CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761270Orig1s000

OTHER REVIEW(S)

Clinical Inspection Summary

Date	October 12, 2022
From	Lee Pai-Scherf, MD Karen Bleich, MD, Team Lead Jenn Sellers, MD, Ph.D., acting Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE/OSI
To	Erica Nakajima, MD Nicole Drezner, MD, Team Lead Harpreet Singh, MD, Division Director Division of Oncology 2/ Office of Oncologic Products
NDA/BLA #	BLA 761270
Applicant	AstraZeneca UK
Drug	Tremelimumab
NME (Yes/No)	Yes
Therapeutic Classification	Monoclonal Antibody
Proposed Indication(s)	In combination with durvalumab and platinum-based chemotherapy for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC)
Consultation Request Date	12/13/2021
Summary Goal Date	10/15/2022
Action Goal Date	11/15/2022
PDUFA Date	11/15/2022

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study D419MC00004 (POSEIDON) were submitted to the Agency in support of a Biological License Application (BLA) 761270 for tremelimumab for the above proposed indication. Two clinical investigators (CI), Dr. Chul Byoung Cho in Seoul, Korea and Dr. Melissa Johnson in Nashville, TN, were selected for clinical inspection.

Based on FDA's inspections of Drs. Cho and Johnson, the data generated by Drs. Cho and Johnson appear acceptable in support of the proposed indication in the BLA.

In addition, the European Medicines Agency (EMA) shared with the Office of Scientific Investigations (OSI) the inspection findings from routine inspections of the CI Schim Rittmeyer (site # E2605), the Contract Research Organization (CRO) (b) (4) and the Sponsor AstraZeneca. The OSI reviewed the inspection reports provided by the EMA and summarized the GCP findings in this Clinical Inspection Summary (CIS). (b) (4)

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2. BACKGROUND

AstraZeneca UK seeks approval for tremelimumab, for use in combination with durvalumab plus platinum-based chemotherapy for the first-line treatment of patients with metastatic NSCLC. Clinical data from Study D419MC00004 (POSEIDON) was submitted to support the BLA.

Study POSEIDON is a randomized, open-label, 3-arm, controlled trial in patients with previously untreated metastatic NSCLC with no sensitizing EGFR or ALK genomic tumor aberrations. Eligible patients had WHO Performance Status of 0 or 1 and were suitable to receive a platinum-based chemotherapy regimen as first-line treatment for metastatic NSCLC. Choice of platinum-based chemotherapy was at the investigator's discretion, The primary (dual) efficacy endpoints are Progression-Free Survival (PFS) based on blinded independent central review (BICR) and Overall Survival (OS).

The safety and efficacy population consists of 1013 randomized subjects: 338 were randomized to receive tremelimumab plus durvalumab and platinum-based chemotherapy (Arm 1), 338 to durvalumab plus chemotherapy (Arm 2), and 337 to chemotherapy alone (Arm 3). Subjects were enrolled at 142 study centers across 18 countries in North and Latin America, Europe, Asia Pacific, and Africa. Only 5.2% of the subjects in the pivotal study were enrolled in the US (12 sites).

Two CIs were selected for inspection: Dr. Byoung Chul Cho, in South Korea, enrolled the largest number of subjects with positive efficacy results in the POSEIDON trial. One domestic site, Dr. Melissa Johnson, was selected for inspection because there have been 4 previous complaints against this CI, including drug dispensing error, non-protocol anticancer treatment while on study and failure to follow the study procedures. (b) (6)

3. RESULTS (by site):

FDA Inspections

1. **Dr. Byoung Chul Cho (site # 6005)**
   Severance Hospital, 50-1
   Yonsei-ro, Seodaemun-gu
   Seoul, NA 120-752
   South Korea
   Inspection dates: 05/09 – 05/13/2022

   Dr. Cho was inspected as a surveillance inspection for Study D419MC00004. This investigator has been previously inspected on 04/26/2019 and classified as NAI.

As of data cutoff date of 03/12/2021, the site had screened 64 subjects and enrolled 45 subjects: 30 had completed the study, 3 subjects remained on active study treatment, 12 subjects had discontinued study treatment (10 due to disease progression, 1 due to an adverse event and one subject withdrew consent).

Source documents for 9 subjects were reviewed. All subjects met protocol specified inclusion and exclusion criteria and signed informed consent. There was no underreporting of AEs or SAEs or significant protocol deviations.

During the inspection, subjects' source documents were reviewed and compared with the eCRF and/or data listing submitted to the BLA for accuracy, completeness and compliance to the protocol and applicable regulations which included at least the following: informed consent form, electronic medical records, imaging report, laboratory reports, vitals, dosing records and adverse events/serious adverse events and deaths.

The primary efficacy measure of survival was verifiable based on the medical records. Radiographic scans to determine disease response/progression were performed per protocol and submitted for central review. No discrepancies or issues with the imaging process were identified when compared to the information submitted to the BLA.

Other documents reviewed during the inspection include IRB communication and documentation, training records, financial disclosure forms, investigational drug accountability, site monitoring records by Sponsor's employee, and other source documents. No discrepancies or regulatory violations were observed.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Cho at the conclusion of the inspection.

2. **Dr. Melissa Johnson (site # 7801)**
Sarah Cannon Research Institute at Tennessee Oncology
250 25th Ave N Ste 100
Nashville, TN 37203
USA
Inspection dates: 05/02 – 05/06/2022

Dr. Johnson was inspected for Study D419MC00004. This investigator was previously inspected on 12/20/2018 and classified as NAI.

At the time of the inspection, the site had screened 17 subjects and enrolled 10 subjects: 3 of the 10 subjects had completed treatment period, 6 subjects had died and 1 withdrew consent prior to receiving study treatment.

The inspection included the review of informed consents, signed investigator agreements, financial disclosure statements, IRB submissions and correspondence, adverse event/serious adverse event reporting, clinical source data, study test article accountability, concomitant medications, and sponsor monitoring activities.

All 10 enrolled subjects enrolled at the site had signed informed consent form. Source documents for 7 subjects were reviewed. All reviewed subjects met protocol specified inclusion and exclusion criteria. There was no underreporting of AEs or SAEs.

The following protocol deviations were observed:

Two subjects received investigational drugs (tremelimumab and durvalumab) in reverse order and there was no one hour interval wait between the drugs, as specified in the protocol.

Per section 7.1.1. of the protocol, "*Patients will receive 1 dose of tremelimumab (75 mg) via IV infusion over 1 hour, which will be followed by durvalumab (MEDI4736; 1500 mg) via IV infusion over 1 hour, starting approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion.*

- Subject ID # (b) (6) a 78 years-old male subject was randomized to Arm 1 (tremelimumab + durvalumab + chemotherapy) on (b) (6) At cycle 1 day 1, the subject received the IP drugs in reverse order (durvalumab prior to tremelimumab) with only 2 minutes interval between infusion instead of protocol specified hour.

- Subject ID # (b) (6), a 76 years-old male was randomized to Arm 1 on (b) (6). At the study Cycle 4, Day 1, IP drugs were administered in reverse order (durvalumab prior to tremelimumab) with also only 2 minutes interval between the infusions.

Reviewer's comment: *no acute or delayed infusion reactions were reported for subjects ID # (b) (6) following durvalumab, tremelimumab and chemotherapy administration. It is noted that subject ID # (b) (6) was hospitalized with sepsis 10 days after C1D1 and died on study day 12 despite intensive therapy. Sepsis was attributed to chemotherapy and underlying disease and not to tremelimumab or durvalumab. Based on the available information, there was no evidence of harm to the study subjects related to the protocol deviation.*

The above protocol deviations were discussed with the site investigators who indicated that the electronic process has since been updated to indicates the intended order of the investigational products administration and the length of observation time.

The primary efficacy measure of survival was verifiable with source data and was consistent with the data provided in the BLA. Radiographic scans to measure disease response/progression were performed at protocol specified time points and scans were submitted to the CRO for independent assessment.

Other documents reviewed during the inspection include financial disclosure forms, training records, delegation of authority log, investigational drug accountability, electronic medical records, monitoring records, and other source documents. No discrepancies or regulatory violations were observed in these areas.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Johnson at the conclusion of the inspection.

Additional Information: Review of EMA Inspection Findings

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CC:

DARRTS: BLA 761270
Review Division /Project Manager/Idara Ojofeitimi
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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JENN W SELLERS
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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: August 26, 2022

To: Idara Ojofeitimi, M.S, Chief Regulatory Project Manager, Division of Oncology 2 (DO2)

From: Adesola Adejuwon, PharmD, MBA, Regulatory Review Officer Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, MS, RN, RAC, Team Leader, OPDP

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

BLA: 761270

Background:
In response to DO2's consult request dated January 10, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for the original BLA submission for IMJUDO (tremelimumab-xxxx) injection, for intravenous use, (Imjudo).

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 12, 2022, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on August 25, 2022.

Thank you for your consult. If you have any questions, please contact Adesola Adejuwon at 240 402 5773 or Adesola.Adejuwon@fda.hhs.gov.

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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 25, 2022
To:	Idara Ojofeitimi Chief, Project Management Staff **Division of Oncology 2 (DO2)**
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)** Adesola Adejuwon, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	IMJUDO (tremelimumab-actl)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761270
Applicant:	AstraZeneca AB

1 INTRODUCTION

On November 12, 2021, AstraZeneca AB submitted for the Agency's review an original Biologics License Application (BLA) 761270 for IMJUDO (tremelimumab-actl) injection. The proposed indication for IMJUDO (tremelimumab-actl) injection, in combination with durvalumab and platinum-based chemotherapy, is for the first-line treatment of adult patients with metastatic Non-Small Cell Lung Cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

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 2 (DO2) on January 10, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for IMJUDO (tremelimumab-actl) injection.

2 MATERIAL REVIEWED

- Draft IMJUDO (tremelimumab-actl) injection MG received on November 12, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 12, 2022.
- Draft IMJUDO (tremelimumab-actl) injection Prescribing Information (PI) received on November 12, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 12, 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 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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08/25/2022 12:07:02 PM

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:	April 21, 2022
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	BLA 761270
Product Name, Dosage Form, and Strength:	Imjudo (tremelimumab-actl)[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:	November 15, 2021
OSE RCM #:	2021-2225
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Janine Stewart, PharmD

[a] The proposed nonproprietary name (tremelimumab-actl) is only conditionally accepted for this product until the application is approved; see Mena-Grillasca, C M. Suffix Review for Nonproprietary Name for Imjudo (IND (b) (4) and BLA 761270). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 APRIL 15. OSE RCM No.: 2020-80 and 2021-70.

1 REASON FOR REVIEW

As part of the approval process for Imjudo (tremelimumab-actl) injection, the Division of Oncology 2 (DO2) 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 labels and labeling, we note that AstraZeneca is proposing to market the following strengths for Imjudo (tremelimumab-actl) injection: 25 mg/1.25 mL and 300 mg/15 mL packaged in single-dose vials. We noticed the 300 mg/15 mL strength doesn't seem to match up with the proposed doses for the non-small cell lung cancer (NSCLC) indication (e.g., 75 mg, 1 mg/kg for patients weighing less than 30 kg), and that much of the 300 mg/15 mL single-dose vial will be wasted when preparing a dose. We also noticed in a prior proprietary name review[b] for Imjudo (tremelimumab-actl) that the company previously proposed a usual dosage of 300 mg for the proposed indication of hepatocellular carcinoma (HCC). We emailed the review team on December 3, 2021 to ask if they have knowledge of AstraZeneca studying the 300 mg dose for the treatment of HCC in anticipation of a future supplement to BLA

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761270. We also asked if the review team finds the proposal of the 300 mg/15 mL strength to BLA 761270 appropriate at this time. The review team responded on December 14, 2021 that a single 300 mg dose is what is being proposed for the HCC indication, and that the proposal of the 300 mg/15 mL strength to BLA 761270 may not be appropriate at this time as it doesn't match up with the proposed doses for the NSCLC indication (e.g., 75 mg, 1 mg/kg for patients weighing less than 30 kg). We provide a related recommendation in Section 4 below, deferring the resolution of this issue to the review team.

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 2 (DO2)

A. General Recommendations

1. Upon review of the labels and labeling, we note that AstraZeneca is proposing to market the following strengths for Imjudo (tremelimumab-actl) injection: 25 mg/1.25 mL and 300 mg/15 mL packaged in single-dose vials. We noticed the 300 mg/15 mL strength doesn't seem to match up with the proposed doses for the non-small cell lung cancer (NSCLC) indication (e.g., 75 mg, 1 mg/kg for patients weighing less than 30 kg), and that much of the 300 mg/15 mL single-dose vial will be wasted when preparing a dose. We defer to the review team on determining the appropriateness of AstraZeneca's proposal to market the 300 mg/15 mL strength vial for the NSCLC indication under BLA 761270 at this time.
2. 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-actl" across the labels and labeling.

B. Prescribing Information

1. Dosage and Administration Section, Highlights and Full PI
    a. We note inconsistency in the fifth Imjudo doses for patients weighing less than 30 kg as stated in the Dosage and Administration Sections of the Highlights versus what is stated in the Full PI [e.g., (b) (4) versus "a fifth dose of 1 mg/kg Imjudo (b) (4) durvalumab dose 6 at week 16"]. Clarify what is the recommended fifth dose of Imjudo for this patient group.
    b. It is unclear how long after the fourth cycle of the "(b) (4) " phase that the first dose of durvalumab and histology-based pemetrexed (b) (4) therapy during the (b) (4)

[redacted] phase should be given (e.g., 3 weeks after or 4 weeks after). We recommend specifying the intended timeframe in the dosing instructions. In addition, if the first dose of durvalumab and histology-based pemetrexed [redacted] therapy during the "[redacted]" phase should be given 4 weeks after the fourth cycle of the "[redacted]" phase, then clarify if instead of "A fifth dose of 75 mg TRADENAME [redacted] durvalumab dose 6 at week 16" the timeframe should be "…dose 6 at week 17".

c. If applicable, clarify if a duration (e.g., until disease progression or unacceptable toxicity) should be specified for the [redacted] phase.

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.[c]

2. Dosage and Administration Section, Highlights

a. We recommend specifying that Imjudo should be given in combination with durvalumab and platinum-based chemotherapy for 4 cycles, as follows:

- "Weight 30 kg and more: 75 mg every 3 weeks in combination with durvalumab 1500 mg and platinum-based chemotherapy for 4 cycles, and then administer durvalumab 1500 mg every 4 weeks as a single agent with histology-based pemetrexed [redacted] therapy every 4 weeks, and a fifth dose of TRADENAME 75 mg [redacted] durvalumab dose 6 at week 16."
- "Weight less than 30 kg: 1 mg/kg every 3 weeks in combination with durvalumab 20 mg/kg and platinum-based chemotherapy for 4 cycles, and then administer durvalumab 20 mg/kg every 4 weeks as a single agent with histology-based pemetrexed [redacted] therapy every 4 weeks, and a fifth dose of TRADENAME 75 mg [redacted] durvalumab dose 6 at week 16." (underline intended to show location of edit and not for implementation)

[c] 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.

b. We recommend revising the route of administration statement to specify that the proposed product should be diluted prior to intravenous infusion, as follows: "Administer Imjudo as an intravenous infusion over 60 minutes after dilution."

c. We recommend adding the following statement at the end of the Highlights, Dosage and Administration section to alert the end-user that there is 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 preparation and administration instructions and dosage modifications for adverse reactions."

3. Dosage and Administration Section, Full PI

a. Consider reformatting Table 1 to display more clearly the (b) (4) dosing regimens with the corresponding cycles and associated medications with dosing specified.

b. We recommend adding the route of administration (intravenously) to the dosing regimens provided in the Dosage and Administration section.

c. (b) (4) we recommend revising footnote (b) (4)

d. We note footnote (b) (4)

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

f. Clarify if pemetrexed (b) (4) therapy should also be added to the first sentence in the fourth bullet under the "Administration" section: "(b) (4) are administered as separate intravenous infusions."

g. Consider adding the fifth bullet "Separate infusion bags and filters for each infusion should be used." to the fourth bullet under the "Administration" section, as follows:

"[redacted] (b) (4) administered as separate intravenous infusions using separate infusion bags and filters for each infusion." (underline intended to indicate the recommended edit and not for implementation)

h. We note specific administration instructions provided in the sixth bullet under the "Administration" section beginning with [redacted] (b) (4) We recommend relocating these instructions [redacted] (b) (4) under the "Administration" section, if applicable.

4. Dosage Forms and Strengths Section, Highlights

   a. To improve readability, add a space between the total mg numerical strength and the unit of measure in the description of the 300 mg/15 mL vial (e.g., 300 mg/15 mL instead of 300mg/15 mL).[d]

5. Dosage Forms and Strengths Section, Full PI

   a. To improve readability, add a space between the total mL numerical volume and the unit of measure in the description of the 25 mg/1.25 mL vial (e.g., 25 mg/1.25 mL instead of 25 mg/1.25mL).[e]

6. 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[f] 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

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[d] 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.

[e] 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.

[f] 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

intravenous infusion bag containing the diluted tremelimumab-actl 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. Medication Guide (MG)

1. We recommend defining the EGFR (epidermal growth factor receptor) mutation and ALK (anaplastic lymphoma kinase) gene abbreviations the first time they are used in the MG.

2. We note the description of the proposed dosing regimen in the MG does not include the [redacted] (b) (4) phase dosing. We recommend adding the additional dosing for completeness and defer to the review team on how to best word the dosing (e.g., something like: [redacted] (b) (4), followed by durvalumab and histology-based pemetrexed [redacted] (b) (4) therapy every 4 weeks.", with underline intended to indicate the recommended edit and not for implementation).

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.[g]

2. Revise the font color of the proprietary name (green color) or revise the color scheme of the 25 mg/1.25 mL strength ([redacted] (b) (4)), so that either the strength or the proprietary name appears in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths. The use of the

[g] 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

[redacted] color font for the proprietary name and one of the product's strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors.[h]

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:

    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.[i]

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 "For Intravenous [redacted]" with the statement "[redacted]." 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.

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[h] 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

[i] 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.

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

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.[k]

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 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-actl) 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.[l]

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

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

[l] 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

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 storage information (e.g., “Store in a refrigerator… <to> Keep vial in original carton to protect from light.”) and the usual dose statement (“Recommended dosage: See Prescribing Information”), as the side panel already contains this information.

    b. Remove the statement “(b) (4).”, as the route of administration statement (“For Intravenous Infusion After Dilution.”) already coveys this important information.

    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 November 15, 2021 from AstraZeneca UK Ltd (AstraZeneca).

Table 2. Relevant Product Information for Imjudo	
Initial Approval Date	N/A
Nonproprietary Name	tremelimumab-actl
Indication	Imjudo is indicated in combination with durvalumab and platinum-based chemotherapy for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.
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 • Metastatic NSCLC: o Weight 30 kg and more: 75 mg every 3 weeks in combination with durvalumab 1500 mg and platinum-based chemotherapy for 4 cycles, and then administer durvalumab 1500 mg every 4 weeks as a single agent with histology-based pemetrexed (b) (4) therapy every 4 weeks, and a fifth dose of Imjudo 75 mg (b) (4) durvalumab dose 6 at week 16 o Weight less than 30 kg: 1 mg/kg every 3 weeks in combination with durvalumab 20 mg/kg and platinum-based chemotherapy for 4 cycles, and then administer durvalumab 20 mg/kg every 4 weeks as a single agent with histology-based pemetrexed (b) (4) therapy every 4 weeks, and a fifth dose of Imjudo 75 mg (per Dosage and Administration Section in the Highlights) or 1 mg/kg (per Dosage and Administration Section in the Full PI) (b) (4) durvalumab dose 6 at week 16 o Administer up to a maximum of 5 doses unless there was disease progression or unacceptable toxicity • See Section 2.2 and Table 2 for Dosage Modifications for Adverse Reactions

How Supplied	Imjudo (tremelimumab-actl) 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,[m] along with postmarket medication error data, we reviewed the following Imjudo labels and labeling submitted by AstraZeneca UK Ltd (AstraZeneca).

- Container labels received on November 15, 2021
- Carton labeling received on November 15, 2021
- Prescribing Information and Medication Guide (Image not shown) received on November 15, 2021, available from \\CDSESUB1\evsprod\bla761270\0001\m1\us\nonannotated-draft-label-poseidon.pdf

G.2 Label and Labeling Images

Container Labels

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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