CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761289Orig1s000

OTHER REVIEW(S)

Clinical Inspection Summary Addendum

Date	9/13/2022
From	Michele Fedowitz, MD, Primary Reviewer Karen Bleich, MD, Team Leader Jenn Sellers, MD, PhD, Acting Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Timil Patel MD, Clinical Reviewer Jamie Brewer MD, Clinical Team Leader Christina Leach, Regulatory Project Manager Division of Oncology 3 (DO3)
BLA #	761289
Applicant	AstraZeneca Pharmaceuticals
Drug	Tremelimumab
NME (Yes/No)	Yes
Therapeutic Classification	Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking antibody
Proposed Indication	Indicated in combination with durvalumab, for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC)
Consultation Request Date	04/07/2022
Summary Goal Date	08/11/2022
Summary Uploaded Into DARRTS	08/02/2022
Action Goal Date	10/23/2022
PDUFA Date	10/21/2022

Three clinical investigators, Drs. Chan (Site 3201), De Toni (Site 2604) and Kang (Site 6001) were selected for clinical inspections of Study 419CC00002 (HIMALAYA). The results were reported in the Clinical Inspection Summary uploaded into DARRTS on 08/02/2022. This is an addendum to that report providing OSI input on data anomalies found by the Sponsor at site 6208 in Russia (Principal Investigator: Dr. Oleg Lipatov).

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

There were discrepancies in survival data from site 6208, Dr. Oleg Lipatov, in Russia. Namely, there were incorrect dates of death for 4 out of 14 subjects enrolled in Study 419CC00002 (HIMALAYA). According to the information provided by the Sponsor, these errors appear to be isolated to the creation of erroneous source documents by a single sub-investigator. The data discrepancies would not have been picked up on routine monitoring and

do not appear to be related to a broader study conduct issue such as inadequate monitoring. We recommend the review division consider using dates of death on the death certificates for these 4 subjects in the overall survival analysis.

II. BACKGROUND

On August 23, 2022, the Applicant, AstraZeneca notified the review division of date of death discrepancies for four subjects at Site 6208 (Dr. Lipatov, Bashkortostan, Russia). AstraZeneca conducted an additional onsite monitoring visit on August 24-26, 2022, to evaluate the discrepancies and provided follow up of this onsite visit/investigation to the review division on September 8, 2022. The Sponsor communications were reviewed, and the pertinent findings presented here.

III. RESULTS

During a routine monitoring visit on June 16, 2022, the death data for Subject (b) (6) was found to be inaccurate. At the data cutoff date, August 27, 2021, the subject was reported alive, and the case report form and source data were consistent; however, they did not match the local oncology registry in the country. The site obtained the patient's death certificate which documents a date of death of (b) (6), matching the local oncology registry date. Three additional subjects (b) (6) were found at the time to have inaccurate dates of death, compared to the local oncology registry.

On a site visit August 24-26, 2022, the Sponsor reviewed medical records/source documents for the 14 subjects randomized at Site 6208, including review of documentation supporting informed consent collection, randomization, dosing, treatment discontinuation and safety data. They also reviewed available data from the local oncology registry for these 14 subjects, as well as death certificates for the 13 deceased subjects. The audit confirmed that four subjects had incorrect dates of death compared to the local oncology registry and death certificates (Table 1). There were no additional errors with date of death and no other documentation errors.

Table 1: Survival Data for Site 6208 for Subjects with Date of Death Discrepancies

Subject Number	Randomization Date	Treatment Arm	Survival Status/Date of Death					Sub-investigator
			Case Report Form	Source Document/ Medical Record	Local Oncology Registry	Death Certificate	Variance	
(b) (6)		S	(b) (6)	N/A*		(b) (6)	1	Felix Zainullin
		S	Alive on (b) (6)	Alive on (b) (6)			22	Stanislav Potapov
		T300+D	(b) (6)	(b) (6)			11	Stanislav Potapov
		D	(b) (6)	(b) (6)			275	Stanislav Potapov
Table source: Excerpted from AstraZeneca's September 8, 2022, communication								

* Medical record not available during onsite review, as it is being held by the prosecutor's office due to pending litigation initiated by the patient's wife. S=sorafenib, D=durvalumab monotherapy, T75+D=tremelimumab 75 mg plus durvalumab, T300+D=tremelimumab 300 mg plus durvalumab, N/A=Not Applicable

In each case, the source documents consisted of a note signed by the sub-investigator documenting a phone call with the subject or the subject's family. For Subject (b) (6) the discrepancy of 1 day is attributed to human error. The patient died during the night, and patient's relative inadvertently provided the incorrect day during phone contact with the site. Three of the four subjects with inaccurate data were associated with a single sub-investigator, Stanislav Potapov, who is no longer at the site and could not be reached. The Principal Investigator acknowledged he provided inadequate oversight for the Sub-Investigator Potapov, who had limited experience with clinical trials. The local oncology registry went into effect while the trial was underway, and he first became aware of the discrepancies on June 16, 2022.

Reviewer's comments:
According to the information provided by the Sponsor, it appears the data discrepancies resulted from errors in source documentation by sub-investigators at the site, the most notable errors from a single sub-investigator. It is not known why the sub-investigator generated the source records with erroneous information as he no longer works at the site. The errors appear to be isolated to the date of death for 4 subjects and are distributed throughout the treatment arms and do not appear to show a pattern "in favor" of the study drug.

There was no protocol requirement for acquiring death certificates. According to the study protocol: "Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician." The eCRF instructions require one of 3 sources for the date of death: a hospital record, death certificate, or other acceptable death documentation. A note from a physician documenting contact and date of death in the hospital record would qualify under this protocol. These errors, therefore, were due to the creation of erroneous source documents by the sub-investigator. The data discrepancies would not have been picked up on routine monitoring and do not appear to be

related to a broader study conduct issue such as inadequate monitoring.

{See appended electronic signature page}

Michele Fedowitz, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Karen Bleich, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Review Division /Division Director/'Lola Fashoyin-Aje
Review Division /Project Manager/ Christina Leach
Review Division/Cross Discipline Team Lead/Jamie Brewer
Review Division/Clinical Reviewer/Timil Patel
OSI/Office Director/Dave Burrow
OSI/Deputy Office Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB Acting Branch Chief/Jenn Sellers
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague

APPEARS THIS WAY ON ORIGINAL

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/s/

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KAREN B BLEICH
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JENN W SELLERS
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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:	August 23, 2022
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761289
Product Name and Strength:	Imjudo (tremelimumab-actl) Injection, 25 mg/1.25 mL (20 mg/mL) and 300 mg/15 mL (20 mg/mL)
Applicant/Sponsor Name:	AstraZeneca UK Ltd (AstraZeneca)
OSE RCM #:	2022-420-1
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on August 16, 2022 for Imjudo. The Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Imjudo (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.[a]

2 CONCLUSION

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

[a] Thomas Sarah. Label and Labeling Review for Imjudo (BLA 761289). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 MAY 20. RCM No.: 2022-420.

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/s/

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ASHLEIGH V LOWERY
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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:	August 4, 2022
To:	Christina Leach, PharmD Regulatory Project Manager **Division of Oncology III (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TRADENAME (tremelimumab-xxxx)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761289
Applicant:	AstraZeneca Pharmaceuticals, LP

1 INTRODUCTION

On February 23, 2022, AstraZeneca Pharmaceuticals, LP submitted for the Agency's review an original Biologics License Application (BLA) 761289 for TRADENAME (tremelimumab-xxxx) injection with proposed indication, in combination with durvalumab, for the treatment of adults with unresectable hepatocellular carcinoma (uHCC).

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 III (DO3) on March 10, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADENAME (tremelimumab-xxxx) injection.

2 MATERIAL REVIEWED

- Draft TRADENAME (tremelimumab-xxxx) injection MG received on February 23, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 25, 2022.
- Draft TRADENAME (tremelimumab-xxxx) injection Prescribing Information (PI) received on February 23, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 25, 2022.
- Approved OPDIVO (nivolumab) injection comparator labeling dated March 4, 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)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

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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/s/

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LASHAWN M GRIFFITHS
08/04/2022 10:58:43 AM

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

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

Memorandum

Date: August 03, 2022

To: Christina Leach, PharmD, Regulatory Project Manager,
Division of Oncology 3 (DO3)

Doris Auth, PharmD, Associate Director for Labeling, DO3

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for IMJUDO (tremelimumab-xxxx) injection, for intravenous use

BLA: 761289

In response to DO3's consult request dated March 10, 2022, OPDP has reviewed the proposed product labeling (PI), Medication Guide (MG), and carton and container labeling for the original NDA submission for IMJUDO (tremelimumab-xxxx) injection, for intravenous use (Imjudo).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO3 (Christina Leach) on July 25, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 23, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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REBECCA A FALTER
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Clinical Inspection Summary

Date	8/02/2022
From	Michele Fedowitz, MD Karen Bleich, MD Jenn Sellers, MD, PhD (Acting) Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Timil Patel, Clinical Reviewer Jamie Brewer MD, Clinical Team Leader Christina Leach, Regulatory Project Manager Division of Oncology 3 (DO3)
BLA #	761289
Applicant	AstraZeneca Pharmaceuticals LP
Drug	Tremelimumab
NME (Yes/No)	Yes
Therapeutic Classification	Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking antibody
Proposed Indication	Indicated in combination with durvalumab, for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC)
Consultation Request Date	04/07/2022
Summary Goal Date	08/11/2022
Action Goal Date	10/23/2022
PDUFA Date	10/21/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, AstraZeneca., submitted clinical data from Study D419CC00002 (NCT03298451) to the Agency in support of a Biologics License Application (BLA 761289) for tremelimumab. The proposed indication is for use of tremelimumab in combination with durvalumab for the first-line treatment of adult patients with unresectable hepatocellular carcinoma (HCC).

Three clinical investigators, Drs. Chan (Site 3201), De Toni (Site 2604) and Kang (Site 6001) were selected for clinical inspections. Dr. Chan's site was unable to be inspected onsite due to inability to travel within the region due to the Covid-19 pandemic and country-specific restrictions; therefore, a remote regulatory assessment was performed.

The conducted onsite inspections of Drs. De Toni and Kang and the remote regulatory assessment of Dr. Chan's site did not find significant concerns regarding the management of the clinical trial, GCP compliance, or the data generated.

II. BACKGROUND

Astra Zeneca seeks approval for a new molecular entity, tremelimumab, in combination with durvalumab for the above indication. In support of the BLA, the Applicant submitted clinical data from Study D419CC00002, also known as the HIMALAYA study, a randomized, open-label, multi-center, phase 3 study that evaluates the efficacy and safety of tremelimumab in combination with durvalumab and of durvalumab monotherapy vs. sorafenib for patients with unresectable HCC who are not eligible for locoregional therapy and have not received prior therapy.

The study included 3 periods: screening, treatment, and follow-up. Subjects were to undergo a screening evaluation to determine their eligibility 28 days prior to randomization. Eligible subjects were to be stratified by microvascular invasion (MVI: yes vs. no), etiology of liver disease (confirmed hepatitis B virus vs. hepatitis C virus vs. other), and Eastern Cooperative Oncology Group performance status (0 vs. 1).

Subjects were to be randomized 1:1:1:1 to receive either:

- Durvalumab 1500 mg every 4 weeks (D)
- Tremelimumab 300 mg as a single priming dose + durvalumab 1500 mg; followed by durvalumab 1500 mg every 4 weeks (T300 + D)
- Sorafenib 400 mg twice daily (S)
- Tremelimumab 75 mg + durvalumab 1500 mg followed by durvalumab 1500 mg every 4 weeks (T75 + D)*

** Following a benefit-risk assessment based on the results of a pre-planned analysis, recruitment in the T75+D treatment arm was closed due to non-meaningful differentiation in terms of efficacy from D.*

The primary objective was to compare the efficacy of T300 + D versus Sorafenib S 400 mg twice daily (BID) using the endpoint of overall survival (OS) as the primary endpoint.

The key secondary endpoints were OS at 18 months (OS18), OS24, OS36 progression-free survival (PFS), time to progression (TTP), objective response rate (ORR), disease control rate (DCR), and duration of response (DOR) according to RECIST v1.1 using investigator assessment.

Radiological tumor assessments were to be performed at randomization then every 8 weeks (± 1 week) for the first 48 weeks after randomization, and then every 12 weeks (± 1 week) until confirmed PD. The imaging schedule was to be followed regardless of any delays in dosing. Subjects were to receive their assigned randomized treatment regimen until confirmed progressive disease (PD) by RECIST 1.1, unacceptable toxicity, or any discontinuation criteria were met. After the initial RECIST 1.1-defined PD, a follow-up scan was to be collected preferably at the next visit, but no earlier than 4 weeks after the prior assessment of PD. Subjects who permanently discontinued study treatment for reasons other than confirmed PD were to continue to have radiological scans performed per the schedule until confirmed PD. After completion of the treatment period, subjects were to enter the follow-up period. All subjects were to follow-up for survival until the end of the study, unless they withdrew consent to survival follow-up.

Subjects were enrolled at 181 sites and randomized at 170 study centers in 16 countries: Brazil (13 centers), Canada (9), France (14), Germany (10), Hong Kong (5), India (10), Italy (8), Japan (27), South Korea (8), Russian Federation (10), Spain (6), Taiwan (9), Thailand (9), Ukraine (8), United States of America (USA; 21) and Vietnam (3). **The data cutoff for the current submission is August 27, 2021.**

III. RESULTS

1. **Dr. Yoon-Koo Kang (Site 6001)**
   Asan Medical Center,
   88 Olympic-ro 43-gil,
   Songpa-gu, Seoul, NA 05505 South Korea

   Inspection Dates: May 16 - 23, 2022

   This investigator was inspected as an onsite surveillance inspection for Study D419CC00002. This was the first FDA inspection for this investigator.

   At the time of data cutoff, there were 81 subjects screened, 57 subjects enrolled and 39 were randomized and treated at the site.

   The source documents were reviewed for all enrolled subjects for informed consent and eligibility, and 9 of 39 subjects for randomization, concomitant medications, adverse events, serious adverse events, survival, and tumor progression. Reviewed records included the individual subject study binders and the hospital's EMR system. Study related documents were also reviewed including financial disclosures, investigator agreement form, delegation of responsibilities log, screening and enrollment log, training records, monitoring records, Ethics Committee approvals, informed consent, site protocol with amendments, protocol deviations, and investigational product (IP) records (storage, accountability, dispensation, and destruction).

   The source records for survival follow-up and subject disposition used to generate the primary endpoint of OS, and key secondary endpoints related to OS at different timepoints were reviewed and compared with the data listings. There were no discrepancies.

   The tumor assessment data for the secondary endpoints related to imaging (ORR, PFS, TTP, DCR, and DOR) were reviewed and compared to the data listings in the background material, and there were no discrepancies. All protocol required scans were taken at the study site in adherence to the protocol. The RECIST assessments were made by the CI or subinvestigator as specified in the protocol.

   No unreported protocol deviations were identified. No unreported adverse events were identified.

2. Dr. Enrico De Toni (Site 2604)
Ludwig-Maximilians-Universitat
Munchen, Marchioninistr. 15
Munchen, NA 81377 Germany

Inspection dates: July 4 - 8, 2022.

This investigator was inspected as an onsite surveillance inspection for Study D419CC00002. This was the first FDA inspection for this investigator.

At the time of data cutoff, there were 37 subjects screened, 30 subjects enrolled and treated at the site. The source documents were reviewed for all 37 screened subjects for informed consent. The complete source documents were reviewed for 16 of 30 subjects (10 in the T300 arm and 6 in the S arm) for eligibility, treatment allocation, drop-outs/discontinuations, adverse events, protocol violations, overall survival, concomitant medications, and laboratory tests. Reviewed records included the individual subject study binders, paper-based medical records, and electronic radiology and laboratory records. Study related documents were also reviewed including financial disclosures, statement of investigator, delegation of responsibilities log, screening and enrollment log, training records, communications between Sponsor and monitor, monitoring records, Ethics Committee approvals, German regulatory authority approvals, informed consent, site protocol with amendments, protocol deviations, and investigational product (IP) accountability records.

The survival documentation for the primary endpoint of OS was compared to the data listings and there were no discrepancies. The tumor assessment data for the secondary endpoints related to imaging were reviewed and compared to the data listings in the background material, and there were no discrepancies. All protocol required scans were taken at the study site in adherence to the protocol.

No unreported protocol deviations were identified. No unreported adverse events were identified.

3. Dr. Stephen Lam Chan (Site 3201)
Prince of Wales Hospital – Department of Clinical Oncology
30-32 Ngan Shing St.
Shatin Hong Kong, New Territories, China

Remote Regulatory Assessment Dates: June 29 – July 11, 2022

A remote regulatory assessment was conducted due to travel restrictions during the Covid-19 pandemic. Video conferencing via Zoom and document sharing via an online platform (Box.com) were utilized for the assessment of Study D419CC00002. There was no inspectional history for this clinical investigator.

There were 48 subjects screened and 33 subjects enrolled at the site. At the time of data cut-

off, six subjects completed the trial (b) (6) There were no significant discrepancies between the source documents and the data line listings for subject enrollment and disposition.

The remote regulatory assessment reviewed redacted records for all 12 subjects in the T300 + D arm, all eleven subjects in the S arm and 3 of 10 subjects in the D arm. It included a review of screening and enrollment logs, eligibility, randomization/stratification, disposition data, CT scan reports, adverse events, and protocol adherence; as well as the study records including informed consent, financial disclosures, delegation of authority logs, IEC approvals and communications.

The survival documentation for the primary endpoint of OS was compared to the data listings and there were no discrepancies. The imaging source data (measurements and interpretations from the clinical investigator) were compared to the data listings and found no discrepancies in the T300 + D arm or the S arm.

There was a single subject with a protocol discrepancy in the D arm: Subject (b) (6) was evaluated with a CT dated (b) (6) and found to have progressive disease due to a new lesion. As per the protocol, the subject was continued on treatment and had a follow up CT on (b) (6) which confirmed PD. The date of progression was entered as (b) (6) instead of the correct date (b) (6) which is the time of progression.

No significant unreported adverse events were identified; no unreported SAEs were identified.

Reviewer's comment: *The misreporting of the date of PD would not impact the OS.*

{See appended electronic signature page}

Michele Fedowitz, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Karen Bleich, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., PhD.
(Acting) Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Review Division /Associate Division Director/ 'Lola Fashoyin-Aje, MD
Review Division /Project Manager/ Christina Leach
Review Division/Cross Discipline Team Lead/ Jamie Brewer MD
Review Division/Clinical Reviewer/ Timil Patel MD
OSI/Office Director/ Dave Burrow
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/GCPAB/Jenn Sellers

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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:	May 20, 2022
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761289
Product Name, Dosage Form, and Strength:	Imjudo (tremelimumab-xxxx)[a] injection, 25 mg/1.25 mL (20 mg/mL) and 300 mg/15 mL (20 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AstraZeneca UK Ltd (AstraZeneca)
FDA Received Date:	February 23, 2022
OSE RCM #:	2022-420
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

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

1 REASON FOR REVIEW

As part of the approval process for Imjudo (tremelimumab-xxxx) injection, the Division of Oncology 3 (DO3) requested that we review the proposed Imjudo prescribing information (PI), Medication Guide (MG), container labels, and carton labeling 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 – N/A
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

Upon review of the proposed container labels, carton labeling, PI and MG, we note areas of the labels and labeling that could be improved to promote the safe use of this product and so provide related recommendations in Section 4 below.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container labels, carton labeling, PI, and MG may be improved to promote the safe use of the product as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 3 (DO3)

A. General Recommendations

1. We recommend replacing the TRADENAME placeholder with the conditionally acceptable proprietary name, Imjudo, on the container labels, carton labeling, PI, and MG. In addition, ensure the nonproprietary name is provided as "tremelimumab-xxxx" across the labels and labeling.

B. Prescribing Information

1. Dosage and Administration Section, Highlights and Full PI

   a. We recommend revising the route of administration statements to specify that the proposed product should be diluted prior to intravenous infusion, as follows:

      Highlights: "Administer TRADENAME as an intravenous infusion over 60 minutes after dilution."

      Full PI: "TRADENAME is administered as an intravenous infusion over 60 minutes after dilution."

   b. It is not clear in the dosing instructions provided for patients weighing less than 30 kg how many doses of tremelimumab-xxxx 4 mg/kg should be given in combination with durvalumab 20 mg/kg (e.g., single dose given on Day 1 of Cycle 1 similar to patients weighing 30 kg or more?). Clarify if 4 mg/kg tremelimumab-xxxx should also be administered as a single dose in combination with durvalumab on Day 1 of Cycle 1, and if so, specify this in the dosing instructions.

   c. We recommend specifying the durvalumab dosing regimen in the instructions ",…followed by durvalumab as a single agent every 4 weeks".

   d. In order to improve legibility of the proposed larger numerical dose and prevent the reader from misinterpreting numbers in the thousands ("1000") as hundreds ("100") or ten-thousands ("10000"), consider stating the 1500 mg durvalumab dose with a comma, as follows: 1,500 mg.[b]

2. Dosage and Administration Section, Highlights

   a. We recommend adding the duration of therapy description from the Full PI, Section 2 (e.g., "as long as clinical benefit is observed or until unacceptable toxicity"), to the durvalumab dosing regimen after the instructions ",…followed by durvalumab as a single agent every 4 weeks" for both dosing regimens.

   b. We recommend adding the following statement at the end of the Highlights, Dosage and Administration section to alert the end-user that there are additional preparation and administration instructions and dosage modifications for adverse reactions provided in the Dosage and Administration section of the full PI: "See full Prescribing Information for

[b] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2022 FEB 21]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

preparation and administration instructions and dosage modifications for adverse reactions."

3. Dosage and Administration Section, Full PI

    a. Under the "Storage of [redacted] (b) (4)" section, if data is available to support, we recommend revising the storage and stability information if the infusion solution is not administered immediately from [redacted] (b) (4) to "the total time from [redacted] (b) (4) to the completion of the infusion should not exceed:".

    b. We recommend revising the first three bullet instructions under the "Administration" section to reduce redundancy as well as to more clearly state that the tremelimumab-xxxx infusion should be given first followed by the durvalumab infusion given over 60 minutes. In addition, we recommend adding the timeframe after the end of the tremelimumab-xxxx infusion at which point durvalumab should be administered (see proposed edits below).

        - Administer TRADENAME infusion solution first intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron filter.
        - Next, administer durvalumab as a separate intravenous infusion over 60 minutes approximately <timeframe> after the end of the TRADENAME infusion. Separate infusion bags and filters for each infusion should be used.

4. How Supplied/Storage and Handling Section

    a. We recommend adding the mg/mL concentration (e.g., 20 mg/mL) after the 25 mg/1.25 mL and 300 mg/15 mL strengths[c] in section 16, in accordance with USP General Chapter <7> Labeling.

    b. We note the instruction to "Store in a refrigerator…in original carton to protect from light." provided in Section 16. Clarify whether the intravenous infusion bag containing the diluted tremelimumab-xxxx product needs to be protected from light as well during storage and administration. If so, we recommend providing instruction for this in Section 2.

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

4.2 RECOMMENDATIONS FOR ASTRAZENECA UK LTD (ASTRAZENECA)

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

A. General Comments (Container labels & Carton Labeling)

1. We note the format of the expiration date is not specified on the container labels or carton labeling. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a slash be used to separate the portions of the expiration date.[d]

2. Revise the font color of the proprietary name (b) (4) or revise the color scheme of the 25 mg/1.25 mL strength (b) (4)

B. Container Labels

1. We note the linear barcode is missing on the container labels. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Thus, we request you add the product's linear barcode to each container label as required per 21 CFR 201.25(c)(2), as well as consider the following:

[d] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf

[e] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

a. Ensure the barcode is surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(1)(i).

b. In accordance with 21 CFR 201.25(c)(1)(ii), ensure the barcode is placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).

c. Ensure the linear barcode is oriented in a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.[f]

2. We encourage AstraZeneca to add an NDC placeholder to the container labels per 21 CFR 201.2.

3. If space permits, we recommend revising the storage information on the container labels to align with that presented in Section 16 of the PI, as follows: "Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze or shake."

4. Combine the route of administration statement that reads (b) (4) (b) (4) to read "For Intravenous Infusion After Dilution." We recommend this to minimize the risk of administering the drug as an intravenous push.

5. We note the absence of a lot number and expiration date on the proposed 25 mg/1.25 mL vial container label. Add the lot number and expiration date in accordance with 21 CFR 610.60(a)(3) and 21 CFR 610.60(a)(4), respectively.

   a. Ensure the lot number and expiration date are clearly differentiated from one another.[g]

   b. Also, ensure that the lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.[h]

6. Revise the container labels so important product information critical for the use of the proposed drug product is prominently displayed on the Principal Display Panel (PDP). This may be achieved by relocating other information to a side

[f] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

[g] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

[h] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

panel. Example layout for the 25 mg/1.25 mL vial below demonstrates our recommendation only (not to size, spacing, color, etc.).

PDP	Side Panel
Rx Only NDC# XXXXX-XXX-XX Imjudo (tremelimumab-xxxx) Injection 25 mg/1.25 mL (20 mg/mL) For Intravenous Infusion After Dilution Single-dose vial. Discard unused portion.	Recommended dosage: See Prescribing Information No preservative. Storage Information Manufacturer/Distributor information Lot Exp

C. Carton Labeling

1. Consider decreasing the size of the graphics present on the PDP of the carton labeling, as they can potentially compete in size with the presentation of the proprietary name placeholder and distract the reader from other important information on the labeling.[i]
2. We recommend the following edits to the PDP in order to free up space on the PDP for important product information critical for the use of the product:
   a. Remove the (b) (4) information (b) (4)
   b. Remove the statement (b) (4)

[i] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

c. Relocate the statement “Do not use if vial seal is broken or missing,” to the side panel.

3. In order to ensure consistency with the PI, we recommend revising the usual dose statement on the side panel (b) (4) to the following: "Recommended Dosage: See prescribing information. Must be diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP before Intravenous Infusion.”. Consider bolding the statement “Must be diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP before Intravenous Infusion.” as shown to highlight its importance and to avoid errors associated with using a wrong solution for dilution.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Imjudo received on February 23, 2022 from AstraZeneca UK Ltd (AstraZeneca).

Table 2. Relevant Product Information for Imjudo	
Initial Approval Date	N/A
Nonproprietary Name	tremelimumab-xxxx
Indication	Imjudo is indicated in combination with durvalumab for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC).
Route of Administration	intravenous
Dosage Form	injection
Strength	25 mg/1.25 mL (20 mg/mL) and 300 mg/15 mL (20 mg/mL)
Dose and Frequency	• Administer Imjudo as an intravenous infusion over 60 minutes • uHCC: o Weight 30 kg and more: 300 mg as a single (b) (4) dose in combination with durvalumab 1,500 mg at Cycle 1/Day 1, followed by durvalumab as a single agent every 4 weeks. o Weight less than 30 kg: 4 mg/kg in combination with durvalumab 20 mg/kg followed by durvalumab as a single agent every 4 weeks o Continue treatment as long as clinical benefit is observed or until unacceptable toxicity. • See Section 2.2 and Table 2 for Dosage Modifications for Adverse Reactions
How Supplied	Imjudo (tremelimumab-xxxx) Injection is a clear to slightly opalescent, colorless to slightly yellow solution supplied in a carton containing one single-dose vial as follows: • 25 mg/1.25 mL (NDC 0310-4505-25) • 300 mg/15 mL (NDC XXX-XXXX-XX)
Storage	Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.
Container Closure	Glass vial with stopper and seal

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,[j] along with postmarket medication error data, we reviewed the following Imjudo labels and labeling submitted by AstraZeneca UK Ltd (AstraZeneca).

- Container labels received on February 23, 2022
- Carton labeling received on February 23, 2022
- Prescribing Information (PI) and Medication Guide (MG) (Image not shown) received on February 23, 2022, available from \\CDSESUB1\evsprod\bla761289\0001\m1\us\draft-labeling-text-nonannotated-treme-himalaya.docx

G.2 Label and Labeling Images

Container Labels

(b) (4)

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

3 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

SARAH E THOMAS
05/20/2022 01:38:46 PM

ASHLEIGH V LOWERY
05/20/2022 02:37:46 PM