CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761334Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 10, 2023
To:	Autumn Zack-Taylor, MS Senior Regulatory Health Project Manager **Division of Oncology 3 (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Mispa Ajua-Alemanji, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ZYNYZ (retifanlimab)
Dosage Form and Route:	injection
Application Type/Number:	BLA 761334
Applicant:	Incyte Corporation

1 INTRODUCTION

On August 8, 2022, Incyte Corporation submitted for the Agency's review an original Biologics License Application (BLA) 761334 for ZYNYZ (retifanlimab) injection for the proposed indication for the treatment of adults (b) (4) with metastatic or recurrent locally advance Merkel cell carcinoma (MCC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 3 (DOP3) on August 8, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ZYNYZ (retifanlimab) injection.

2 MATERIAL REVIEWED

- Draft ZYNYZ (retifanlimab) MG received on August 8, 2022.
- Draft ZYNYZ (retifanlimab) Prescribing Information (PI) received on August 8, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on December 23, 2022.
- Approved JEMPERLI (dostarlimab-gxly) injection [BLA 761174] comparator labeling dated April 28, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 10, 2023

To: Autumn Zach-Taylor, Regulatory Project Manager, DO3

Doris Auth, Associate Director for Labeling, DO3

From: Mispa Ajua-Alemanji, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZYNYZ™(retifanlimab-dlwr) Injection, for intravenous use

BLA: 761334

Background:

In response to DO3's consult request dated December 23, 2022, OPDP has reviewed the proposed product labeling (PI), medication guide (MG), and carton and container labeling for the original BLA submission for ZYNYZ™(retifanlimab-dlwr) injection, for intravenous use (Zynyz).

PI and Medication Guide:

OPDP's comments on the proposed labeling are based on the draft labeling emailed to OPDP on December 23, 2022, and later updated and accessed in SharePoint on January 9, 2023, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the MG was completed on January 6, 2023, and comments on the proposed MG sent under separate cover.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room December 20, 2022, and our comments are provided below.

PI:

Section	Statement from Draft (if applicable)	OPDP Comment
HIGHLIGHTS OF PRESCRIBING INFORMATION: WARNINGS AND PRECAUTIONS **6.1 CLINICAL TRIAL EXPERIENCE**	"Adverse reactions" (b) (4)	OPDP notes that the incidence cut-off rate or most common adverse reactions that is used in the Highlights is ≥10%, (b) (4)
14 CLINICAL STUDIES	"Patients with (b) (4) HIV on anti-retroviral therapy (b) (4) were eligible" (emphasis added)	(b) (4) If the information regarding inclusion of patients with HIV is retained, OPDP recommends revising this language to instead provide specific information (b) (4) (e.g., were patients required to have an undetectable viral load and be taking an anti-retroviral regimen?) Additionally, we are concerned with the inclusion of this eligibility criteria as part of the description of the clinical trial—were any HIV+ patients actually included in the study? If not, is this information necessary to describe the safe and effective use of the drug? We note the sponsor's comment regarding this issue; however, this may have promotional implications if it is included in labeling. OPDP defers to the RD regarding whether this information is necessary and appropriate to include in approved labeling.

Carton and Container Labeling:

OPDP recommends revising the established name on the proposed carton and container labeling to be in accordance with 21CFR 201.10(g)(2) which states that, '[t]he established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Specifically, we note that the proprietary name is presented in a bolded blue and green font, whereas the established name is presented (b) (4).

Thank you for your consult. If you have any questions, please contact Mispa Ajua-Alemanji at Mispa.Ajua-Alemanji@fda.hhs.gov.

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MISPA L AJUA-ALEMANJI
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 17, 2023
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761334
Product Name and Strength:	Zynyz (retifanlimab-xxxx)[a] Injection, 500 mg/20 mL (25 mg/mL)
Applicant/Sponsor Name:	Incyte Corporation
OSE RCM #:	2022-771-2
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on January 27, 2023 for Zynyz. Division of Oncology 3 (DO3) requested that we review the revised container label and carton labeling for Zynyz (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to a recommendation that OPDP made after DMEPA's previous label and labeling memorandum.[b] The OPDP sent the following comment via DO3 regarding the container label and carton labeling:

> Revise the established name on the proposed carton and container labeling to be in accordance with 21CFR 201.10(g)(2) which states that, '[t]he established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Specifically, we note that the proprietary name is presented in a bolded blue and green font, whereas the established name is presented (b) (4).

[a] Since the nonproprietary name for suffix for retifanlimab-xxxx has not yet been determined, "retifanlimab-xxxx" is used throughout this review as the nonproprietary name for this product.
[b] Stewart, J. Label and Labeling Memo for Zynyz (BLA 761334). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2022 DEC 21. RCM No.: 2022-771-1.

Thus, Inctyte Corporation submitted a revised container label and carton labeling for review.

2 CONCLUSION

We found the revised container label and carton labeling acceptable form a medication error perspective and we have no additional recommendations at this time.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 21, 2022
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761334
Product Name and Strength:	Zynyz (retifanlimab-xxxx)[a] Injection, 500 mg/20 mL (25 mg/mL)
Applicant/Sponsor Name:	Incyte Corporation
OSE RCM #:	2022-771-1
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on December 20, 2022 for Zynyz. Division of Oncology 3 (DO3) requested that we review the revised container label and carton labeling for Zynyz (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Since the nonproprietary name for suffix for retifanlimab-xxxx has not yet been determined, "retifanlimab-xxxx" is used throughout this review as the nonproprietary name for this product.
[b] Stewart, J. Label and Labeling Review for Zynyz (BLA 761334). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2022 DEC 21. RCM No.: 2022-771.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 21, 2022
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761334
Product Name, Dosage Form, and Strength:	Zynyz (retifanlimab-xxxx)[a] Injection, 500 mg/20 mL (25 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Incyte Corporation
FDA Received Date:	August 8, 2022
TTT ID #:	2022-771
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

[a] Since the nonproprietary name for suffix for retifanlimab-xxxx has not yet been determined, "retifanlimab-xxxx" is used throughout this review as the nonproprietary name for this product.

1 REASON FOR REVIEW

As part of the approval process for Zynyz (retifanlimab-xxxx) Injection, the Division of Oncology 3 (DO3) requested that we review the proposed Zynyz prescribing information (PI), container labels, and carton labeling and medication guide (MG) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the Zynyz PI, container label, carton labeling, and MG to identify areas of vulnerability that may lead to medication errors and other areas of improvement.

Our review of Section 2 of the PI identified confusing preparation instructions where users are instructed to prepare a fixed 500 mg dose of Zynyz within a wide final concentration range (1.4 mg/mL to 10 mg/mL) (b) (4) whether Zynyz is diluted in either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. From labeling meeting discussions regarding strategies to simplify the preparation instructions and subsequent email communications between DMEPA and OPQ, we propose revised preparation instructions that yield a solution (b) (4) regardless of whether 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP is used for dilution.

Further, our review of the container label and the carton labeling identified a storage statement that was inconsistent with the information in the PI. Our review of the MG found it acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Zynyz PI, container label, and carton labeling can be improved to promote the safe and effective use of the product. We provide recommendations for DO3 in Section 4.1 and a recommendations for Incyte Corporation in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 3 (DO3)

A. Prescribing Information

1. Dosage and Administration Section

a. Consider revising Section 2.3 Preparation and Administration for improved clarity and readability, and to mitigate the risk of medication errors as follows:

[redacted] (b) (4) particulate matter and discoloration prior to administration. ZYNYZ is a clear to slightly opalescent, colorless to pale yellow solution and is free of particles. Discard the vial if the solution is cloudy, discolored, or contains particulate matter.

Do not shake the vial.

Preparation

1. Withdraw 20 mL (500 mg) of ZYNYZ from one vial and discard vial with any unused portion.
2. Dilute ZYNYZ [redacted] (b) (4) either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Use polyvinylchloride (PVC) and di-2-ethylhexyl phthalate (DEHP), polyolefin copolymer, polyolefin with polyamide, or ethylene vinyl acetate infusion bags.
3. Mix diluted solution by gentle inversion. Do not shake.
4. Visually inspect for particulate matter and discoloration prior to administration. Discard if [redacted] (b) (4).

Storage of diluted ZYNYZ solution

Protect from light.

Store diluted ZYNYZ solution:

- At room temperature up to 25°C (77°F) for no more than 8 hours from the time of preparation to the end of the infusion.

OR

- Refrigerated at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of preparation to the end of the infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration. The diluted solution must be administered within 4 hours (including infusion time) once it is removed from the refrigerator.

Do not freeze or shake diluted solution.

Administration

- Administer diluted ZYNYZ solution by intravenous infusion over 30 minutes through a polyethylene, (b) (4) or PVC with DEHP intravenous line containing a sterile, non-pyrogenic, low-protein binding polyethersulfone, polyvinylidene fluoride, or cellulose acetate 0.2 micron to 5 micron in-line or add-on filter or 15-micron mesh add-on filter. (b) (4) as an intravenous push or bolus injection.
- Do not co-administer other drugs through the same infusion line.

2. How Supplied/Storage and Handling Section

    a. For improved clarity and brevity, revise the storage statement to read "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake."

4.2 RECOMMENDATIONS FOR INCYTE CORPORATION

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. Revise the storage statement to align with the prescribing information to read: "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zynyz received on August 8, 2022 from Incyte Corporation.

Table 2. Relevant Product Information for Zynyz	
Initial Approval Date	N/A
Nonproprietary Name	retifanlimab-xxxx
Indication	For the treatment of adult (b) (4) patients (b) (4) with metastatic or recurrent locally advanced Merkel cell carcinoma.
Route of Administration	Intravenous Infusion
Dosage Form	Injection
Strength	500 mg/20 mL (25 mg/mL)
Dose and Frequency	500 mg as an intravenous infusion over 30 minutes every 4 weeks
How Supplied	Carton containing 1 single-dose vial
Storage	Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Protect from light. Do not freeze or shake
Container Closure	Type (b) (4) glass vial, closed with a (b) (4) rubber stopper and secured with an aluminum flip-off cap as overseal.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 28, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Zynyz. Our search identified 2 previous reviews[b,c], and we considered our previous recommendations to see if they are applicable for this current review.

[b] Stewart J. Label and Labeling Review for Zynyz (BLA 761209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 23. RCM No.: 2020-2488-1.

[c] Stewart J. Label and Labeling Review for Zynyz (BLA 761209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 25. RCM No.: 2020-2488.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Zynyz labels and labeling submitted by Incyte Corporation.

- Container label received on August 8, 2022
- Carton labeling received on August 8, 2022
- Prescribing Information (Image not shown) received on August 8, 2022, available from \\CDSESUB1\EVSPROD\bla761334\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text.docx
- Medication Guide received on August 8, 2022, available from \\CDSESUB1\EVSPROD\bla761334\0001\m1\us\114-labeling\draft\labeling\draft-med-guide-text.docx

G.2 Label and Labeling Images

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Clinical Inspection Summary

Date	12/20/2022
From	Michele Fedowitz, MD, Primary Reviewer and Acting Team Leader Jenn Sellars, MD, PhD, Acting Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Vaibhav Kumar, MD, Clinical Reviewer Leslie Doros MD, Clinical Team Leader Autumn Zack-Taylor, Regulatory Project Manager Division of Oncology 3 (DO3)
BLA #	761334
Applicant	Incyte Corporation.
Drug	retifanlimab-dlwr
NME (Yes/No)	Yes
Therapeutic Classification	Programmed death receptor-1 (PD-1)–blocking antibody
Proposed Indication	Adult (b) (4) patients (b) (4) with metastatic or recurrent locally advanced Merkel cell carcinoma
Consultation Request Date	08/31/2022
Summary Goal Date	12/30/2022
Action Goal Date	02/07/2023
PDUFA Date	02/07/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Incyte Corporation, submitted clinical data from Study INCMGA 0012-201 (NCT03599713) and INCMGA 0012-101 (NCT03059823) to the Agency in support of a Biologics License Application (BLA 761334) for retifanlimab for the treatment of adult (b) (4) patients (b) (4) with metastatic or recurrent locally advanced Merkel cell carcinoma.

Three clinical investigators (CIs), Drs. Burgess (Site 1), De Braud (Site 506), and Guida (Site 502) were inspected for Study INCMGA 0012-201 given they were high enrolling sites with high treatment effect. One clinical investigator, Dr. Girda (Site US005), was inspected for Study INCMGA 0012-101.

Although there were some regulatory violations related to unreported adverse events (AEs) at Dr. Girda's site, these events were not serious and did not lead to study discontinuation. They were determined by the CI not to be related to the study drug and some have been included in the labeling proposed by the sponsor. There were also regulatory violations at Dr. Burgess's site related to late reporting of serious adverse events (SAEs), missed reconsenting of subjects of new versions of the informed consent form, and unreported adverse events. All SAEs were reported, and all subjects signed the initial informed consent and eventually were reconsented on updated versions of the informed consent form. The unreported adverse events were not serious and did not lead to study discontinuation and there were no other unreported adverse events upon review of the subject charts at the site.

Despite these regulatory violations, the conducted onsite inspections did not find significant concerns regarding the management of the clinical trial, GCP compliance, or the data generated for Study INCMGA 0012-201 and Study INCMGA 0012-101.

II. BACKGROUND

Incyte Corporation seeks approval for an indication for retifanlimab. In support of the BLA, the Applicant submitted clinical data from two studies:

Study INCMGA 0012-201 is an open-label, single-arm, multiregional, Phase 2 study of retifanlimab in participants with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC) who had not received prior systemic therapy for their advanced disease also known as the PODIUM-201 Study).

The primary objective is to determine the efficacy of retifanlimab in terms of the objective response rate (ORR) in chemotherapy-naïve participants with advanced/metastatic MCC. The primary endpoint was objective response rate (ORR), defined as the percentage of participants having an objective response (complete response [CR] or partial response [PR]), as assessed by independent central review (ICR) according to RECIST version 1.1. Key secondary efficacy endpoints include duration of response (DOR), determined by RECIST according to IRC, and overall survival (OS).

Subjects were to receive retifanlimab 500 mg intravenously once every 4 weeks. Treatment was to continue in 28-day cycles for up to 2 years or until disease progression, toxicity, death, or withdrawal. Imaging assessments were to be performed at baseline and every 8 weeks for the first 12 months, then every 12 weeks thereafter; assessments were to occur based on the calendar and not be delayed for treatment interruption.

Participants who discontinue study treatment without experiencing disease progression were to continue to undergo tumor assessments according to the schedule of activities until they experience disease progression, the start of a new anticancer treatment, withdrawal of consent, lost to follow-up, the end of the study, or death.

The study was initiated on February 25, 2019, as of the data cutoff date of **January 21, 2022**, 107 subjects had received at least 1 dose of retifanlimab.

Study INCMGA 0012-101 is a Phase 1, open-label, dose escalation, and cohort expansion study in subjects with relapsed/refractory, unrespectable locally advanced or metastatic solid tumors.

The objective of the Dose Escalation Phase is to initially characterize the safety and tolerability of INCMGA00012, to characterize the dose limiting toxicities (DLTs), and to define the MTD. The Cohort Expansion Phase is designed to characterize the safety, tolerability, PK, PD, immunogenicity, and preliminary anti-tumor activity of INCMGA00012 administered IV every 2, 3, or 4 weeks

Safety Assessments

- AEs were to be collected from the time of first administration of study drug and SAEs were to be collected from the time the patient signs informed consent. Protocol-related AEs and SAEs will be collected from the time the patient has consented to study participation.

- Progression of the underlying neoplasm resulting in hospitalization or will be documented as an anti-tumor activity outcome and not as an SAE. If an SAE occurs in a patient and it is unclear whether the event is related to progressive disease (PD), the SAE should be reported.

III. RESULTS

1. **Dr. Eugenia Girda (Site US005)**
   195 Little Albany St,
   New Brunswick, NJ,
   08901-1914 USA

   Inspection Dates: October 11-18, 2022

   This investigator was inspected as an onsite surveillance inspection for Study INCMGA 0012-101. This was the first FDA inspection for this investigator.

   At the time of data cutoff, there were 38 subjects screened, 28 subjects enrolled and treated at the site.

   The source documents were reviewed for all 28 enrolled subjects for protocol compliance, eligibility, informed consent, and data accuracy. The reviewed records included informed consent forms and subject medical records including electronic medical records and RECIST reports. Study related documents were also reviewed protocol deviations, adverse event reports, case report forms, IRB approvals, sponsor communications regarding adverse event, Form FDA 1572s, site protocols, training records, delegation of responsibilities log, and investigational product (IP) accountability/disposition records.

Radiographic scans and related investigators assessments were performed as specified in the protocol and there were no discrepancies with the data listings. No unreported protocol deviations were identified.

There were 3 subjects who had the following unreported adverse events:

Subject ID	Adverse Event Description
Subject US005 (b) (6)	Nausea, anorexia, arthralgia bilateral – hands, urinary frequency
Subject US005	taste change. black stools
Subject US005	Constipation, vaginal itching, urinary incontinence, fall, whooshing sensation, bilateral ears

Dr. Girda responded on October 31, 2022, and noted that these adverse events were captured at the subject's visit, but not transcribed into the case report form (CRF).

Reviewer's Comments: Although Dr. Girda stated that none of the AEs were related to the study drug, nausea and arthralgias are listed in the proposed product labeling as adverse events. These events were not serious and did not lead to study discontinuation. There were no other unreported adverse events upon review of the subject charts at the site. These events were recorded into the CRF during the inspection and recorded as protocol deviations. Her corrective action and preventive action (CAPA) was acceptable.

2. Dr. Filippo de Braud (Site 506)
IRCCS Instituto Nazionale de Tumori
Via Venezian 1
20133 Milan, Italy

Inspection Dates: November 14-18, 2022

This investigator was inspected as an onsite surveillance inspection for Study INCMGA 0012-201. This was the first FDA inspection for this investigator.

At the time of data cutoff, there were 6 subjects screened, 6 subjects enrolled and treated at the site. Two subjects discontinued due to disease progression and dies (Subjects 506(b) (6) and 506(b) (6)), two subjects (Subjects 506(b) (6) and 506(b) (6)) were discontinued due to disease progression, but were still alive and on survival follow up, and two subjects (Subjects 506(b) (6) and 506(b) (6)) completed 2 years of treatment and were alive and on study follow up.

The complete source documents were reviewed for all 6 enrolled subjects were reviewed for protocol compliance, eligibility, informed consent, data accuracy, and GCP compliance; the reviewed records included informed consent forms, subject case history records, and investigational product accountability. Study related documents were also reviewed protocol deviations, adverse event reports, case report forms, Ethics Committee approvals, sponsor

communications, Form FDA 1572s, financial disclosures, site protocols, training records, delegation of responsibilities log, and investigational product (IP) accountability/disposition records, study staff qualifications and curriculum vitae.

Radiographic scans were performed as specified in the protocol and all local imaging studies were sent to the central radiology facility and had a central interpretation in the listings. No unreported adverse events were identified. No unreported protocol deviations were identified.

3. Dr. Michele Guida (Site 502)
IRCCS Instituto Tumori Giovanni Paolo II
Viale Orazio Flacco 65
70124 Bari, Italy

Inspection Dates: November 7-11, 2022

This investigator was inspected as an onsite surveillance inspection for Study INCMGA 0012-201. This was the first FDA inspection for this investigator.

At the time of data cutoff, there were 6 subjects screened, 6 subjects enrolled and treated at the site. Three of six subjects completed the planned two years of study treatment and continue to be followed for survival. The other three subjects were discontinued from the study treatment early but continue to be followed for survival.

The complete source documents were reviewed for all 6 enrolled subjects were reviewed for protocol compliance, eligibility, informed consent, data accuracy, and GCP compliance; the reviewed records included informed consent forms, subject medical records such as: medical history records, ECG tracings, laboratory reports, CT scan reports, RECIST forms, biopsy reports and clinic visit notes, and investigational product accountability records. Study related documents were also reviewed protocol deviations, adverse event reports, case report forms, Ethics Committee approvals, sponsor communications, Form FDA 1572s, financial disclosures, site protocols, training records, monitoring records, delegation of responsibilities log, and investigational product (IP) accountability/disposition records, study staff qualifications and curriculum vitae.

Radiographic scans were performed as specified in the protocol and all local imaging studies were sent to the central radiology facility and had a central interpretation in the listings. No unreported protocol deviations were identified.

There were three unreported adverse events for Subject 502(b) (6) from (b) (6): lumbosciatalgia Grade 2, hyperuricemia Grade 1, and impotence Grade 1; all were determined by the CI to be unrelated to the study drug. They were noted during an (b) (6) monitoring visit, after the data cut-off. These events were entered into the case report form in (b) (6). No other unreported adverse events were identified.

Reviewer Comment: These adverse events were likely not related to the study drug and all low

grade. They were correctly identified and reported at an (b) (6) *monitoring visit. Since they were identified after the data cutoff date, they were not in the data listings. There were no additional unreported adverse events, suggesting adequate management of adverse event reporting at the site.*

4. Dr. Melissa Burgess (Site 1)
5150 Centre Ave, Pittsburgh, PA,
15232-1309, US

Inspection Dates: November9-16, 2022

This investigator was inspected as an onsite surveillance inspection for Study INCMGA 0012-201. This was the first FDA inspection for this investigator.

At the time of data cutoff, there were 6 subjects screened and 5 subjects enrolled and treated at the site. Three subjects (Subjects 001(b) (6), 001(b) (6), and 001(b) (6)) were alive and remained on long term survival follow up at the time of the inspection. One subject (Subject 001(b) (6)) withdrew consent on (b) (6) and one subject (Subject 001(b) (6)) expired on (b) (6).

The complete source documents were reviewed for all 6 enrolled subjects were reviewed for protocol compliance, eligibility, informed consent, data accuracy, and GCP compliance. The reviewed records included subject informed consent documents and subject source records such as study visit progress notes, medical history, physician office visit narratives, ECGs, CT/MRI narrative reports, laboratory reports, and correspondence records. Study related documents were also reviewed protocol deviations, adverse event reports, case report forms, IRB approvals, sponsor communications, Form FDA 1572s, financial disclosures, site protocols, training records, delegation of responsibilities log, and investigational product (IP) accountability/disposition records, and study staff qualifications.

Radiographic scans were performed as specified in the protocol and all local imaging studies were sent to the central radiology facility and had a central interpretation in the listings. No unreported protocol deviations were identified.

Source documents showed that 3 subjects had an unreported adverse event: Subject 001(b) (6) had an adverse event of sciatica nerve pain on (b) (6), Subject 001(b) (6) had an adverse event of diarrhea on (b) (6), and Subject 001(b) (6) had an adverse event of constipation and poor appetite on (b) (6).

Reviewer's Comment: Diarrhea (b) (4) *listed in the proposed product labeling as adverse events. These events were not serious and did not lead to study discontinuation. There were no other unreported adverse events upon review of the subject charts.*

Three SAEs, involving two subjects, were not reported to the sponsor within 24 hours of the investigator being aware of the events.

Subject ID	SAE Description	Onset Date	Date of Awareness	Date Reported to Sponsor	Days Late
001 (b) (6)	Gastric Hemorrhage	(b) (6)			1
	Hypoglycemia				2
001 (b) (6)	Pneumonia				6

Reviewer's Comment: Per the protocol serious adverse events are required to be reported to the sponsor within 24 hours (9.4 Reporting of Serious Adverse Events). It does not appear that there were any subject safety violations as the SAEs were eventually reported. Dr. Burgess did not receive a regulatory violation during the inspection and declined to offer comments.

Three subjects were not consented to the updated versions of the informed consent in a timely manner.

- Subject 001 (b) (6) signed the initial consent on (b) (6), informed consent version 2. Informed consent version 4 was approved by the IRB on (b) (6), but was not signed by the subject. The subject was reconsented with later versions and the last signed consent is version 11, approved by the IRB on (b) (6), and signed 11 months later on (b) (6).

- Subject 001 (b) (6) signed the initial consent on (b) (6) informed consent version 5. Informed consent version 8 was not signed by the subject. The subject was reconsented with later versions and the last signed consent is version 11, approved by the IRB on (b) (6), and signed, on (b) (6).

- Subject 001 (b) (6) signed the initial consent on (b) (6), informed consent version 9. Informed consent version 11 was not signed by the subject. The subject was reconsented with later versions and the last signed consent is version 10 approved by the IRB on 1 (b) (6) signed on (b) (6).

Reviewer's Comment: Per the protocol, participants must provide consent to the most current version of the ICF(s) during their participation in the study (8.1.1 Informed Consent Process). Although each subject has a missed informed consent version, all of the subjects were consented initially before study participation and then eventually. It does not appear that there were interim changes in the consent that would reasonably impact a subject's willingness to participate in the study. Dr Burgess did not receive a regulatory violation during the inspection and declined to offer comments.

{See appended electronic signature page}

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/s/

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