypeptides. Further, Luisi expressly suggests the inclusion of an anti-oxidant, such as 10 mM L-methionine, in therapeutic antibody formulations so as to prevent oxidation and thereby preserve the formulation (see [0129] and [0131] of Luisi). Given the extensive teachings of Sharma, Li and Luisi demonstrating various antibody formulations, the artisan would have had a reasonable expectation that the addition of L-methionine to the anti-PD-1 antibody formulation of Sharma would be successful in preventing oxidation of the antibody. Therefore, the combined teachings of the above prior art references render obvious the presently recited invention of claims **1-4, 6-7, 9-15** and **17-30**.

8. Claim(s) **1-4, 6-15** and **17-30** is/are rejected under 35 U.S.C. 103 as being unpatentable over **Sharma et al**. (US 9,220,776 B2) as evidenced by Wang et al. (*Oncoimmunology*, 2021, 10(1):1896643) and in view of **Li et al**. (WO 2017/054646 A1[2]; Pub April 6, 2017 with priority to earlier filing date) and **Luisi et al**. (US

[2] This document is in Chinese; however, US 2018/0339045 A1 is the English language equivalent of the WO document (PCT/CN2016/098982) and therefore reference and citations within this rejection will be made with respect to the '045 publication.

2006/0210557 A1) as applied to claims 1-4, 6-7, 9-15 and 17-30 above, and further in view of **Hartl et al**. (*J Pharm Sci*. 2013, 102:4121-4131) (all references listed on 10/01/2025 IDS).

The reasons why the combined teachings of **Sharma**, **Li**, and **Luisi** render obvious the invention of claims 1-4, 6-7, 9-15 and 17-30 is discussed above. However, while Li et al. may teach that cyclodextrins are suitable stabilizers for antibody formulations, the references do not specifically teach that the cyclodextrin stabilizer is (2-hydroxypropyl)-β-cyclodextrin (HPβCD), as in **claims 1, 8** and **24**.

Hartl et al. teach that antibody solutions usually require the addition of suitable excipients, such as surfactants and polyols, to overcome stability problems under mechanical or thermal stress (see abstract). Hartl suggests that because cyclodextrins exhibit weak surface activity (similar to surfactants) and a sugar-based structure (like polyols), they can, in principle, stabilize proteins by a double mechanism. Hartl tested the stabilizing potential of various concentrations of HPβCD on two antibodies compared with polysorbate 80 or sucrose formulations as controls (see abstract). Hartl found that increasing concentrations of HPβCD lead to a gradual protein stabilization under mechanical stress, and generally performed better than sucrose in monomer recovery (see abstract and Fig. 1 at p. 4124). Hartl conclude that low concentrations of HPβCD (such as about 2.5 to 50 mM) can be a viable option to stabilize antibody solutions (see conclusion at p. 4130). Note that 6-8% w/v HPβCD is equivalent to about 40-60 mM.

It would have been obvious to one of ordinary skill in the art to have used HPβCD, as taught by Hartl, for the cyclodextrin stabilizer as taught by the combination of Li, and thereby arrive at the presently claimed antibody formulation. Given that Li teaches that cyclodextrins can reasonably be used as stabilizing agents in antibody formulations, and given that Hartl demonstrates that HPβCD performs similarly to sucrose (as taught in Sharma) for antibody stabilization, it would have been obvious to have substituted sucrose with HPβCD as presently claimed. This is because the artisan has good reason to pursue the known options within his or her technical grasp to achieve predictable results. In the instant case, this would amount to the simple

substitution of functionally equivalent elements (i.e., stabilizing agents, HPβCD for sucrose) to arrive at a predictable outcome.

9. Claim(s) **1-4, 6-7, 14-16** and **20-30** is/are rejected under 35 U.S.C. 103 as being unpatentable over **Sharma et al**. (US 9,220,776 B2) as evidenced by Wang et al. (*Oncoimmunology*, 2021, 10(1):1896643) as applied to claims 1-4, 6, 14 and 20-30 above, and in view of **Kang et al**. (*BioProcess Intl*. 2016, 14(4): 40-45) (all references listed on 10/01/2025 IDS).

The reasons why the teachings of **Sharma et al**. render obvious the invention of claims 1-4, 6, 14 and 20-30 is discussed above. Sharma teaches that sucrose and trehalose are examples of suitable sugars useful to provide stability in antibody formulations (col. 13 lines 32-41). Sharma teaches a formulation that comprises 7% sucrose. However, Sharma does not explicitly teach a formulation that comprises trehalose instead of sucrose, as in **claim 7**. And while Sharma teaches that the antibody formulation comprises polysorbate 80 (PS80) as a surfactant, the reference does not teach that the surfactant is polysorbate 20 (PS20) or poloxamer 188, as in **claims 15** and **16**, respectively.

Kang et al. provide a review of the excipients used in commercial monoclonal antibody formulations and teach that most (80%) formulations used one of three surfactants: polysorbate 80, polysorbate 20, or poloxamer 188. Kang also teaches that all commercial antibody formulations used one or a mixture of polyol/disaccharide/polysaccharide, such as mannitol, sorbitol, sucrose, trehalose, and dextran 40. Kang teaches that sucrose was the most popular excipient and was included in over 80% of lyophilized formulations, 15% of liquid formulations, and 35% of all monoclonal antibody (Mab) formulations (Table 1). Trehalose was the next most frequently used sugar in commercial preparations, with inclusion in 18% of lyophilized formulations, 12% of liquid formulations, and 14% of all Mab formulations (Table 1).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time of filing to have substituted PS20 or poloxamer 188, as taught by Kang, for PS80 as taught by Sharma, and thereby arrive at the presently claimed antibody formulation. Similarly, it would have been obvious to have substituted the sucrose with trehalose,

because they are both taught by Kang to be functionally equivalent stabilizing agents. This is because the artisan has good reason to pursue the known options within his or her technical grasp to achieve predictable results. In the instant case, this would amount to the simple substitution of functionally equivalent elements (i.e., surfactants; sugars) to arrive at a predictable outcome.

Double Patenting

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 § 2146 *et seq.* 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 filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual 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/apply/applying-online/eterminal-disclaimer.

10. Claims **1-4, 6-7** and **9-30** are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-7 and 13 of U.S. Patent No. **9,220,776** in view of **Li et al**. (US 2018/0339045 A1), **Luisi et al**. (US 2006/0210557 A1), and **Kang et al**. (*BioProcess Intl*. 2016, 14(4): 40-45).

The patented '776 claims recite a stable antibody formulation comprising 25-100 mg/mL of antibody; about 70 mg/mL sucrose (which is about 7% w/v); 0.2 mg/mL polysorbate 80 (which is about 0.02% w/v); and about 10 mM histidine buffer at pH 5.0-6.0, wherein the antibody comprises a light chain and heavy chain sequences that are comprised by the antibody pembrolizumab as instantly claimed. However, the patented claims do not recite that the formulation comprises a different buffer (acetate or citrate), stabilizer (trehalose, mannitol, sorbitol, L-arginine, L-proline or glycine), or an antioxidant, such as L-methionine. The '776 patented claims also recite a method of treating cancer in a human subject comprising administering the anti-PD-1 antibody formulation, wherein the subject has melanoma.

The teachings of **Li et al**., **Luisi et al**., and **Kang et al**. are cumulative and are discussed above and provide for the use of alternative buffering agents, such as an acetate or citrate buffer ([0015] of Li; Kang), stabilizing agents (such as trehalose, mannitol, sorbitol, L-arginine, L-proline or glycine) (as in present **claims 3-4, 7** and **9-13**), as well as the addition of an anti-oxidant, such as 10 mM L-methionine, to be included in stable antibody formulations. Li teaches PS20 and PS80 as suitable surfactants, as in **claims 14-15**, and Kang teaches that poloxamer 188 is another suitable surfactant, as in **claim 16**. Each of the references teach that the addition of an anti-oxidant, such as methionine, to a formulation is beneficial in reducing oxidation of the antibody and for preventing the formation of aggregation and/or fragmentation of the antibody. Li additionally teaches that stable anti-PD-1 antibody formulations can be administered subcutaneously ([0064]), as in present **claim 27**.

Accordingly, it would have been obvious to have used a different buffer, such as citrate or acetate, one or more of the stabilizing agents, a different surfactant (PS20 or poloxamer 188), an antioxidant such as L-methionine, or to have administered the antibody subcutaneously and thereby arrive at the claimed invention. The prior art references provide both motivation to include the listed agents as well as a reasonable expectation that such substitution or addition to the formulation would be predictable or else improve the stability and reduce oxidation of the anti-PD-1 antibody contained therein.

11. Claim **5** is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-7 and 13 of U.S. Patent No. **9,220,776** in view of **Li et al**. (US 2018/0339045 A1), **Luisi et al**. (US 2006/0210557 A1) and **Kang et al**. (*BioProcess Intl.* 2016, 14(4): 40-45) as applied to claims 1-4, 6-7 and 9-30 above, and further in view of **Wang et al**. (*Mol. Pharmaceutics*, 2015, 12, 4478-4487; hereinafter "Wang 2015") and **Barry et al**. (US 2009/0060906 A1).

The reasons why the patented claims in view of Li, Luisi and Kang render obvious the invention of claims 1-4, 6-7 and 9-30 are discussed above. However, neither the patented claims nor the prior art teach that the composition further comprises L-arginine or a salt thereof as in **claim 3**.

The teachings of **Wang 2015** and **Barry et al.** are discussed above and provide for the inclusion of L-arginine in an antibody formulation to improve viscosity.

Therefore, it would have been obvious to have included L-Arg in the antibody formulation of the patented '776 claims and thereby arrive at the presently claimed invention. The motivation to do so comes from the Wang and Barry references, and their teachings provide a reasonable expectation that the addition of L-arg to an antibody composition would be predictably beneficial.

12. Claim **8** is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-7 and 13 of U.S. Patent No. **9,220,776** in view of **Li et al**. (US 2018/0339045 A1), **Luisi et al**. (US 2006/0210557 A1) and **Kang et al**.

(*BioProcess Intl*. 2016, 14(4): 40-45) as applied to claims 1-4, 6-7 and 9-30 above, and further in view of **Hartl et al**. (*J Pharm Sci*. 2013, 102:4121-4131).

The reasons why the patented claims in view of Li, Luisi and Kang render obvious the invention of claims 1-4, 6-7 and 9-30 are discussed above. However, neither the patented claims nor the prior art teach that the composition comprises (2-hydroxypropyl)-β-cyclodextrin (HPβCD) as the stabilizer, as in **claim 5**.

The teachings of Hartl et al. are discussed above and provide for the use of HPβCD as a suitable stabilizing agent.

Given that Li teaches that cyclodextrins can reasonably be used as stabilizing agents in antibody formulations, and given that Hartl demonstrates that HPβCD performs similarly to sucrose (as recited in the '776 claims) for antibody stabilization, it would have been obvious to have substituted HPβCD for sucrose as presently claimed. This is because the artisan has good reason to pursue the known options within his or her technical grasp to achieve predictable results. In the instant case, this would amount to the simple substitution of functionally equivalent elements (i.e., stabilizing agents; HPβCD for sucrose) to arrive at a predictable outcome.

13. Claims **1-7** and **9-30** are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-7, 10-13, 16 and 18-21 of U.S. Patent No. **11,633,476** in view of **Li et al**. (US 2018/0339045 A1), **Luisi et al**. (US 2006/0210557 A1), and **Kang et al**. (*BioProcess Intl*. 2016, 14(4): 40-45).

The patented '476 claims recite a stable anti-human PD-1 antibody formulation comprising 100-200 mg/mL (or 125-200 mg/ml, or 165-170 mg/ml) of antibody; about 6% to 8% w/v sucrose; about 0.01% to about 0.1% w/v polysorbate 80; about 5 mM to about 20 mM histidine buffer at pH 5.0-6.0; and about 1 mM to about 20 mM L-methionine (or L-methionine HCl), wherein the antibody is pembrolizumab. The patented claims also recite that the formulation further comprises about 1% to about 3% w/v L-arginine. Finally, the patented claims recite a method for treating cancer in a human patient comprising administering the claimed antibody formulation, wherein the formulation is administered by subcutaneous administration.

However, the patented claims do not recite that the formulation comprises a different buffer (acetate or citrate), a different stabilizer (trehalose, mannitol, sorbitol, L-arginine, L-proline or glycine), different surfactants (PS20 or poloxamer 188), or that the cancer is one of the types of cancer listed in present **claim 28**.

The combined teachings of **Li et al**., **Luisi et al**. and **Kang et al**. are discussed above and provide for the use of alternative buffers (such as acetate or citrate), stabilizing agents (such as trehalose, mannitol, sorbitol, L-arginine, L-proline or glycine), and surfactants (such as polysorbate 20 or poloxamer 188) to be included in stable antibody formulations. Li additionally teaches that anti-PD-1 antibody formulations can be used in the treatment of cancer, such as breast cancer, lung cancer, stomach cancer, intestinal cancer, kidney cancer, or melanoma ([0035]-[0037]).

Accordingly, it would have been obvious to have used one or more of the alterative buffers, stabilizing agents, or surfactants as taught by Li, Luisi, and Kang, or to have treated a particular type of cancer as taught by Li, and thereby arrive at the presently claimed invention. This is because the artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. Such would amount to the simple substitution of known equivalent elements (i.e., buffers, stabilizing agents, surfactants) to achieve a predictable outcome. Similarly, given the teachings of Li indicating that cancers such as breast, liver and lung cancers, etc. can be treated using anti-PD-1 antibodies, it would have been obvious and predictable to have applied the patented method of treating cancer to any of the specific types of cancer taught by Li.

14. Claim **8** is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-21 of U.S. Patent No. **11,633,476** in view of **Li et al**. (US 2018/0339045 A1), **Luisi et al**. (US 2006/0210557 A1), and **Kang et al**. (*BioProcess Intl*. 2016, 14(4): 40-45) as applied to claims 1-7 and 9-30 above, and further in view of **Hartl et al**. (*J Pharm Sci*. 2013, 102:4121-4131).

The reasons why the patented claims in view of Li, Luisi and Kang render obvious the invention of claims 1-7 and 9-30 are discussed above. However, neither the

patented claims nor the prior art teach that the composition comprises (2-hydroxypropyl)-β-cyclodextrin (HPβCD) as the stabilizer, as in **claim 8**.

The teachings of **Hartl et al**. are discussed above and provide for the use of HPβCD as a suitable stabilizing agent.

Given that Li teaches that cyclodextrins can reasonably be used as stabilizing agents in antibody formulations, and given that Hartl demonstrates that HPβCD performs similarly to sucrose (as recited in the '476 claims) for antibody stabilization, it would have been obvious to have substituted HPβCD for sucrose as presently claimed. This is because the artisan has good reason to pursue the known options within his or her technical grasp to achieve predictable results. In the instant case, this would amount to the simple substitution of functionally equivalent elements (i.e., stabilizing agents; HPβCD for sucrose) to arrive at a predictable outcome.

15. Claims **1-30** are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-16 and 19-30 of copending Application No. **19/346,648** in view of **Kang et al**. (*BioProcess Intl.* 2016, 14(4): 40-45).

The co-pending '648 claims recite an anti-human PD-1 antibody formulation comprising: pembrolizumab (5-100 mg/ml; 25 mg/ml; or 165-170 mg/ml); histidine buffer (5-20 mM), stabilizer (6-8% w/v trehalose or 2-hydroxypropyl-β-cyclodetrin; 3-5% w/v mannitol, sorbitol, L-Arg or L-Pro; 1.8-2.2% w/v glycine); surfactant (0.01-0.1% PS80, PS20 or poloxamer 188), additional agents (1-3% w/v L-Arg), and antioxidants (1-20 mM L-methionine) and the therapeutic subcutaneous administration of the formulation for the treatment of cancer. Further, co-pending claim 26 recites the same types of cancer that are recited in present claim 28. The only difference between the present claims and the co-pending '648 claims is that the present claims recite that the formulation comprises a different buffer: acetate or citrate.

Kang et al. teach that the most commonly used buffers in commercial antibody formulations to keep pH levels between 4.7 and 7.4 include acetate, citrate, histidine, succinate, phosphate, and Tris. Following histidine and phosphate, acetate and citrate buffers are the next most commonly used types of buffers (Table 1).

Accordingly, it would have been obvious to one of ordinary skill in the art to have substituted either acetate or citrate buffer as taught by Kang for histidine buffer as recited by the co-pending '648 claims and thereby arrive at the presently claimed invention. This is because the artisan has good reason to pursue the known options within his or her technical grasp to achieve predictable results. In the instant case, this would amount to the simple substitution of functionally equivalent elements (i.e., buffers) to arrive at a predictable outcome. This is a provisional nonstatutory double patenting rejection.

19. Claims **1-3, 5-15, 17-27** and **29** are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11, 14-21, 23-26, 29-30, 33-43, 46-60 and 64-65 of copending Application No. **18/182,135** (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because in each case the claims recite an anti-human PD-1 antibody liquid formulation comprising the same elements (pembrolizumab, acetate buffer, stabilizer, surfactant (PS20 or PS80), additional agents (L-arginine), and antioxidant (L-methionine)) at the same concentrations/amounts, and used in the treatment of cancer in a human patient. The only difference between the present claims and the co-pending '135 claims is that the present claims recite that the formulation comprises about 5 mg/ml to about 200 mg/ml antibody, and the co-pending claims recite that the formulation comprises about 100 mg/ml to about 200 mg/ml of antibody. However, the narrower range of the co-pending '135 application anticipates the more broadly claimed range of the instant claims.

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

20. Claims **4, 16, 28** and **30** are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11, 14-21, 23-26, 29-30, 33-43, 46-60 and 64-65 of copending Application No. **18/182,135** in view of **Kang et al**. (*BioProcess Intl.* 2016, 14(4): 40-45) and **Sharma et al.** (US 9,220,776).

The reasons why the claims of the '135 application anticipate or render obvious present claims 1-3, 5-15, 17-27 and 29 are discussed above. However, the co-pending claims do not recite that the buffer is citrate, as in **claims 4** and **30**, surfactant is poloxamer 188 as in **claim 16**, the concentration of pembrolizumab is about 25 mg/ml, as in **claims 22** and **25**, or the types of cancer as in **claim 28**.

The teachings of **Kang et al**. are discussed above and provide for the use of citrate as a commonly used alternative buffer, and poloxamer 188 as an alternative suitable surfactant.

The teachings of **Sharma et al**. are also set forth above and provide for a liquid antibody formulation comprising pembrolizumab, wherein the concentration of the antibody is 25-100 mg/ml (col. 4 lines 1-4 and 49-51), or more specifically, 25 mg/ml (col. 19 lines 1-3). Consistent with Kang, Sharma indicates that citrate can be used as a suitable buffer (col. 13 lines 1-5). Sharma also teaches that pembrolizumab can be used in the treatment of the different types of cancer as recited in present claim 28 (col. 6 lines 51-67; col. 7 lines 7-20 and 30-38).

It would have been obvious to one of ordinary skill in the art to have used citrate buffer as taught by Kang and by Sharma, to have substituted poloxamer 188 for PS80 as recited by the '476 claims, and thereby arrive at the presently claimed antibody formulation. This is because the artisan has good reason to pursue the known options within his or her technical grasp to achieve predictable results. In the instant case, this would amount to the simple substitution of functionally equivalent elements (i.e., buffers, surfactants) to arrive at a predictable outcome.

It similarly would have been obvious to have used a lower concentration of pembrolizumab, or to treat a specific type of cancer, as taught by Sharma, and thereby arrive at the presently claimed invention. In particular, Sharma teaches the same antibody, pembrolizumab, and its formulation and therapeutic use, and therefore provides both motivation to use different antibody concentrations or treat specific types of cancer, but also a reasonable expectation that such concentrations/therapeutic applications would be successful. This is a provisional nonstatutory double patenting rejection.

21. Claims **1-30** are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-16 and 19-30 of copending Application No. **19/346,623** in view of **Kang et al**. (*BioProcess Intl*. 2016, 14(4): 40-45).

The claims of the '623 co-pending application and the instant claims are both drawn to an anti-human PD-1 antibody formulation comprising the same amounts (5-200 mg/ml, 25-100 mg/ml, 25 mg/ml, 165-170 mg/ml) of the same antibody (pembrolizumab) and having the same stabilizing agents and amounts (trehalose, HPβCD, mannitol, sorbitol, L-Arg, L-Pro, glycine), non-ionic surfactants (0.01-0.1% w/v PS80, PS20, or poloxamer 188), and anti-oxidants (1-20 mM L-methionine HCl). The co-pending claims also recite a method of treating cancer in a human patient, comprising administering the aforementioned antibody formulation, wherein the type of cancer is the same as those recited in present claim 28, and administration is by subcutaneous administration. However, the '623 claims recite that the formulation comprises 5-20 mM histidine buffer, whereas the instant claims recite that the buffer is 5-20 mM acetate or citrate. The present claims also recite that the stabilizer is sucrose.

Kang et al. provide a review of the excipients used in commercial monoclonal antibody formulations and teach that six commonly used buffers keep pH levels between 4.7 and 7.4: acetate, citrate, histidine, succinate, phosphate, and Tris. Following histidine and phosphate, acetate and citrate buffers are the next most commonly used types of buffers (Table 1). Kang further teaches that sucrose is the most commonly used sugar stabilizing agent.

Therefore, it would have been obvious to have substituted to acetate or citrate buffer, as taught by Kang for the histidine buffer of the '623 application, or to have substituted sucrose for trehalose, and thereby arrive at the presently claimed invention. This is because the artisan has good reason to pursue the known options within his or her technical grasp to achieve predictable results. In the instant case, this would amount to the simple substitution of functionally equivalent elements (i.e., common buffers or sugar stabilizers) to arrive at a predictable outcome. This is a provisional nonstatutory double patenting rejection.

22. Claims **1-7** and **9-30** are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-7, 10-20, 23-24 and 27-35 of copending Application No. **18/182,097** (reference application) in view of **Li et al**. (US 2018/0339045 A1), **Luisi et al**. (US 2006/0210557 A1) and **Kang et al**. (*BioProcess Intl*. 2016, 14(4): 40-45).

The co-pending '097 claims recite a stable anti-human PD-1 antibody formulation comprising 100-200 mg/mL (or 125-200 mg/ml, or 165-170 mg/ml) of antibody; about 6% to 8% w/v sucrose; about 0.01% to about 0.1% w/v polysorbate 80; about 5 mM to about 20 mM histidine buffer at pH 5.0-6.0; and about 1 mM to about 20 mM L-methionine (or L-methionine HCl), wherein the antibody is pembrolizumab. The co-pending claims also recite that the formulation is a reconstituted solution (i.e., a liquid) and that it further comprises about 1% to about 3% w/v L-arginine. Finally, the co-pending '097 claims recite a method for treating cancer in a human patient comprising administering the claimed antibody formulation, wherein the formulation is administered by subcutaneous administration.

However, the co-pending claims do not recite that the formulation comprises a different buffer (acetate or citrate), different stabilizer (trehalose, mannitol, sorbitol, L-arginine, L-proline or glycine), or that the cancer is one of the types of cancer listed in present claim 28.

The teachings of **Li et al**., **Luisi et al**. and **Kang et al**. are discussed above and provide for the use of alternative buffers (such as acetate or citrate), stabilizing agents (such as trehalose, mannitol, sorbitol, L-arginine, L-proline or glycine), and surfactants (PS20 or poloxamer 188) to be included in stable antibody formulations. Li additionally teaches that anti-PD-1 antibody formulations can be used in the treatment of cancer, such as breast cancer, lung cancer, stomach cancer, intestinal cancer, kidney cancer, or melanoma ([0035]-[0037]).

Accordingly, it would have been obvious to have used one or more of the alternative buffers, stabilizing agents or surfactants as taught by Li, Luisi and Kang, or to have treated a particular type of cancer as taught by Li, and thereby arrive at the presently claimed invention. This is because the artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. Such would

amount to the simple substitution of known equivalent elements (i.e., buffers, stabilizing agents, surfactants) to achieve a predictable outcome. Similarly, given the teachings of Li indicating that cancers such as breast, liver and lung cancers, etc. can be treated using anti-PD-1 antibodies, it would have been obvious and predictable to have applied the claimed co-pending method of treating cancer to the treatment of any of the specific types of cancer taught by Li.

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

23. Claim **8** is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-7, 10-20, 23-24 and 27-35 of copending Application No. **18/182,097** (reference application) in view of **Li et al**. (US 2018/0339045 A1), **Luisi et al**. (US 2006/0210557 A1) and **Kang et al**. (*BioProcess Intl*. 2016, 14(4): 40-45) as applied to claims 1-7 and 9-30 above, and further in view of **Hartl et al**. (*J Pharm Sci*. 2013, 102:4121-4131).

The reasons why the co-pending '097 claims in view of Li, Luisi and Kang render obvious the invention of claims 1-7 and 9-30 are discussed above. However, neither the co-pending claims nor the prior art teach that the composition comprises (2-hydroxypropyl)-β-cyclodextrin (HPβCD) as the stabilizer, as in **claim 8**.

The teachings of **Hartl et al**. are discussed above and provide for the use of HPβCD as a suitable stabilizing agent.

Given that Li teaches that cyclodextrins can reasonably be used as stabilizing agents in antibody formulations, and given that Hartl demonstrates that HPβCD performs similarly to sucrose (as recited in the '097 claims) for antibody stabilization, it would have been obvious to have substituted HPβCD for sucrose or trehalose as presently claimed. This is because the artisan has good reason to pursue the known options within his or her technical grasp to achieve predictable results. In the instant case, this would amount to the simple substitution of functionally equivalent elements (i.e., stabilizing agents; HPβCD for sucrose) to arrive at a predictable outcome. This is a provisional nonstatutory double patenting rejection.

Conclusion

24. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is (571)272-2150. The examiner can normally be reached Mon-Fri 8AM - 5PM EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached at 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/KIMBERLY BALLARD/
Primary Examiner, Art Unit 1675

Notice of References Cited	Application/Control No. 19/346,638	Applicant(s)/Patent Under Reexamination Sharma et al.	
	Examiner Kimberly A Ballard	Art Unit 1675	Page 1 of 1

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	19/346,638	Sharma et al.
	Examiner	Art Unit
	Kimberly A Ballard	1675

CPC - Searched*		
Symbol	Date	Examiner
A61K 9/19, 39/3955, 39/39591, 47/183, 47/26, 47/34	12/10/2025	KB

CPC Combination Sets - Searched*		
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US Classification - Searched*			
Class	Subclass	Date	Examiner

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Search Notes		
Search Notes	Date	Examiner
Inventor, Assignee search	12/10/2025	KB
PE2E Search (USPAT, USOCR, USPGPUB, DERWENT, EPO, JPO, FIT, FPRS)	12/10/2025	KB
PE2E Search	01/06/2026	KB
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	First Named Inventor	Manoj K. SHARMA
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	Examiner Name	~~TBD~~ Kimberly Ballard
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	110	20170056347	A1	2017-03-02	Glick et al.	
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	114	20170210792	A1	2017-07-27	Mason et al.	
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	116	20170216433	A1	2017-08-03	Li et al.	
	117	20170218069	A1	2017-08-03	Rosengren, Sanna et al.	
	118	20170267759	A1	2017-09-21	Liang, Linda	
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	121	20180044419	A9	2018-02-15	Rosengren, Sanna et al.	
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	125	20180339045	A1	2018-11-29	Li, Jie et al.	
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	131	20200262922	A1	2020-08-20	Bhattacharya, Soumendu et al.	
	132	20200354453	A1	2020-11-12	De, Arnab et al.	
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	4	2918888	CA	A1	2015-01-29	Ono Pharmaceutical Co., Ltd.		☐
	5	2956000	CA	A1	2016-02-04	AKESO BIOPHARMA, INC		☐
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	9	1703233	CN	A	2005-11-30	MEDAREX INC.		☐
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	11	101600457	CN	A	2009-12-09	Wyeth Corp.		☐
	12	101883588	CN	A	2010-11-10	CHUGAI PHARMACEUTICAL CO. LTD et al.		☐
	13	101970499	CN	A	2011-02-09	Curetech Ltd.		☐
	14	102131828	CN	A	2011-07-20	ORGANON NV		☐
	15	102753570	CN	A	2012-10-24	Althea Technologies Inc.		☐
	16	101426817	CN	B	2013-07-10	NOVARTIS AG et al.		☐
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	20	104945508	CN	A	2015-09-30	MSD OSS B.V.		☐
	21	103501814	CN	B	2016-09-07	REGENERON PHARMACEUTICALS INC.		☐
	22	107001470	CN	A	2017-08-01	MERCK SHARP & DOHME CORP.		☐
	23	107249624	CN	A	2017-10-13	MERCK SHARP & DOHME		☐
	24	107743401	CN	A	2018-02-27	BRISTOL-MYERS SQUIBB COMPANY		☐
	25	107854439	CN	A	2018-03-30	MERCK SHARP & DOHME		☐
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	29	104684933	CN	B	2021-11-30	BAYER HEALTHCARE LLC		☐

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	31	031972	EA	B1	2019-03-29	F. HOFFMANN-LA ROCHE AG		☐
	32	033817	EA	B1	2019-11-28	GENENTECH, INC.		☐
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	42	3636752	EP	A1	2020-04-15	Alteogen, Inc.		☐
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	45	2005536285	JP	A	2005-12-02	PHARMACIA		☐
	46	2006502116	JP	A	2006-01-19	MEDAREX INC.		☐
	47	2006249081	JP	A	2006-09-21	PHARMACIA & UPJOHN CO LLC		☐
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	53	2014525915	JP	A	2014-10-02	REGENERON PHARMACEUTICALS INC.		☐
	54	2015528464	JP	A	2015-09-28	BAYER HEALTHCARE		☐
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	57	2016531849	JP	A	2016-10-13	BRISTOL-MYERS SQUIBB CO.		☐
	58	2017501167	JP	A	2017-01-12	Cheung, Jeanne et al.		☐
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	64	20100054780	KR	A	2010-05-25	Organon NV		☐
	65	20140026434	KR	A	2014-03-05	MERCK SHARP & DOHME CORP.		☐
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	67	20180069056	KR	A	2018-06-22	MERCK SHARP & DOHME CORP.		☐
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	69	2348615	RU	C2	2009-03-10	AVENTIS FARMA S.A.		☐
	70	2560701	RU	C2	2015-08-20	ABBVIE BIOTECHNOLOGY LTD.		☐
	71	2015123476	RU	A	2015-10-20	MERCK SHARP & DOHME CORP.		☐
	72	2589691	RU	C2	2016-07-10	OBSHSHESTVO S OGRANICHENNOJ OTVETSTVENNOSTYU "PROM		☐
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	75	1989011297	WO	A1	1989-11-30	Centocor, Inc.		☐
	76	1992004381	WO	A1	1992-03-19	Scotgen Limited		☐
	77	1994006448	WO	A1	1994-03-31	The Scripps Research Institute		☐
	78	199704801	WO	A1	1997-02-13	Genetech, Inc.		☐
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	81	2001018051	WO	A2	2001-03-15	Schering Corporation		☐
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	88	2004007520	WO	A2	2004-01-22	MEDAREX INC et al.		☐
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	90	2004024068	WO	A2	2004-03-25	Genentech		☐
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	97	2005120571	WO	A2	2005-12-22	Ramot at Tel Aviv University Ltd.		☐
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	100	2006133486	WO	A1	2006-12-21	The MacFarlane Burnet Institute For Medical Resear		☐
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	108	2008057240	WO	A2	2008-05-15	Abbott Biotechnology LTD.		☐
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	119	2008157409	WO	A1	2008-12-24	ELAN PHARMACEUTICAL, INC.		☐
	120	2009009407	WO	A1	2009-01-15	Smithkline Beecham Corp.		☐
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	123	2009101611	WO	A1	2009-08-20	Curetech Ltd.		☐
	124	2009120684	WO	A1	2009-10-01	Medimmune, LLC		☐
	125	2009126688	WO	A2	2009-10-15	Genentech, Inc.		☐
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	131	2010148337	WO	A1	2010-12-23	WYETH LLC		☐
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	133	2011012637	WO	A2	2011-02-03	HOFFMANN LA ROCHE		☐
	134	2011012637	WO	A2	2011-02-03	Hoffman-LaRoche		☐
	135	2011017070	WO	A1	2011-02-10	Merck Sharp & Dohme Corp.		☐
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	137	2011029892	WO	A2	2011-03-17	F. HOFFMANN-LA ROCHE AG		☐
	138	2011034822	WO	A1	2011-03-24	Shenoy, Bhami		☐
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	142	2011097372	WO	A2	2011-08-11	APTUIT LAURUS PRIVATE LIMITED		☐
	143	2011116090	WO	A1	2011-09-22	Abbott Research B.V.		☐
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	147	2012018538	WO	A2	2012-02-09	Schering Corporation		☐
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	152	2012165917	WO	A1	2012-12-06	LG Life Sciences Ltd.		☐
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	155	2013151999	WO	A1	2013-10-10	President and Fellows of Harvard College		☐
	156	2013167720	WO	A1	2013-11-14	NOVARTIS AG		☐
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	158	2014036071	WO	A1	2014-03-06	BAYER HEALTHCARE LLC		☐
	159	2014036076	WO	A1	2014-03-06	BAYER HEALTHCARE LLC		☐
	160	2015009856	WO	A2	2015-01-22	Genentech, Inc.		☐
	161	2015011199	WO	A1	2015-01-29	Novaliq GMBH		☐

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	163	2015038782	WO	A1	2015-03-19	Arsia Therapeutics, Inc.		☐
	164	2015038811	WO	A2	2015-03-19	Arsia Therapeutics, Inc.		☐
	165	2015038818	WO	A2	2015-03-19	Arsia Therapeutics, Inc.		☐
	166	2015042246	WO	A1	2015-03-26	Bristol Myers Squibb Co.		☐
	167	2015048520	WO	A1	2015-04-02	GENENTECH, INC.;F. HOFFMANN-LA ROCHE AG		☐
	168	2015095423	WO	A2	2015-06-25	GENENTECH, INC. et al.		☐
	169	2015143343	WO	A2	2015-09-24	THE BRIGHAM AND WOMEN'S HOSPITAL, INC.		☐
	170	2016011264	WO	A1	2016-01-21	Genentech, Inc. and Hoffman-La AGRoche		☒
	171	2016015675	WO	A1	2016-02-04	Akeso Biopharma, Inc.	Equivalent=US20170216433	☐
	172	2016024228	WO	A1	2016-02-18	Acerta Pharma B.V.		☐

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	174	2016028672	WO	A1	2016-02-25	MERCK SHARP & DOHME CORP.		☐
	175	2016035006	WO	A1	2016-03-10	DR. REDDY'S LABORATORIES LIMITED		☐
	176	2016035006	WO	A1	2016-03-10	DR. REDDY'S LABORATORIES LIMITED		☐
	177	2016040238	WO	A1	2016-03-17	CELGENE CORPORATION		☐
	178	2016070051	WO	A2	2016-05-06	ONCOMED PHARMACEUTICALS, INC.		☐
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	181	2016118654	WO	A1	2016-07-28	IMMUNEXCITE, INC.		☐
	182	2016137850	WO	A1	2016-09-01	Merck Sharp & Dohme Corp.		☐
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	190	2017009813	WO	A1	2017-01-19	LAURUS LABS PRIVATE LIMITED		☐
	191	2017015560	WO	A2	2017-01-26	SORRENTO THERAPEUTICS, INC.		☐
	192	2017021526	WO	A1	2017-02-09	AMGEN RESEARCH (MUNICH) GMBH		☐
	193	2017025498	WO	A1	2017-02-16	PIERIS PHARMACEUTICALS GMBH		☐
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	195	2017037203	WO	A1	2017-03-09	IMMUTEP S.A.S.		☐
	196	2017040790	WO	A1	2017-03-09	Agenus Inc.		☐
	197	2017040864	WO	A1	2017-03-09	FIRST WAVE BIOPHARMA		☐
	198	2017048824	WO	A1	2017-03-23	COMPASS THERAPEUTICS LLC		☐
	199	2017053748	WO	A2	2017-03-30	GENENTECH, INC.		☒
	200	2017054646	WO	A1	2017-04-06	Jiangsu Hengrui Medicine Co.		☐
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	211	2018158332	WO	A1	2018-09-07	MEDIMMUNE LIMITED		☐
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Examiner Signature	/KIMBERLY BALLARD/	Date Considered	01/10/2026

*EXAMINER: Initial if reference considered and whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.B/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT		
	Application Number	
	Filing Date	
	First Named Inventor	Manoj K. SHARMA
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	24439-US-CNT-4

TIMING STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached timing statement under 37 CFR 1.97(e).

☐ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING FEE

☐ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

COPIES

☒ An identification of an earlier application pursuant to 37 CFR 1.98(d)(1) is attached.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and the IDS Auto-Load Instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☐ No IDS size fee is required under 37 CFR 1.17(v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☒ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Patrick Rehfuss, Reg. No. 75,367/	Date (YYYY-MM-DD)	2025-09-19
Name/Print	Patrick Rehfuss	Registration Number	75,367

PC.1.19.25

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.B/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT		
	Application Number	
	Filing Date	
	First Named Inventor	Manoj K. SHARMA
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	24439-US-CNT-4

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you 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.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.B/

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 the Freedom of Information Act requires disclosure of these record s.

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 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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.B/

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L3	100	(Artificial Intelligence) Similar to: 19/346,638 with 0 CPC Selections and 0 Text Selections Text: (KR-102614259-B1 OR JP-2024527517-A OR EP-3504241-B1 OR US-10688186-B2 OR WO-2021123202-A1 OR WO-2018044948-A1 OR KR-20240024941-A OR US-12024561-B2 OR ES-2986900-T3 OR EP-4088740-A1 OR JP-2022119854-A OR US-20230048612-A1 OR JP-2019526627-A OR CA-3162976-A1 OR CN-117561079-A OR JP-2024075713-A OR CA-3220545-A1 OR AU-2021251661-A1 OR FI-3506886-T3 OR JP-2018199720-A OR WO-2010100200-A2 OR US-20150343058-A1 OR US-20230355757-A1 OR AU-2013360812-A1 OR WO-2025191489-A1 OR WO-2014096051-A1 OR NZ-748681-A OR AU-2013360812-B2 OR US-20190010224-A1 OR US-20170252437-A1 OR CA-3032596-A1 OR AU-2017319318-A1 OR US-20210403568-A1 OR AU-2003267744-C1 OR CN-109843920-B OR JP-2023109938-A OR US-20220016244-A1 OR CN-102770157-A OR CA-2805388-A1 OR WO-2017054646-A1 OR AU-2009324371-A1 OR AU-2008228823-A1 OR	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO))	OR	ON	ON	2026/01/10 10:21 PM

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		OR JP-2020203889-A OR TW-I753087-B OR CN-106163567-A).did.					
L4	100	(Artificial Intelligence) Similar to: 19/346,638 with 1 CPC Selection and 2 Text Selections Text: (JP-2024527517-A OR KR-20240024941-A OR US-20230355757-A1 OR US-20210030868-A1 OR WO-2021021924-A1 OR WO-2021123202-A1 OR CN-112805566-A OR CA-3220545-A1 OR JP-2024534185-A OR US-20230112956-A1 OR WO-2022006091-A1 OR US-20210403568-A1 OR AU-2021251661-A1 OR AU-2003267744-C1 OR JP-6845973-B1 OR JP-5231810-B2 OR JP-2021119199-A OR JP-2019163319-A OR EP-1977763-A1 OR JP-6590803-B2 OR US-20150343058-A1 OR CA-3125927-A1 OR CA-3162976-A1 OR CA-2999118-A1 OR WO-2015075201-A1 OR US-10617764-B2 OR US-20200246477-A1 OR US-20240091373-A1 OR US-20160279258-A1 OR MA-45450-B1 OR KR-20250156121-A OR WO-2016162819-A1 OR EP-4400116-A1 OR SG-11202104269P-A OR CA-3230383-A1 OR CN-109952093-A OR SI-2376533-T1 OR MY-166050-A OR MA-33023-B1 OR MY-157772-A OR JP-7461401-B2 OR CA-3156713-A1 OR CN-113521016-A OR CU-20120080-A7 OR US-10688186-B2 OR JP-	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO))	OR	ON	ON	2026/01/10 10:22 PM

		2024075713-A OR KR-20210064112-A OR JP-2023520597-A OR RU-2020100596-A OR WO-2014099636-A1 OR ES-2986900-T3 OR CN-110431153-A OR EP-3504241-B1 OR CA-3032596-A1 OR WO-2018044948-A1 OR EP-4062933-A1 OR US-20250064930-A1 OR JP-7057360-B2 OR US-20150329628-A1 OR JP-2022082757-A OR US-9844594-B2 OR CN-115998859-A OR RU-2019100221-A OR US-20220125921-A1 OR CN-106999591-B OR CA-2618068-C OR CA-2915270-A1 OR CA-2618068-A1 OR US-12171830-B2 OR JP-2016539118-A OR CN-109843920-B OR WO-2017121867-A1 OR KR-102372245-B1 OR AU-2017289085-A1 OR ES-2823279-T3 OR US-6267958-B1 OR AU-2017319318-A1 OR NZ-748681-A OR JP-2019526627-A OR WO-2017054646-A1 OR CA-3029137-A1 OR JP-2022119854-A OR RS-62035-B1 OR JP-2024109816-A OR CN-109415440-B OR US-20150010573-A1 OR KR-20180085801-A OR JP-2018199720-A OR JP-2016508973-A OR EP-3475303-B1 OR EP-3909985-A1 OR AU-2017289085-B2 OR US-20190322742-A1 OR US-20220213190-A1 OR JP-7603201-B2 OR WO-2018002031-A1 OR US-11352423-B2 OR US-20030202972-A1 OR ES-2874640-T3 OR EP-4374874-A1).did.					
L5	100	(Artificial Intelligence)	(US-PGPUB; USPAT;	OR	ON	ON	2026/01/10

		Similar to: 19/346,638 with 1 CPC Selection and 3 Text Selections Text: (US-10688186-B2 OR JP-2022082757-A OR EP-3504241-B1 OR JP-7057360-B2 OR WO-2018044948-A1 OR AU-2017319318-A1 OR JP-2019526627-A OR CN-109843920-B OR JP-2024075713-A OR AU-2003267744-C1 OR KR-20200017553-A OR RU-2019100221-A OR JP-7461401-B2 OR US-20160039926-A1 OR ES-2986900-T3 OR US-9724414-B2 OR US-20190070293-A1 OR FI-3506886-T3 OR US-20190070294-A1 OR KR-20220025196-A OR US-9808525-B2 OR US-20180311351-A1 OR US-20180311352-A1 OR US-10688183-B2 OR US-20160031982-A1 OR RS-62035-B1 OR US-9757454-B2 OR US-10155039-B2 OR US-20160263226-A1 OR US-20180055930-A1 OR US-20190060455-A1 OR ES-2874640-T3 OR US-20190070292-A1 OR JP-7603201-B2 OR WO-2018002031-A1 OR CN-109415440-B OR US-20150191539-A1 OR AU-2017289085-A1 OR AU-2017289085-B2 OR US-9789185-B2 OR US-20180311349-A1 OR JP-2022119854-A OR US-10716853-B2 OR CA-3028238-C OR RU-2748024-C2 OR US-9782479-B2 OR JP-2024109816-A OR US-20160256547-A1 OR JP-2019524671-A OR US-20150190513-A1 OR KR-20230074823-A	USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO))				10:25 PM

		OR CN-115998859-A OR US-9731008-B2 OR US-20160304600-A1 OR US-20180028653-A1 OR NZ-748681-A OR US-9346880-B2 OR US-10286071-B2 OR CA-3029137-A1 OR EP-3475303-B1 OR US-10286072-B2 OR US-20190322742-A1 OR US-20220213190-A1 OR US-11352423-B2 OR US-10722579-B2 OR US-20170312361-A1 OR KR-102533875-B1 OR US-20160303233-A1 OR US-20160303234-A1 OR US-20160304599-A1 OR US-20160303235-A1 OR EP-3909985-A1 OR US-20180021433-A1 OR US-20180140701-A1 OR US-10195275-B2 OR US-9724415-B2 OR US-9782480-B2 OR US-9770507-B2 OR US-9731009-B2 OR US-9682145-B2 OR US-20160256545-A1 OR US-20180311350-A1 OR CN-109415440-A OR US-20180028655-A1 OR US-20180028656-A1 OR US-20180028657-A1 OR US-20180055929-A1 OR US-9861695-B2 OR EA-029215-B1 OR US-20150190512-A1 OR US-20180043018-A1 OR US-9340611-B2 OR KR-102362829-B1 OR US-20160256546-A1 OR US-9707293-B2 OR US-10159733-B2 OR US-20180043019-A1 OR US-10772960-B2 OR CA-2884182-C OR US-10786566-B2).did.					

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Bibliographic Data

Application No: 19/346,638

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /KIMBERLY BALLARD/ Examiner's Signature | Initials

Title: STABLE FORMULATIONS OF PROGRAMMED DEATH RECEPTOR 1 (PD-1) ANTIBODIES AND METHODS OF USE THEREOF

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/01/2025	424	1675	24439-US-CNT-4
RULE			

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CONTINUING DATA

This application is a CON of 18182135 03/10/2023

18182135 is a CON of 16609612 10/30/2019 PAT 11633476

16609612 is a 371 of PCT/US18/30459 05/01/2018

PCT/US18/30459 has PRO of 62500238 05/02/2017

FOREIGN APPLICATIONS

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PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	584	((("MERCK") near3 ("SHARP") near3 ("DOHME") near3 ("LLC"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2025/12/10 02:19 PM
L2	529	((("SHARMA") near3 ("Manoj")) OR (("BENJAMIN") near3 ("Wendy")) OR (("MITTAL") near3 ("Sarita")) OR (("BASARKAR") near3 ("Ashwin")) OR (("NARASIMHAN") near3 ("Chakravarthy")) OR (("KASHI") near3 ("Ramesh")) OR (("SHAMEEM") near3 ("Mohammed")) OR (("BHATTACHARYA") near3 ("Soumendu")) OR (("FORREST") near3 ("William")) OR (("KRISHNAMACHARI") near3 ("Yogita"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2025/12/10 02:19 PM
L3	142957	((programmed near2 death NEAR receptor NEAR "1") (programmed NEAR cell NEAR death NEAR "1") PD-1 PD1 cd279) WITH antibody	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/12/10 02:25 PM
L4	108759	pembrolizumab MK-3475	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH,	OR	ON	ON	2025/12/10 02:27 PM

			TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L5	948	(L1 L2) AND (L3 L4)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/12/10 02:29 PM
L6	14142	(A61K39/39591).cpc. AND (A61K39/395)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/12/10 03:09 PM
L7	84862	(A61K9/19).cpc.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/12/10 03:10 PM
L8	119203	(A61K39/395).cpc.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV,	OR	ON	ON	2025/12/10 03:13 PM

			MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L9	270631	(A61K47/183 A61K47/26 A61K47/34).cpc.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/12/10 03:14 PM
L10	3055	L6 AND L7 AND L9	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/12/10 03:24 PM
L11	167	L10 AND (L3 L4)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/12/10 03:26 PM
L12	10364	antibody SAME (histidine WITH (buffer HCL)) SAME (trehalose "(2-hydroxypropyl)-ß-	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU,	OR	ON	ON	2025/12/10 04:57 PM

		cyclodextrin" mannitol sorbitol l-arginine l-proline glycine) SAME (polysorbate NEAR ("80" "20"))	CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L13	8341	antibody SAME (histidine WITH (buffer HCL)) SAME (trehalose) SAME ((polysorbate NEAR ("80" "20")) (poloxamer NEAR "188"))	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/12/10 04:59 PM
L14	34098	antibody WITH (("20" "25" "15" "30") near2 mg/ml)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/12/10 05:01 PM
L15	64184	(("0.01-0.10" "0.01" "0.02" "0.03" "0.05" "0.1") NEAR ("%" percent)) WITH (surfactant polysorbate-80 (polysorbate NEAR "80") poloxamer)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/12/10 05:18 PM

L16	2843803	pH near3 ("5" "5-6" "5.5" "6")	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/12/10 05:19 PM
L17	394	L13 AND L14 AND L15 AND L16	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2025/12/10 05:20 PM
L18	112304	pembrolizumab MK-3475 keytruda	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 04:53 PM
L19	814	L1 AND (L3 L18)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH,	OR	ON	ON	2026/01/06 04:54 PM

			TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L20	313897	trehalose WITH sucrose	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 06:31 PM
L21	2021	mannitol AND sorbitol AND l-argnine AND l-prolineand glycine AND ("(2-hydroxypropyl)-ß-cyclodextrin" 2-hydroxypropyl-beta-cyclodextrin)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 06:33 PM
L22	1061	L20 AND L21	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 06:33 PM
L23	29803	("polysorbate 80" PS80 PS-80) AND ("polysorbate 20" PS20 PS-20) AND (poloxamer NEAR "188")	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV,	OR	ON	ON	2026/01/06 06:35 PM

			MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L24	27	L22 AND L23	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 06:35 PM
L25	39439	("polysorbate 80" PS80 PS-80) AND ("polysorbate 20" PS20 PS-20) AND ((poloxamer NEAR "188") "pluronic F-68" F68)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 09:30 PM
L26	2819671	(mannitol AND sorbitol) ((l-argnine arginine) AND (l-proline proline)) glycine ("(2-hydroxypropyl)-ß-cyclodextrin" 2-hydroxypropyl-beta-cyclodextrin HP-ß-CD HPßCD)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 09:33 PM
L27	240932	L26 SAME stabilizer	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU,	OR	ON	ON	2026/01/06 09:33 PM

			CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L28	12220	L27 AND L25	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 09:34 PM
L29	8967	L28 AND L20	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 09:35 PM
L30	55908	(stable stabilized stability) WITH (antibody immunoglobulin IgG) WITH (formulation formula composition)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 09:35 PM

L31	3841	L29 AND L30	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 09:36 PM
L32	121118	(antioxidant anti-oxidant) SAME (methionine "L-methionine HCl")	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 09:37 PM
L33	2331	L31 AND L32	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 09:37 PM
L34	183011	"diethylenetriaminopentaacetic acid" DTPA!	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH,	OR	ON	ON	2026/01/06 09:38 PM

			TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)				
L35	506	L33 AND L34	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 09:38 PM
L36	2226	L33 AND subcutaneous	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2026/01/06 09:39 PM
L37	100	(Artificial Intelligence) Similar to: Unpublished Application # with 0 CPC Selections and 0 Text Selections Text: (US-20230119778-A1 OR EP-3504241-B1 OR DK-2691112-T3 OR JP-2016104780-A OR WO-2018044948-A1 OR WO-2024171082-A1 OR US-12024561-B2 OR ES-2986900-T3 OR JP-2022119854-A OR KR-20240024941-A OR EP-4088740-A1 OR US-20230048612-A1 OR JP-2018199720-A OR JP-2019526627-A OR CA-3162976-A1 OR CN-117561079-A OR CN-114616249-A OR JP-2024075713-A OR	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO))	OR	ON	ON	2026/01/08 11:49 PM

		AU-2013360812-A1 OR RU-2024101251-A OR US-20150343058-A1 OR US-20210403568-A1 OR US-20230355757-A1 OR CA-3220545-A1 OR WO-2014096051-A1 OR EP-2934582-B1 OR US-20190010224-A1 OR TW-202415407-A OR WO-2025191489-A1 OR US-12433947-B2 OR CA-2866128-A1 OR JP-2022513693-A OR CA-3032596-A1 OR BR-112012016618-A2 OR CN-109843920-B OR WO-2017054646-A1 OR US-20220016244-A1 OR NZ-748681-A OR CA-2895869-C OR CA-2895869-A1 OR CN-104159612-A OR US-20160280781-A1 OR CN-106999591-B OR KR-20130028894-A OR EP-4076385-B1 OR WO-2016066688-A1 OR WO-2021013689-A1 OR JP-2016508973-A OR JP-7057360-B2 OR CN-112805566-A OR JP-2023109938-A OR EP-3428189-A1 OR EP-3766481-A1 OR EP-3823594-B1 OR BR-PI0806313-A2 OR AU-2009324371-A1 OR US-20180339045-A1 OR WO-2020008035-A1 OR US-9376491-B2 OR KR-101730694-B1 OR CN-116617387-A OR WO-2013016648-A2 OR US-10786567-B2 OR US-20200246477-A1 OR WO-2019106206-A1 OR EP-4559485-A2 OR US-20240091373-A1 OR WO-2017112621-A1 OR US-10617764-B2 OR US-20160279258-A1 OR JP-5896471-B2 OR US-20210030868-A1 OR					

		JP-2025525458-A OR JP-2024523443-A OR JP-2015231997-A OR JP-2018168158-A OR WO-2021013372-A1 OR WO-2011017070-A1 OR JP-2016539118-A OR KR-20180085801-A OR JP-2022082757-A OR JP-2020532491-A OR US-20210403550-A1 OR TW-I730310-B OR CN-112516090-B OR KR-102372245-B1 OR TW-I753087-B OR US-20230279138-A1 OR WO-2021038532-A1 OR KR-20160105535-A OR US-20250043027-A1 OR KR-20140134689-A OR CN-113521016-A OR JP-2024515968-A OR CN-112543627-A OR WO-2022132636-A1 OR US-20210292434-A1 OR TW-202034898-A OR EP-2501408-B1 OR EP-1409018-B1).did.					
L38	100	(Artificial Intelligence) Similar to: Unpublished Application # with 1 CPC Selection and 3 Text Selections Text: (US-20230119778-A1 OR KR-20240024941-A OR WO-2024171082-A1 OR US-20230355757-A1 OR EP-4076385-B1 OR CA-3220545-A1 OR CN-114728064-B OR CN-112805566-A OR JP-7675049-B2 OR WO-2023073469-A1 OR RU-2011151286-A OR US-20210403568-A1 OR JP-2024534185-A OR JP-2025163108-A OR US-20210322550-A1 OR US-20160279258-A1 OR US-20200246477-A1 OR US-10617764-	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO))	OR	ON	ON	2026/01/08 11:52 PM

		B2 OR CA-3234358-A1 OR CU-20120080-A7 OR JP-2024075713-A OR WO-2016066688-A1 OR EP-4190352-A1 OR US-20210030868-A1 OR CN-113521016-A OR KR-102372245-B1 OR US-20220016244-A1 OR EP-3428189-A1 OR RU-2024101251-A OR WO-2013186230-A1 OR CA-3217391-A1 OR CN-106163567-B OR CN-120242000-A OR US-12171830-B2 OR CA-3007481-A1 OR WO-2021013689-A1 OR CA-3156713-A1 OR US-11260125-B2 OR US-20220184210-A1 OR US-20240091373-A1 OR EP-3909985-A1 OR JP-2023109938-A OR US-20220273796-A1 OR EP-2501408-B1 OR KR-20240038735-A OR WO-2016162819-A1 OR WO-2019106206-A1 OR JP-7461401-B2 OR JP-2016539118-A OR JP-2025522442-A OR JP-2023532326-A OR WO-2025041000-A1 OR JP-2022116305-A OR WO-2017121867-A1 OR DE-25179059-T1 OR AU-2009324371-A1 OR WO-2015075201-A1 OR EP-4559485-A2 OR CN-109843920-B OR AU-2020387034-A1 OR AU-2013360812-A1 OR IL-321343-A OR TW-202224702-A OR JP-2019163319-A OR CN-112972674-B OR KR-20220098046-A OR KR-20210064112-A OR EP-3766481-A1 OR US-20150343058-A1 OR WO-2020053301-A1 OR DE-202015009619-U1 OR JP-2024515968-A OR JP-2021119199-A OR					

		DE-202015009016-U1 OR DE-202015009509-U1 OR EP-3823594-B1 OR DE-202015009509-U9 OR US-20230112956-A1 OR CN-114728064-A OR US-20030202972-A1 OR CN-102245639-A OR JP-7286595-B2 OR EP-4062933-A1 OR US-20230279138-A1 OR JP-2022513693-A OR US-20240150479-A1 OR TW-202415407-A OR US-11723976-B2 OR WO-2025191489-A1 OR JP-2016104780-A OR US-20220125921-A1 OR US-20190070293-A1 OR US-20150191538-A1 OR CN-109248315-B OR JP-6590803-B2 OR US-9346880-B2 OR US-20250064930-A1 OR US-12433947-B2 OR CN-119365216-A OR US-20180140701-A1).did.					
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		US-20140100236-A1 OR CN-112516090-A OR CN-104994854-A OR CN-110403922-A OR JP-2025163108-A OR FI-3479819-T3 OR CN-113975385-A OR JP-5102949-B2 OR US-20230119778-A1 OR US-20110218173-A1 OR US-20210322550-A1 OR WO-2024171082-A1 OR US-20160279258-A1 OR US-20200246477-A1 OR US-10617764-B2 OR CU-20120080-A7 OR JP-2024075713-A OR FI-4218797-T3 OR CA-3039796-A1 OR JP-2006083171-A OR CN-119745811-A OR EP-4190352-A1 OR WO-2016066688-A1 OR CN-113521016-A OR WO-2018085551-A2 OR KR-102372245-B1 OR US-20220016244-A1 OR WO-2007072218-A2 OR EP-3428189-A1 OR CA-3217391-A1 OR CN-120242000-A OR JP-2024515968-A OR IL-281818-A OR NZ-603076-A OR CN-106163567-B OR WO-2013186230-A1 OR CA-3007481-A1 OR US-12171830-B2 OR WO-2021013689-A1 OR WO-2022222945-A1 OR HR-P20160295-T1 OR CA-2903611-A1 OR CA-2903611-C OR EP-3909985-A1 OR CA-3156713-A1 OR US-11260125-B2 OR US-20240091373-A1 OR US-20220184210-A1 OR US-20220273796-A1 OR KR-20240038735-A OR EP-3399979-B9 OR EP-3399979-B1 OR CN-105189559-A OR EP-2970465-B1 OR WO-2016162819-A1					

		OR AU-2004234176-B2 OR JP-2025522442-A OR AU-2004234176-A1 OR JP-2023109938-A OR WO-2019106206-A1 OR RU-2024101251-A OR EP-2501408-B1 OR JP-7461401-B2 OR US-20190060240-A1 OR WO-2022035397-A1 OR AU-2021326382-A9 OR US-11576863-B2 OR JP-2016539118-A OR EA-035278-B1 OR WO-2025041000-A1 OR CA-2523079-C OR US-20230355757-A1 OR EP-4338752-A2 OR US-20160022585-A1 OR US-11433029-B2 OR US-20140271636-A1 OR US-20240009227-A1 OR JP-2023532326-A OR WO-2025149100-A2 OR CN-110279693-A OR ES-2358330-T5).did.					
L40	100	(Artificial Intelligence) Similar to: Unpublished Application # with 0 CPC Selections and 6 Text Selections Text: (HR-P20201573-T1 OR CN-114728064-B OR US-20170312361-A1 OR US-20210322550-A1 OR US-20160256546-A1 OR US-20220125921-A1 OR US-20190070293-A1 OR US-12171830-B2 OR CN-120242000-A OR US-10722579-B2 OR US-11260125-B2 OR US-11723976-B2 OR US-20190060455-A1 OR US-20190070292-A1 OR US-20190070294-A1 OR CA-3220545-A1 OR US-20250064930-A1 OR US-20220184210-A1 OR JP-6845973-B1 OR WO-2021100794-	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO))	OR	ON	ON	2026/01/09 12:04 AM

		A1 OR CN-114616249-A OR CN-114728064-A OR JP-7675049-B2 OR US-9340612-B2 OR US-9782479-B2 OR JP-2021169448-A OR US-20180028653-A1 OR JP-6889344-B2 OR EP-4062933-A1 OR CA-3217391-A1 OR KR-102238677-B1 OR JP-6783845-B2 OR JP-WO2021100794-A1 OR EP-4190352-A1 OR CN-119386173-A OR JP-2016104780-A OR US-9724415-B2 OR US-20230119778-A1 OR JP-6463268-B2 OR JP-2022116305-A OR KR-20210040470-A OR CN-112543627-A OR KR-20210064112-A OR US-10286072-B2 OR US-20240287191-A1 OR CA-3156713-A1 OR US-10716853-B2 OR US-20180311350-A1 OR EP-2892550-B1 OR US-20180311349-A1 OR RU-2024101251-A OR US-10772960-B2 OR KR-20220098046-A OR US-20180055930-A1 OR US-10155039-B2 OR KR-20240024941-A OR US-20180311351-A1 OR US-20160039926-A1 OR US-9724414-B2 OR US-10688183-B2 OR US-20180311352-A1 OR US-10772959-B2 OR US-10799585-B2 OR US-10716854-B2 OR KR-20210028673-A OR KR-101730694-B1 OR US-10207000-B2 OR JP-2022082757-A OR WO-2009037190-A2 OR WO-2022022464-A1 OR TR-201810815-T4 OR IL-293099-A OR FI-3061445-T3 OR WO-2023140807-A1 OR US-20150191539-A1 OR RU-2021122280-A					

		OR KR-20130028894-A OR AU-2018208699-A1 OR US-20190060240-A1 OR JP-2023532326-A OR US-9382317-B2 OR JP-2016539118-A OR WO-2024171082-A1 OR KR-20220025196-A OR JP-2021529800-A OR KR-20180038290-A OR US-10786567-B2 OR JP-7473603-B2 OR AU-2019298656-A1 OR US-20230279138-A1 OR US-20180064781-A1 OR WO-2020008035-A1 OR DE-25179059-T1 OR US-10780163-B2 OR RU-2013152751-A OR US-20160256545-A1 OR US-9682145-B2 OR US-9757454-B2 OR US-20160263226-A1 OR CN-106999591-B).did.					

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	601	((("MERCK") near3 ("SHARP") near3 ("DOHME") near3 ("LLC"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2026/01/06 04:56 PM
N2	177	N1 AND (PD-1 pembrolizumab keytruda MK-3475)	(US-PGPUB; USPAT)	OR	ON	ON	2026/01/06 04:57 PM
N4	127	N1 AND (antibody.clm.)	(US-PGPUB; USPAT)	OR	ON	ON	2026/01/06 06:04 PM
N5	4545	((("MERCK") near3 ("SHARP") near3 ("DOHME"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2026/01/06 06:20 PM
N6	498	N5 AND (PD-1 pembrolizumab keytruda MK-3475)	(US-PGPUB; USPAT)	OR	ON	ON	2026/01/06 06:20 PM

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     (FILE 'HOME' ENTERED AT 21:59:51 ON 11 JAN 2026)
               D SET
               D CLUSTER
               D CLUSTER .BIOQUICK .BIOTECH
               D SEL

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 22:00:18 ON 11 JAN 2026
L1         88005 SEA SPE=ON  ABB=ON  "PEMBROLIZUMAB" OR H409A11 OR MK-3475 OR
                 LAMBROLIZUMAB OR KETRUDA
L2          4432 SEA SPE=ON  ABB=ON  ANTIBODY(2A) FORMULAT?
L3         14604 SEA SPE=ON  ABB=ON  ANTIBODY(S) FORMULAT?
L4         88496 SEA SPE=ON  ABB=ON  (HISTIDINE OR ACETATE OR CITRATE)(S)
                 BUFFER?
L5         23294 SEA SPE=ON  ABB=ON  (SUCROSE AND TREHALOSE)
L6           568 SEA SPE=ON  ABB=ON  MANNITOL AND SORBITOL AND GLYCINE AND
                 (ARGININE OR L-ARGININE) AND (PROLINE OR L-PROLINE)
L7         13370 SEA SPE=ON  ABB=ON  SURFACTANT AND ((POLYSORBATE(A)(80 OR 20))
                 OR PS80 OR PS20 OR (POLOXAMER 188) OR (PLURONIC F-68))
L8            38 SEA SPE=ON  ABB=ON  L2 AND L4 AND (L5 OR L6) AND L7
L9            35 DUP REM L8 (3 DUPLICATES REMOVED)
                       ANSWER '1' FROM FILE MEDLINE
                       ANSWERS '2-35' FROM FILE CAPLUS
L10           38 SEA SPE=ON  ABB=ON  L1 AND L2
L11          119 SEA SPE=ON  ABB=ON  L1 AND L3
L12           42 SEA SPE=ON  ABB=ON  L3 AND L4 AND (L5 OR L6) AND L7
L13            3 SEA SPE=ON  ABB=ON  L12 AND L1
L14            3 DUP REM L13 (0 DUPLICATES REMOVED)
                       ANSWERS '1-2' FROM FILE CAPLUS
                       ANSWER '3' FROM FILE EMBASE
                  D L14 1-3
L15           39 DUP REM L12 (3 DUPLICATES REMOVED)
                       ANSWER '1' FROM FILE MEDLINE
                       ANSWERS '2-39' FROM FILE CAPLUS
                  D L15 1-20
L16        70130 SEA SPE=ON  ABB=ON  ANTI-PD-1 OR (ANTIBODY(S)(PD-1 OR "PROGRAMM
                 ED DEATH RECEPTOR 1" OR "PROGRAMMED CELL DEATH PROTEIN 1"))
L17          472 SEA SPE=ON  ABB=ON  L3 AND L16
L18            6 SEA SPE=ON  ABB=ON  L17 AND L4 AND L7
L19            6 DUP REM L18 (0 DUPLICATES REMOVED)
                       ANSWERS '1-6' FROM FILE CAPLUS
                  D L19 1-6
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