# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761069Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION[1]

| | | |
|---|---|---|
| NDA #<br>BLA # 761069 | NDA Supplement #<br>BLA Supplement # | If NDA, Efficacy Supplement Type:<br>*(an action package is not required for SE8 or SE9 supplements)* |
| Proprietary Name: Imfinzi®<br>Established/Proper Name: durvalumab<br>Dosage Form: Injection | | Applicant: AstraZeneca UK Limited<br>Agent for Applicant (if applicable): |
| RPM: Janice Kim | | Division: DOP1 |

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

**For ALL 505(b)(2) applications, two months prior to EVERY action:**

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

***Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.***

| | |
|---|---|
| ❖ Actions | |
| • Proposed action<br>• User Fee Goal Date is June 13, 2017 | ☒ AP ☐ TA ☐ CR |
| • Previous actions *(specify type and date for each action taken)* | ☒ None |
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?<br>Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain | ☒ Received |
| ❖ Application Characteristics [3] | |

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
***(confirm chemical classification at time of approval)***

☐ Fast Track
☒ Rolling Review
☐ Orphan drug designation
☒ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

***(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;***
***Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)***

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☒ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

| | |
|---|---|
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)* | ☐ Yes ☒ No |
| ❖ Public communications *(approvals only)* | |
| • Office of Executive Programs (OEP) liaison has been notified of action | ☒ Yes ☐ No |
| • Indicate what types (if any) of information were issued | ☐ None<br>☐ FDA Press Release<br>☐ FDA Talk Paper<br>☐ CDER Q&As<br>☒ Other **ASCO Burst** |
| ❖ Exclusivity | |
| • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?<br>• If so, specify the type | ☒ No ☐ Yes |
| ❖ Patent Information (NDAs only) | |
| • Patent Information:<br>Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. | ☐ Verified<br>☐ Not applicable because drug is an old antibiotic. |

## CONTENTS OF ACTION PACKAGE

### Officer/Employee List

| | |
|---|---|
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)* | ☒ Included |
| Documentation of consent/non-consent by officers/employees | ☒ Included |

| Action Letters | |
|---|---|
| ❖ Copies of all action letters *(including approval letter with final labeling)* | Action(s) and date(s) AP, May 1, 2017 |
| **Labeling** | |
| ❖ Package Insert *(write submission/communication date at upper right of first page of PI)* | |
| • Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)* | ☒ Included April 4, 2017 |
| • Original applicant-proposed labeling | ☒ Included October 13, 2016 |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)* | ☒ Medication Guide<br>☐ Patient Package Insert<br>☐ Instructions for Use<br>☐ Device Labeling<br>☐ None |
| • Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)* | ☒ Included |
| • Original applicant-proposed labeling | ☒ Included October 13, 2016 |
| ❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)* | |
| • Most-recent draft labeling | ☒ Included February 8, 2017 |
| ❖ Proprietary Name<br>• Acceptability/non-acceptability letter(s) *(indicate date(s))*<br>• Review(s) *(indicate date(s)* | December 16, 2016<br>December 14, 2016 |
| ❖ Labeling reviews *(indicate dates of reviews)* | RPM: ☒ None<br>DMEPA: ☒ None<br>DMPP/PLT (DRISK): ☒ None<br>OPDP: ☒ None<br>SEALD: ☐ None x<br>CSS: ☐ None x<br>Product Quality ☐ None x<br>Other: ☐ None |
| **Administrative / Regulatory Documents** | |
| ❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)*<br>❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee | December 9, 2016<br>☒ Not a (b)(2) |
| ❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)* | ☐ Completed (Do not include) |
| ❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| • Applicant is on the AIP | ☐ Yes ☒ No |

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

| | |
|---|---|
| • This application is on the AIP<br>○ If yes, Center Director's Exception for Review memo *(indicate date)*<br>○ If yes, OC clearance for approval *(indicate date of clearance communication)* | ☐ Yes ☒ No<br>☐ Not an AP action |
| ❖ Pediatrics *(approvals only)*<br>• Date reviewed by PeRC January 18, 2017<br>If PeRC review not necessary, explain: | |
| ❖ Breakthrough Therapy Designation | ☐ N/A |
| • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) | February 16, 2016 |
| • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)* | December 18, 2015 |
| • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)*<br><br>*(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)* | N/A |
| ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)* | Yes |
| ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) | Yes |
| ❖ Minutes of Meetings | |
| • If not the first review cycle, any end-of-review meeting *(indicate date of mtg)* | ☒ N/A or no mtg |
| • Pre-NDA/BLA meeting *(indicate date of mtg)* | ☐ No mtg 9/13/16 |
| • EOP2 meeting *(indicate date of mtg)* | ☒ No mtg |
| • Mid-cycle Communication *(indicate date of mtg)* | ☐ N/A 1/31/2017 |
| • Late-cycle Meeting *(indicate date of mtg)* | ☐ N/A 3/6/2017 |
| • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)* | |
| ❖ Advisory Committee Meeting(s) | ☒ No AC meeting |
| • Date(s) of Meeting(s) | |
| **Decisional and Summary Memos** | |
| ❖ Office Director Decisional Memo *(indicate date for each review)* | ☐ None May 1, 2017 |
| Division Director Summary Review *(indicate date for each review)* | ☐ None May 1, 2017 |
| Cross-Discipline Team Leader Review *(indicate date for each review)* | ☐ None April 27, 2017 |
| PMR/PMC Development Templates *(indicate total number)* | ☐ None 1 PMR, 5 PMC |
| **Clinical** | |

| | |
|---|---|
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) *(indicate date for each review)* | ☐ No separate review 4/27/17 |
| • Clinical review(s) *(indicate date for each review)* | March 6, 2017 (combined with stats) |
| • Social scientist review(s) (if OTC drug) *(indicate date for each review)* | ☐ None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)* | March 6, 2017 |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5] | ☒ None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)* | ☒ N/A |
| ❖ Risk Management<br>• REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))*<br>• REMS Memo(s) and letter(s) *(indicate date(s))*<br>• Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* | ☒ None March 7, 2017 |
| ❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)* | ☐ None requested March 8, 2017 |
| **Clinical Microbiology** ☒ None | |
| ❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)* | ☐ No separate review |
| Clinical Microbiology Review(s) *(indicate date for each review)* | ☒ None |
| **Biostatistics** ☐ None | |
| ❖ Statistical Division Director Review(s) *(indicate date for each review)* | ☒ No separate review |
| Statistical Team Leader Review(s) *(indicate date for each review)* | ☒ No separate review |
| Statistical Review(s) *(indicate date for each review)* | ☐ None March 6, 2017 (combined with clinical) |
| **Clinical Pharmacology** ☐ None | |
| ❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)* | ☒ No separate review |
| Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)* | ☒ No separate review |
| Clinical Pharmacology review(s) *(indicate date for each review)* | ☐ None March 6, 2017 |
| ❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)* | ☒ None requested |

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

| **Nonclinical** ☐ None | |
|---|---|
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) *(indicate date for each review)* | ☐ No separate review March 16, 2017 |
| • Supervisory Review(s) *(indicate date for each review)* | ☐ No separate review March 15, 2017 |
| • Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | ☐ None March 6, 2017 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)* | ☒ None |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | ☒ No carc |
| ❖ ECAC/CAC report/memo of meeting | ☒ None<br>Included in P/T review, page |
| ❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)* | ☒ None requested |
| **Product Quality** ☐ None | |
| ❖ Product Quality Discipline Reviews[6] | |
| • Tertiary review (*indicate date for each review*) | ☒ None |
| • Secondary review (e.g., Branch Chief) *(indicate date for each review)* | ☐ None March 6, 2017 |
| • Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)* | ☒ None |
| ❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)* | ☐ None Immunogenicity – March 6, 2017<br>Drug Substance – March 3, 2017<br>Drug Product – March 6, 2017 |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)* | March 6, 2017 |
| ☐ Review & FONSI *(indicate date of review)* | |
| ☐ Review & Environmental Impact Statement *(indicate date of each review)* | |
| ❖ Facilities Review/Inspection | |
| ☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)* | ☒ Acceptable<br>☐ Withhold recommendation<br>☐ Not applicable |

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

| Day of Approval Activities | |
|---|---|
| ❖ For all 505(b)(2) applications:<br>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) | ☐ No changes<br>☐ New patent/exclusivity *(Notify CDER OND IO)* |
| • Finalize 505(b)(2) assessment | ☐ Done |
| ❖ For Breakthrough Therapy (BT) Designated drugs:<br>• Notify the CDER BT Program Manager | ☒ Done<br>*(Send email to CDER OND IO)* |
| ❖ For products that need to be added to the flush list (generally opioids): Flush List<br>• Notify the Division of Online Communications, Office of Communications | ☐ Done |
| ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email | ☒ Done |
| ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter | ☐ Done |
| ❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name | ☒ Done |
| ❖ Ensure Pediatric Record is accurate | ☒ Done |
| ❖ Send approval email within one business day to CDER-APPROVALS | ☒ Done |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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JANICE H KIM
05/03/2017

**PEDIATRIC PAGE**
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 761069 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Oncology Prodcuts 1 PDUFA Goal Date: June 13, 2017 Stamp Date: October 13, 2016

Proprietary Name: Imfinzi

Established/Generic Name: durvalumab

Dosage Form: injection

Applicant/Sponsor: AstraZeneca UK Limited

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

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Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** urothelial cancer

**Q1:** Is this application in response to a PREA PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

**Q3:** Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A**: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☒ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☒ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☒ Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B:** Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

| | | | | Reason (see below for further detail): | | | |
|---|---|---|---|---|---|---|---|
| | | minimum | maximum | Not feasible# | Not meaningful therapeutic benefit* | Ineffective or unsafe† | Formulation failedΔ |
| ☐ | Neonate | __ wk. __ mo. | __ wk. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C:** Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

| **Deferrals (for each or all age groups):** | | | | **Reason for Deferral** | | | **Applicant Certification** † |
|---|---|---|---|---|---|---|---|
| **Population** | | minimum | maximum | Ready for Approval in Adults | Need Additional Adult Safety or Efficacy Data | Other Appropriate Reason (specify below)* | Received |
| ☐ | Neonate | __ wk. __ mo. | __ wk. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | All Pediatric Populations | 0 yr. 0 mo. | 16 yr. 11 mo. | ☐ | ☐ | ☐ | ☐ |
| | Date studies are due (mm/dd/yy): _____ | | | | | | |

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

*† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)*

*If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section D:** Completed Studies (for some or all pediatric subpopulations).

| Pediatric subpopulation(s) in which studies have been completed (check below): | | | | | |
|---|---|---|---|---|---|
| Population | | minimum | maximum | PeRC Pediatric Assessment form attached?. | |
| ☐ | Neonate | __ wk. __ mo. | __ wk. __ mo. | Yes ☐ | No ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | Yes ☐ | No ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | Yes ☐ | No ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | Yes ☐ | No ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | Yes ☐ | No ☐ |
| ☐ | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | Yes ☐ | No ☐ |

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable*.

**Section E:** Drug Appropriately Labeled (for some or all pediatric subpopulations):

| Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed: | | | |
|---|---|---|---|
| Population | | minimum | maximum |
| ☐ | Neonate | __ wk. __ mo. | __ wk. __ mo. |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. |
| ☐ | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. |

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F:** Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

| Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations: | | | | | |
|---|---|---|---|---|---|
| Population | | minimum | maximum | Extrapolated from: | |
| | | | | Adult Studies? | Other Pediatric Studies? |
| ☐ | Neonate | __ wk. __ mo. | __ wk. __ mo. | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ |
| ☐ | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | ☐ | ☐ |

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** _____

**Q1:** Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A**: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B:** Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

| | | | | Reason (see below for further detail): | | | |
|---|---|---|---|---|---|---|---|
| | | minimum | maximum | Not feasible# | Not meaningful therapeutic benefit* | Ineffective or unsafe† | Formulation failedΔ |
| ☐ | Neonate | __ wk. __ mo. | __ wk. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the*

*PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C:** Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

| **Deferrals (for each or all age groups):** | | | | **Reason for Deferral** | | | **Applicant Certification †** |
|---|---|---|---|---|---|---|---|
| **Population** | | minimum | maximum | Ready for Approval in Adults | Need Additional Adult Safety or Efficacy Data | Other Appropriate Reason (specify below)* | Received |
| ☐ | Neonate | __ wk. __ mo. | __ wk. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ | ☐ | ☐ |
| ☐ | All Pediatric Populations | 0 yr. 0 mo. | 16 yr. 11 mo. | ☐ | ☐ | ☐ | ☐ |
| | Date studies are due (mm/dd/yy): _____ | | | | | | |

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

*† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)*

*If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section D:** Completed Studies (for some or all pediatric subpopulations).

| Pediatric subpopulation(s) in which studies have been completed (check below): | | | | | |
|---|---|---|---|---|---|
| Population | | minimum | maximum | PeRC Pediatric Assessment form attached? | |
| ☐ | Neonate | __ wk. __ mo. | __ wk. __ mo. | Yes ☐ | No ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | Yes ☐ | No ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | Yes ☐ | No ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | Yes ☐ | No ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | Yes ☐ | No ☐ |
| ☐ | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | Yes ☐ | No ☐ |

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E:** Drug Appropriately Labeled (for some or all pediatric subpopulations):

| Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed: | | | |
|---|---|---|---|
| Population | | minimum | maximum |
| ☐ | Neonate | __ wk. __ mo. | __ wk. __ mo. |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. |
| ☐ | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. |

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F:** Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

| Population | | minimum | maximum | Extrapolated from: | |
|---|---|---|---|---|---|
| | | | | Adult Studies? | Other Pediatric Studies? |
| ☐ | Neonate | __ wk. __ mo. | __ wk. __ mo. | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ |
| ☐ | Other | __ yr. __ mo. | __ yr. __ mo. | ☐ | ☐ |
| ☐ | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | ☐ | ☐ |

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.***

**This page was completed by:**

*{See appended electronic signature page}*

**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

**(Revised: 6/2008)**

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/s/

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JANICE H KIM
11/28/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Friday, April 28, 2017 1:29 PM
**To:** 'Gillette, Jamie'
**Subject:** BLA 761069 PMC

Dear Ms. Gillette,

The purpose of this email is to send you some minor edits to the dates to the previous PMC that was sent, please let me know if you are agreeable to these edits by today 4/28/17 COB.

"Conduct a third media fill simulating worst case conditions for the durvalumab aseptic fill process. Include product contact parts and perform growth promotion studies (b) (4) of the medical fill.

| | | |
|---|---|---|
| Final Report Submission: | | 09/25/2017 |
| Other: | Study results will be submitted as a DMF update." | 09/25/2017 |

Thank you.

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@fda.hhs.gov

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/s/

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JANICE H KIM
05/01/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Friday, April 28, 2017 3:08 PM
**To:** 'Gillette, Jamie'
**Subject:** RE: BLA 761069 PMC

Great, thank you. Thank you for your submission. And to clarify OBP is agreeable to the CBE-0.

Regards,

Janice

---

**From:** Gillette, Jamie [mailto:Jamie.Gillette@astrazeneca.com]
**Sent:** Friday, April 28, 2017 2:08 PM
**To:** Kim, Janice
**Subject:** RE: BLA 761069 PMC

Dear Janice,

Thank you for your email and for discussing the PMC language with me on the phone. Please find attached our response to the revised PMC request below. We are submitting as a formal amendment to the BLA today. Please let me know if you need anything else.

Many thanks, and I hope you have a great weekend!

Best regards,
Jamie

**Jamie Gillette, MSc, RAC**
Regulatory Affairs Director, Oncology

**AstraZeneca** | Global Medicines Development | GRAPSQA
200 Orchard Ridge Drive, Gaithersburg, MD 20878
T: (301) 398-5510 F: (301) 398-4018 (b) (6)
**jamie.gillette@astrazeneca.com**

---

**From:** Kim, Janice [mailto:Janice.Kim@fda.hhs.gov]
**Sent:** Friday, April 28, 2017 1:29 PM
**To:** Gillette, Jamie <Jamie.Gillette@astrazeneca.com>
**Subject:** BLA 761069 PMC

Dear Ms. Gillette,

The purpose of this email is to send you some minor edits to the dates to the previous PMC that was sent, please let me know if you are agreeable to these edits by today 4/28/17 COB.

"Conduct a third media fill simulating worst case conditions for the durvalumab aseptic fill process. Include product contact parts and perform growth promotion studies (b) (4) of the medical fill.

| | | |
|---|---|---|
| Final Report Submission: | | 09/25/2017 |
| Other: | Study results will be submitted as a DMF update." | 09/25/2017 |

Thank you.

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
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Fax: 301-796-9845
janice.kim@fda.hhs.gov


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/s/

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JANICE H KIM
05/01/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Monday, May 01, 2017 6:37 AM
**To:** 'Gillette, Jamie'
**Subject:** BLA 761069 IR

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request for BLA 761069 from our clinical reviewer:

1. Please indicate whether data regarding the reason for screen failure due to eligibility criteria not being met are available for the bladder cohort of study 1108.

Please submit a response by COB May 5, 2017 by email to facilitate review and by official submission to your BLA.

Thank you

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
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JANICE H KIM
05/01/2017

## Kim, Janice

**From:** Commerford, Monica
**Sent:** Friday, April 28, 2017 3:00 PM
**To:** Kim, Janice; Hughes, Patricia
**Cc:** Fedenko, Katherine
**Subject:** RE: BLA 761069 PMC

Janice,

We agree to AstraZeneca's response to submit as a CBE-0 no later than 25 September 2017.

Thank you and have a nice weekend,
Monica

---

**From:** Kim, Janice
**Sent:** Friday, April 28, 2017 2:10 PM
**To:** Commerford, Monica; Hughes, Patricia
**Cc:** Fedenko, Katherine
**Subject:** FW: BLA 761069 PMC

Please let me know if you are agreeable to AZs response.

Thank you

Janice

---

**From:** Gillette, Jamie [mailto:Jamie.Gillette@astrazeneca.com]
**Sent:** Friday, April 28, 2017 2:08 PM
**To:** Kim, Janice
**Subject:** RE: BLA 761069 PMC

Dear Janice,

Thank you for your email and for discussing the PMC language with me on the phone. Please find attached our response to the revised PMC request below. We are submitting as a formal amendment to the BLA today. Please let me know if you need anything else.

Many thanks, and I hope you have a great weekend!

Best regards,
Jamie

**Jamie Gillette, MSc, RAC**
Regulatory Affairs Director, Oncology

**AstraZeneca** | Global Medicines Development | GRAPSQA
200 Orchard Ridge Drive, Gaithersburg, MD 20878
T: (301) 398-5510 F: (301) 398-4018 (b) (6)
**jamie.gillette@astrazeneca.com**

**From:** Kim, Janice [mailto:Janice.Kim@fda.hhs.gov]
**Sent:** Friday, April 28, 2017 1:29 PM
**To:** Gillette, Jamie <Jamie.Gillette@astrazeneca.com>
**Subject:** BLA 761069 PMC

Dear Ms. Gillette,

The purpose of this email is to send you some minor edits to the dates to the previous PMC that was sent, please let me know if you are agreeable to these edits by today 4/28/17 COB.

"Conduct a third media fill simulating worst case conditions for the durvalumab aseptic fill process. Include product contact parts and perform growth promotion studies (b) (4) of the medical fill.

| | | |
|---|---|---|
| Final Report Submission: | | 09/25/2017 |
| Other: | Study results will be submitted as a DMF update." | 09/25/2017 |

Thank you.

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
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/s/

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JANICE H KIM
05/01/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, April 26, 2017 1:52 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey the following post marketing commitment for BLA 761069:

PMC Description: Conduct a third media fill simulating worst case conditions for the durvalumab aseptic fill process. Include product contact parts and perform growth promotion studies (b) (4) of the media fill.

PMC Schedule Milestones:

| | | |
|---|---|---|
| Final Protocol Submission: | | MM/DD/YYYY |
| Study/Trial Completion: | | MM/DD/YYYY |
| Final Report Submission: | | MM/DD/YYYY |
| Other: | Study results will be submitted as a DMF update. | 09/25/2017 |

Please submit a response by email by tomorrow COB by email to facilitate review and by official submission to your BLA.

Thank you!

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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janice.kim@fda.hhs.gov

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/s/

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JANICE H KIM
04/26/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Monday, April 17, 2017 6:21 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to send you the following information request in regards to your PMCs. Please review the dates and let me know if you are agreeable to this by 2pm 4/17/2017 by email and by official submission to your BLA.

Thank you.

Confirm that there is no significant growth of organisms at 2 - 8°C in the drug product diluted with 0.9% sodium chloride and 5% dextrose by performing microbiological challenge studies with diverse microorganisms to support the 24 hour storage time. Your study should include Gram-negative microorganisms (such as *E. coli* and/or *E. cloacae*) which are known to proliferate in these solutions. The challenge studies should include at a minimum time points at twice the label claim storage time.

| | |
|---|---|
| Study Completion: | 07/2017 |
| Final Report Submission: | 01/2018 |
| Other: Study results will be submitted as a CBE-0 | 01/2018 |

Reevaluate the anti-drug antibody confirmatory and triple mutation assay cut points using a 1.0% false positive rate.

| | |
|---|---|
| Study Completion: | 10/2017 |
| Final Report Submission: | 04/2018 |

Conduct drug tolerance studies for the screening, confirmatory, titering, and triple mutation assays that are in the range of the trough concentration of 182 mg/ml to better demonstrate that the assay can detect anti-drug antibodies in the presence of drug.

| | |
|---|---|
| Study Completion: | 12/2017 |
| Final Report Submission: | 06/2018 |

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
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APPEARS THIS WAY ON ORIGINAL

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/s/

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JANICE H KIM
04/17/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Tuesday, April 04, 2017 9:21 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 PI
**Attachments:** BLA 761069 package-insert-complementary-annotated.docx.doc

Dear Ms. Gillette,

The purpose of this email is to provide you with FDA's final agreed upon label for durvalumab.

Regards,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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janice.kim@fda.hhs.gov

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

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/s/

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JANICE H KIM
04/04/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Friday, March 31, 2017 1:12 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request for BLA 761069:

The Package Insert section 11 does not include the identity of the cell substrate used to manufacture Imfinzi. Please update section 11 to include the identity of the cell substrate because this information is included in the Package Insert for biotechnology products.

Please provide an updated Package Insert by April 5, 2017 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you.

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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janice.kim@fda.hhs.gov

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JANICE H KIM
04/03/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, March 23, 2017 9:28 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Durvalumab PI
**Attachments:** FDA comments durvalumab PI 3.23.17doc.doc

Dear Ms. Gillette,

The purpose of this email is to convey to you FDA comments and revisions in response to your comments and revisions for your PI for BLA 761069 (durvalumab).

Please submit a WORD and PDF copy of your Final Agreed Upon Label with all changes accepted that you agree with and clearly track those that you don't by COB Wednesday, March 29, 2017. Feel free to contact me if you have any questions and kindly confirm receipt.

Thank you,

Janice

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**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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JANICE H KIM
03/23/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Friday, March 17, 2017 7:00 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Durvalumab
**Attachments:** FDA Comments Durvalumab package-insert-complementary-diagnostic-annotated.doc

Dear Ms. Gillette,

The purpose of this email is to convey to you information for Section 14 as well as send you your FDA comments and revisions in response to your comments and revisions for BLA 761069 (durvalumab). Regarding Section 14: "It is acceptable to include 182 pts in the breakdown of RR by PD-L1 high, PD-L1 low, and not evaluable in Section 14. Please revise Section 14 and submit it with the rest of the PI and PPI."

Please submit a WORD and PDF copy of your Final Agreed Upon Label with all changes accepted that you agree with and clearly track those that you don't by COB Wednesday, March 22, 2017. Feel free to contact me if you have any questions and kindly confirm receipt.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
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/s/

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JANICE H KIM
03/17/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, March 08, 2017 5:04 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 FDA Comments - PI
**Attachments:** BLA 761069 FDA Comments.docx

Dear Ms. Gillette,

Please see the attached MS Word document of AstraZeneca's USPI for durvalumab for BLA 761069, with FDA comments and revisions in response to your comments and revisions. Please submit a WORD and PDF copy of your Final Agreed Upon Label with all changes accepted that you agree with and clearly track those that you don't by COB Wednesday, March 15, 2017. Feel free to contact me if you have any questions and kindly confirm receipt.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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/s/

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JANICE H KIM
03/09/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, March 09, 2017 10:48 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request form our clinical review team for your BLA 761069:

We are unable to confirm your revised incidence of Grade 3 or 4 ALT, AST, and bilirubin in the combined safety database (n=1414) under Section 5.2.

We note the following patients based on those with both a baseline and on-study value and with an increased level from baseline.

| Grade 3-4 ALT (n= 43) | Grade 3-4 AST (n=61) | Grade 3-4 Bilirubin (n=39) |
|---|---|---|
| D4191C00003/E1001021 | D4191C00003/E1001011 | D4191C00003/E33050 |
| D4191C00003/E2303022 | D4191C00003/E1001021 | D4191C00003/E60040 |
| D4191C00003/E2307013 | D4191C00003/E2303022 | D4191C00003/E66010 |
| D4191C00003/E3305001 | D4191C00003/E3305001 | CD1108/1002501499 |
| D4191C00003/E4108004 | D4191C00003/E4320003 | CD1108/1053601232 |
| D4191C00003/E4313006 | D4191C00003/E4322001 | CD1108/1053601263 |
| D4191C00003/E4315022 | D4191C00003/E6004070 | CD1108/1056201007 |
| D4191C00003/E4320003 | D4191C00003/E6007014 | CD1108/1056201513 |
| D4191C00003/E4322001 | D4191C00003/E7004001 | CD1108/1093501793 |
| D4191C00003/E6005012 | D4191C00003/E7807008 | CD1108/1351901242 |
| D4191C00003/E6007014 | D4191C00003/E7807011 | CD1108/1351901305 |
| D4191C00003/E7807011 | D4191C00003/E7808002 | CD1108/13711012235 |
| D4191C00003/E7808002 | CD1108/10025011792 | CD1108/1371101319 |
| CD1108/1056201757 | CD1108/1002501499 | CD1108/13717011160 |
| CD1108/1093501827 | CD1108/1053601234 | CD1108/13717011266 |
| CD1108/13519012206 | CD1108/1056201007 | CD1108/13717011564 |
| CD1108/1371101319 | CD1108/10562011161 | CD1108/1371701456 |
| CD1108/13717011266 | CD1108/1056201235 | CD1108/1371701533 |
| CD1108/13717011564 | CD1108/1056201394 | CD1108/1371701535 |
| CD1108/1371701456 | CD1108/1056201757 | CD1108/1371701605 |
| CD1108/1371701533 | CD1108/1093501347 | CD1108/13720011686 |
| CD1108/1371701605 | CD1108/1093501793 | CD1108/2000042389 |
| CD1108/13720011472 | CD1108/12455011922 | CD1108/2000042552 |
| CD1108/13720011686 | CD1108/13519012206 | CD1108/20000451705 |
| CD1108/2000042407 | CD1108/13711011104 | CD1108/20000891201 |
| CD1108/2000042505 | CD1108/13711012202 | CD1108/20001121747 |

CD1108/2000044515
CD1108/20000451705
CD1108/20000891201
CD1108/20001122442
CD1108/20001131289
CD1108/2000133906
CD1108/20001371882
CD1108/20001971137
CD1108/2000199725
CD1108/2000208798
CD1108/20002101125
CD1108/20002101149
CD1108/20002101971
CD1108/20002211322
CD1108/20002351002
CD1108/20010772122
CD1108/20010772293

CD1108/13711012235
CD1108/1371101319
CD1108/13717011266
CD1108/13717011564
CD1108/13717012363
CD1108/1371701456
CD1108/1371701526
CD1108/1371701533
CD1108/1371701535
CD1108/1371701557
CD1108/1371701605
CD1108/13720011472
CD1108/13720011686
CD1108/2000042407
CD1108/2000042505
CD1108/2000042552
CD1108/2000042622
CD1108/2000042982
CD1108/20000432516
CD1108/20000441079
CD1108/20000441274
CD1108/2000044515
CD1108/20000451705
CD1108/20000891201
CD1108/2000136655
CD1108/20001971137
CD1108/2000199725
CD1108/2000208798
CD1108/20002091978
CD1108/20002101125
CD1108/20002101149
CD1108/2000211787
CD1108/20002351002
CD1108/20006781075
CD1108/20010772122

CD1108/20001331545
CD1108/2000133820
CD1108/20001352214
CD1108/2000136655
CD1108/20001971137
CD1108/2000199986
CD1108/20002091162
CD1108/20002091978
CD1108/20002101092
CD1108/20002101125
CD1108/20002101149
CD1108/2000211787
CD1108/20006781075

Please submit a response to this request with your revised label.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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JANICE H KIM
03/09/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**INFORMATION REQUEST**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated and received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for durvalumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB March 7, 2017 in order to continue our evaluation of your application.

**DRUG SUBSTANCE**

1. Amend the applicable sections of the BLA to include the increased testing volume for the (b) (4) sample as described in amendment 0048 and update the bioburden action limit for the test.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly Ballard

Digitally signed by Kelly Ballard
Date: 3/07/2017 10:58:01AM
GUID: 57e29be6020b38ae4817a9d8118b31c1

## Kim, Janice

**From:** Kim, Janice
**Sent:** Monday, February 27, 2017 6:25 AM
**To:** 'Gillette, Jamie'
**Subject:** RE: BLA 761069 IR

Please see the revisions to the information request I sent to you (Re: PMCs/PMRs) Friday Afternoon:

The purpose of this email is to convey the following information request:

1. Please commit in writing that you commit to the following Post Marketing Commitment: "Conduct updated analyses of the duration of response for the patients with urothelial cancer who had received prior platinum-based therapy (N = 182) in the clinical trial entitled "A Phase 1-2 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects with Advanced Solid Tumors." Present the median and updated information on the range of the duration of response for all patients, patients whose tumor have high PD-L1 staining, and patients whose tumors have low PD-L1 staining. Submit the final report with datasets and labeling.

| | |
|---|---|
| Study/Trial Completion: | MM/DD/YYYY |
| Final Report Submission: | MM/DD/YYYY |
| Other: _____ | MM/DD/YYYY" |

2. In addition, please see the following post marketing requirement (PMR) and reply that you acknowledge the PMR. And please fill in what you think are feasible and realistic dates: "Please Submit the final report with datasets and labeling for the clinical trial entitled "A Phase II, Randomized, Open-label, Controlled, Multi-center, Global Study of First-line MEDI4736 Monotherapy and MEDI4735 in Combination with Tremelimumab Versus Standard of Care Chemotherapy in Patients with Unresectable Stage IV Urothelial Cancer."

| | |
|---|---|
| Study/Trial Completion: | MM/DD/YYYY |
| Final Report Submission: | MM/DD/YYYY |
| Other: _____ | MM/DD/YYYY" |

Please submit a response by March 1, 2017 by 2pm EST 1) by email to facilitate review 2) and by official submission to your BLA.

---

**From:** Gillette, Jamie [mailto:Jamie.Gillette@astrazeneca.com]
**Sent:** Friday, February 24, 2017 2:46 PM
**To:** Kim, Janice
**Cc:** Kacuba, Alice
**Subject:** RE: BLA 761069 IR

Dear Janice,
Thank you so much! We will provide our agreement with the proposed PMCs by writing no later than March 1st.
Best regards,
Jamie

**Jamie Gillette, MSc, RAC**
Regulatory Affairs Director, Oncology

**AstraZeneca** | Global Medicines Development | GRAPSQA
200 Orchard Ridge Drive, Gaithersburg, MD 20878
T: (301) 398-5510 F: (301) 398-4018 (b) (6)
jamie.gillette@astrazeneca.com

**From:** Kim, Janice [mailto:Janice.Kim@fda.hhs.gov]
**Sent:** Friday, February 24, 2017 2:44 PM
**To:** Gillette, Jamie <Jamie.Gillette@astrazeneca.com>
**Cc:** Kacuba, Alice <Alice.Kacuba@fda.hhs.gov>
**Subject:** RE: BLA 761069 IR

Dear Ms. Gillette,

Please see my amended information request below to clarify my previous information request that was sent via email.

The purpose of this email is to convey to you the following information request:

1. Please commit in writing that you commit to the following Post Marketing Commitment: "Conduct updated analyses of the duration of response for the clinical trial entitled "A Phase 1-2 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects with Advanced Solid Tumors." Present the median and updated information on the range of the duration of response for all patients, patients whose tumor have high PD-L1 staining, and patients whose tumors have low PD-L1 staining. Submit the final report with datasets and labeling.

| | |
|---|---|
| Study/Trial Completion: | MM/DD/YYYY |
| Final Report Submission: | MM/DD/YYYY |
| Other: _____ | MM/DD/YYYY" |

2. In addition, please see the following post marketing requirement (PMR) and reply that you acknowledge the PMR. And please fill in what you think are feasible and realistic dates: "Please Submit the final report with datasets and labeling for the clinical trial entitled "A Phase II, Randomized, Open-label, Controlled, Multi-center, Global Study of First-line MEDI4736 Monotherapy and MEDI4735 in Combination with Tremelimumab Versus Standard of Care Chemotherapy in Patients with Unresectable Stage IV Urothelial Cancer."

| | |
|---|---|
| Study/Trial Completion: | MM/DD/YYYY |
| Final Report Submission: | MM/DD/YYYY |
| Other: _____ | MM/DD/YYYY" |

Please submit a response by March 1, 2017 by 2pm EST 1) by email to facilitate review 2) and by official submission to your BLA.

Regards,

Janice

**From:** Kim, Janice
**Sent:** Friday, February 24, 2017 2:13 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 IR

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request:

Submit the final report with datasets and labeling for the clinical trial entitled "A Phase II, Randomized, Open-label, Controlled, Multi-center, Global Study of First-line MEDI4736 Monotherapy and MEDI4735 in Combination with Tremelimumab Versus Standard of Care Chemotherapy in Patients with Unresectable Stage IV Urothelial Cancer."

| | |
|---|---|
| Study/Trial Completion: | MM/DD/YYYY |
| Final Report Submission: | MM/DD/YYYY |
| Other: _____ | MM/DD/YYYY |

Conduct updated analyses of the duration of response for the clinical trial entitled "A Phase 1-2 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects with Advanced Solid Tumors." Present the median and updated information on the range of the duration of response for all patients, patients whose tumor have high PD-L1 staining, and patients whose tumors have low PD-L1 staining. Submit the final report with datasets and labeling.

| | |
|---|---|
| Study/Trial Completion: | MM/DD/YYYY |
| Final Report Submission: | MM/DD/YYYY |
| Other: _____ | MM/DD/YYYY |

Please submit a response by March 1, 2017 by 2pm EST 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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janice.kim@fda.hhs.gov

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/s/

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JANICE H KIM
02/27/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**INFORMATION REQUEST**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated and received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for durvalumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB February 28, 2017 in order to continue our evaluation of your application.

We acknowledge your commitment to performing the microbiological challenge study to confirm that there is no significant growth of organisms at 2 – 8C in the drug product diluted with 0.9% sodium chloride and 5% dextrose and to submit the study results as a CBE-0. Please provide a timeline for submitting the CBE-0.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly Ballard

Digitally signed by Kelly Ballard
Date: 2/24/2017 03:06:54PM
GUID: 57e29be6020b38ae4817a9d8118b31c1

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**INFORMATION REQUEST**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated and received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for durvalumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB March 1, 2017 in order to continue our evaluation of your application.

This IR is a follow up to AstraZeneca UK responses on 1/10/2017 and 1/18/2017. The responses are deficient and should be corrected as follows:

1. The AP-1 reporter gene bioassay for the DS specification has been updated in Table S.4.1-1 but not in Table S.7.2-2 in BLA section 3.2.S.7.2. Update Table S.7.2-2 to indicate the new stability acceptance criteria is (b) (4)% reference standard activity.

2. The AP-1 reporter gene bioassay for the DP specification has been updated in Table P.5.1-1 but not in Table P.8.2-2 in BLA section 3.2.P.8.2. Update Table P.8.2-2 to indicate the new stability acceptance criteria is (b) (4)% reference standard activity.

3. The Total Basic Peak Charge Heterogeneity method for the DS specification has been updated in Table S.4.1-1 but not in Table S.7.2-2 in BLA section 3.2.S.7.2. Update Table S.7.2-2 to indicate the new stability acceptance criteria is ≤ (b) (4)% Total Basic Peaks.

4. The Total Basic Peak Charge Heterogeneity method for the DP release and stability specifications has been updated in Table P.5.1-1 but not in Table P.8.2-2 in BLA section 3.2.P.8.2. Update Table P.8.2-2 to indicate the new stability acceptance criteria is ≤ (b) (4)% reference standard activity.

5. The Total Protein method for the DP stability specification has been updated in Table P.8.2-2 but not in Table P.5.1-1 in BLA section 3.2.P.5.1. Update Table P.5.1-1 to

indicate the new stability acceptance criteria is (b) (4) mg/mL for Total Protein method.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly Ballard

Digitally signed by Kelly Ballard
Date: 2/24/2017 04:05:20PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**INFORMATION REQUEST**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated and received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for durvalumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB February 27, 2017 in order to continue our evaluation of your application.


If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly Ballard

Digitally signed by Kelly Ballard
Date: 2/23/2017 07:32:55AM
GUID: 57e29be6020b38ae4817a9d8118b31c1

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, February 22, 2017 7:26 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request for your BLA 761069:

Please address vial size as it pertains to the proposed [redacted] (b) (4) Currently, your proposed vial sizes are 500 mg and 120 mg, which could result in providers "rounding down" the dose to [redacted] (b) (4) or may result in excess waste of product. Please provide your plan for instructing providers regarding the potential for excess product and any plans for mitigation such as the introduction of a [redacted] (b) (4) strength.

Please provide a response by Friday February 24, 2017 by 2pm 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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/s/

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JANICE H KIM
02/22/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, February 22, 2017 11:45 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request for your BLA 761069:

1. Please provide additional details regarding diagnosis, management, and outcome of the cases of hemolysis/hemolytic anemia in the following patients:
    a. CD1108/2000045480
    b. D4191C00003/E4101008

Please submit a response by 2/27 by 2pm 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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JANICE H KIM
02/22/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**INFORMATION REQUEST**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated and received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for durvalumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB February 24, 2017 in order to continue our evaluation of your application.

**DRUG SUBSTANCE**

1. We acknowledge your response to question 2 provided in amendment 0043. However, the current test sample volume used to monitor bioburden (b) (4) may not provide sufficient assay sensitivity and should be increased to (b) (4) mL. Additional replicates may be used to facilitate processing of the sample.

2. Amendment 0043 indicates that the (b) (4) bioburden is currently tested (b) (4) specified in the BLA. Provide the bioburden qualification of the (b) (4) amend all applicable sections of the BLA to include the correct bioburden method(s) used for the (b) (4)

3. Amend the durvalumab Drug Substance Manufacturing Process Flow Diagrams provided in amendment 0043 to include the following:

(b) (4)

**DRUG PRODUCT**

4. Regarding your responses on November 18, 2016:

    a. Describe and provide rationale for the worst case filling assembly used for dose substantiation and dose audits.

    b. Provide the dose audit schedule and indicate when the dose mapping studies will be completed.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly Ballard

Digitally signed by Kelly Ballard
Date: 2/21/2017 07:35:13AM
GUID: 57e29be6020b38ae4817a9d8118b31c1

## Kim, Janice

**From:** Kim, Janice
**Sent:** Tuesday, February 21, 2017 10:13 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request for your BLA 761069:

Please provide narratives for the following subjects:

1. CD1108/1371501700- provide summary of patient's event of hyperparathyroidism including PTH levels, workup, and treatment.
2. CD1108/20002062498 – provide additional details regarding patient's event of pituitary adenoma.
3. CD1108/2000136788 – provide additional details regarding intermittent nystagmus.
4. D4191C00003/E6601023 – provide additional details regarding myoclonus.
5. D4191C00003/E2801010 – provide additional details regarding bilateral posterior vitreous detachment and cystoid macular edema.
6. D4191C00003/E6603006- provide additional details regarding retinopathy.
7. CD1108/13717012454 – provide additional details regarding pulmonary fibrosis.

Please submit a response by February 27, 2017, by 9AM EST 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@fda.hhs.gov

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/s/

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JANICE H KIM
02/21/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Friday, February 17, 2017 7:06 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request
**Attachments:** run651_refined.mod; run651_refined.lst; pknm1co_gt3mgkg.csv; patab651_refined.csv; calculation for label proposal.r

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request from our phamacometrics/clinical pharmacology team:

Reference is made to SN0021 Clinical Pharmacology/Response to Information Request (Date: 12/22/2016). The model run (run651) which incorporated time-varying PK component was terminated due to rounding errors. The following refinements were made by the FDA reviewer, which solved the rounding error issue with successful minimization and covariate step.

1) Update of the dataset by excluding subjects on doses less than or equal to 3 mg/kg
2) Deletion of the Michaelis-Mention clearance component
3) Deletion of ETA on V2
4) Update of the residual error model with a combined additive and proportional model

For model files and other technical details, please refer to the attached files. Please respond if you concur with our refined approach to describe the time-varying PK in section 12.3 of the label. A proposal is provided as follow.
*Durvalumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 22.9% (46.3%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.24 mL/h (37(b)(4)%); the decrease in CLss is not considered clinically relevant.*

Please respond no later than 2/23/2017 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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JANICE H KIM
02/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**INFORMATION REQUEST**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated and received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for durvalumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB February 23, 2017 in order to continue our evaluation of your application.

1) Table 5.1.3-1 in assay validation report V-IM-0077 for the screening, confirmatory, titering, and triple mutation assays shows the impact of 100 ug/ml and 1000 ug/ml on ADA detection. The assay could detect 82 ng/ml of ADA in the presence of 100 ug/ml of drug but could only detect 6.6 ug/ml of ADA in the presence of 1000 ug/ml of drug. Assay sensitivity is acceptable at 100 ug/ml of drug but not at 1000 ug/ml of drug. Results from PK studies indicate that Ctrough at steady state is ~182 ug/ml of drug. Therefore, the Agency does not know whether the sensitivity of the assay is acceptable at expected trough concentrations of drug. The Sponsor should provide information on the sensitivity of the assay at expected drug trough concentrations if they have it. If this information is not available, then we are concerned that ADA positive samples may have been missed in their analysis.

2) The only robustness data provided were freeze thaw results. The Sponsor should provide either validation or development information describing the robustness of critical assay parameters such as incubation times and temperatures for all immunogenicity assays.

3) The Sponsor did not explain how they chose the concentration of unlabeled drug used in the confirmatory assay, and how the concentration of the inhibitory r347TM and r347 antibodies in the triple mutation confirmatory assay were chosen. The Sponsor should provide this information.

4) Table 7.5-1 of validation report V-IM-0085 for the neutralizing antibody (NAb) assay shows that in the presence of 50 ug/ml of drug the assay can only detect 90 ug/ml of

NAb. Expected serum concentrations of drug in immunogenicity samples are around 182 ug/ml of drug. Therefore, the NAb assay may not detect NAb in patient samples. While ADA results indicate that 3 of 37 patients who tested confirmed positive from the screening assay also tested positive for NAb, what assurance can the Sponsor provide that NAb rates are not under-reported because of interference from on-board drug.

5) The immunogenicity results provided in the BLA do not include an analysis of patient samples at an interval most likely to detect IgM ADA, such as 7 - 14 days post treatment. Provide plans to collect serum samples at a post treatment point and analyze the samples for IgM ADA.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly Ballard

Digitally signed by Kelly Ballard
Date: 2/17/2017 09:22:21AM
GUID: 57e29be6020b38ae4817a9d8118b31c1

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**INFORMATION REQUEST**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated and received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for durvalumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB February 21, 2017 in order to continue our evaluation of your application.

*Section 3.2.P.2, Pharmaceutical development*

1. Confirm that there is no significant growth of organisms at 2 - 8°C in the drug product diluted with 0.9% sodium chloride and 5% dextrose by performing microbiological challenge studies with diverse microorganisms to support the 24 hour storage time. Your study should include Gram negative microorganisms (such as E. coli and/or E. cloacae) which are known to proliferate in these solutions. The challenge studies should include at a minimum time points at twice the label claim storage time. These studies can be completed as a post-marketing commitment.

*Section 3.2.P.3.3, Description of Manufacturing Process and Process Controls*

2. Clarify whether the (b) (4) bioburden sample taken (b) (4) is taken (b) (4)

3. State the (b) (4) integrity testing of the (b) (4) in Section 3.2.P.3.3 and/or 3.2.P.3.4.

*Section 3.2.P.3.4, Controls of Critical Steps and Intermediates*

4. We acknowledge the overview of the microbial control strategy provided in Section 3.2.P.3.4, Controls of Critical Steps and Intermediates. However, numerical acceptance criteria are not provided in the updated submission. Provide the numerical acceptance criteria, limits, and/or specifications for critical process parameters (b) (4)

controls in Section 3.2.P.3.4 for microbial quality attributes. Additionally, provide a table listing the qualified hold times from a microbial quality perspective for each process step. Update Section 3.2.P.3.4 accordingly.

*Section 3.2.P.3.5, Process Validation and/or Evaluation*

5. Clarify whether the validated container closure integrity test (CCIT) is the routine test used for container closure integrity.

*Section 3.2.P.5.2, Analytical Procedures*

6. We acknowledge the brief descriptions of the (b) (4) bioburden testing method and the DP release methods in your response. However, Section 3.2.P.5.2 has not been updated with this information. Update Section 3.2.P.5.2 to include brief descriptions of the (b) (4) bioburden testing method and DP release test methods, such as the sterility test and endotoxin method.

*Section 3.2.P.5.3, Validation of Analytical Procedures*

7. Provide summaries of the sterility test validations performed at (b) (4) Include the lots used for testing, the number of units and the total sample volume tested, the (b) (4) and the acceptance criteria for passing the sterility test. Update Section 3.2.P.5.3 of the BLA accordingly.

8. Explain the difference between the maximum valid dilution of (b) (4) used for the endotoxin enhancement/inhibition validation studies performed at (b) (4) and the maximum valid dilution of (b) (4) used in routine testing.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly Ballard

Digitally signed by Kelly Ballard
Date: 2/15/2017 01:06:43PM
GUID: 57e29be6020b38ae4817a9d8118b31c1

**PeRC Meeting Minutes**
**January 18, 2017**

**PeRC Members Attending:**
Lynne Yao
John Alexander
Jacquline Yancy
Gettie Audain
Wiley Chambers
Kevin Krudys
Lily Mulugeta
Freda Cooner
Skip Nelson
Gil Burkhart
Barbara Buch
Gregory Reaman
Gerri Baer
Julia Pinto
Dionna Green
Adrienne Hornatko-Munoz
Rachel Witten
Maura O'leary
George Greeley

**Agenda**

| | |
|---|---|
| 9:00 | NON-RESPONSIVE |
| 9:50 | |
| 10:00 | |
| 10:10 | |
| 10:30 | |
| 10:50 | |
| 11:05 | |
| 11:15 | |
| 11:25 | |
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|---|---|---|---|---|---|
| | BLA 761069 | Imfinzi (durvalumab) Full Waiver with an Agreed iPSP | DOP2 | Janice Kim | Urothelial bladder cancer |

7 Page(s) have been Withheld in Full as NON-RESPONSIVE immediately following this page

NON-RESPONSIVE

**Imfinzi (durvalumab) Full Waiver with an Agreed iPSP**

- Proposed Indication: Urothelial bladder cancer
- *PeRC Recommendations:*
  - The PeRC agreed with the plan for Full Waiver.

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/s/

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JACQULINE A YANCY
02/15/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Tuesday, February 07, 2017 6:41 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request:

1. RS.xpt does not include target response by investigator assessment. Please provide a revised dataset that includes this measure.

Please submit a response by February 9, 2017 by 2pm 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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janice.kim@fda.hhs.gov

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/s/

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JANICE H KIM
02/08/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Tuesday, February 07, 2017 5:18 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request: Promotional Material

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information regarding promotional material:

**PROMOTIONAL MATERIAL**

We will review this application under the provisions of 21 CFR 601 Subpart E – *Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 601.45, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf ).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

Thank you,

Janice Kim

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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janice.kim@fda.hhs.gov


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/s/

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JANICE H KIM
02/08/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, February 08, 2017 9:28 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 IR

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request:

- Please provide the names of the dataset and the variables used to calculate the **Duration of response** and **Ongoing response rate** in Table 14.2_1.1.6.3.1 for the 182 patients.

Please submit a response by February 9, 2017 before 2pm EST 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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janice.kim@fda.hhs.gov

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JANICE H KIM
02/08/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, February 08, 2017 2:41 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request for your BLA 761069:

Reference is made to the CD-ON-MEDI4736-1108, D4191C00003 Population PK Study Report. Please submit the datasets, model control streams, and output files for the simulations in Section 6.7.3 (Comparison of body weight-based versus fixed dosing regimens using simulations). In addition, please summarize the simulation results in a table as shown below.

| PK metric | WT based dosing Geometric Mean (%CV) | Flat dosing Geometric Mean (%CV) | % Difference in Geometric Means | WT based dosing Median ($5^{th}$, $95^{th}$ Percentile) | Flat dosing Median ($5^{th}$, $95^{th}$ Percentile) |
|---|---|---|---|---|---|
| $AUC_{ss,\ 0\text{-}14\ days}$ | | | | | |
| $Cmax_{ss}$ | | | | | |
| $Cmin_{ss}$ | | | | | |

Please response no later than 2/13/2017 by 2pm 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
Tel: 301-796-9628
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janice.kim@fda.hhs.gov

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/s/

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JANICE H KIM
02/08/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Friday, February 03, 2017 2:30 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 IR

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request for your BLA 761069:

1. Please provide the full CRFs (including prior therapy) for all bladder cancer patients with narratives. Provide a timeline when these will be available.

Please provide a response by Monday February 6, 2017 by 2pm 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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janice.kim@fda.hhs.gov

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/s/

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JANICE H KIM
02/06/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Friday, February 03, 2017 2:30 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 IR

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request for your BLA 761069:

1. Please provide the full CRFs (including prior therapy) for all bladder cancer patients with narratives. Provide a timeline when these will be available.

Please provide a response by Monday February 6, 2017 by 2pm 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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/s/

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JANICE H KIM
02/06/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Friday, February 03, 2017 9:54 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request from our clinical team regarding your BLA 761069:

1. Two patients have a missing histology per the FA.xpt dataset and do not have CRFs available. Please confirm the histology of these two patients:

CD1108/13720012551
CD1108/20011902365

Please indicate histology for these patients.

Please submit a response by Monday, February 6, 2017 2pm EST 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
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JANICE H KIM
02/03/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**INFORMATION REQUEST**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated and received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for durvalumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB February 9, 2017 in order to continue our evaluation of your application.

***Section 3.2.S.2.2, Description of Manufacturing Process and Process Controls***

1. Provide a diagram of the durvalumab drug substance manufacturing process indicating the following for each step:

(b) (4)

2. It appears that the test volume used for durvalumab (b) (4) prior to harvest is (b) (4) mL. Increase the (b) (4) testing volume to (b) (4) mL to allow sufficient sensitivity of the bioburden test.

3. Clarify if bioburden test or microbial checks are routinely performed (b) (4) .

(b) (4)

a. If [redacted] bioburden limits being exceeded.

b. If bioburden and endotoxin are monitored [redacted]

***Section 3.2.S.4, Control of Drug Substance***

5. Submit to the BLA (section 3.2.S.4.2) a description of the bioburden test method used for [redacted] release samples; include test sample volumes, dilutions used (if applicable), preparation of positive and negative controls, and incubation conditions. In addition, clarify what samples are analyzed [redacted]

6. Submit to the BLA (section 3.2.S.4.3) the qualification report demonstrating suitability of the bioburden [redacted] release samples.

***Section 3.2.P.2, Pharmaceutical development***

[redacted]

***Section 3.2.P.3.3, Description of Manufacturing Process and Process Controls***

[redacted]

(b) (4)

***Section 3.2.P.3.4, Controls of Critical Steps and Intermediates***

13. Provide a summary of the critical process parameters (b) (4) controls in Section 3.2.P.3.4 from a microbial control and sterility assurance perspective.

***Section 3.2.P.3.5, Process validation and/or evaluation***

14. Summarize the results of the process validation studies performed for the two durvalumab presentations in Section 3.2.P.3.5 from a sterility assurance perspective.

15. Indicate the temperatures for the summer and winter profiles used in the shipper qualification studies.

16. Provide the details of routine drug product shipping, [redacted]

17. Provide a summary description of studies and data supporting the shipping validation for ground and air shipping of durvalumab drug product, clarify the temperature profiles used during these studies, and summarize the TempTale monitoring data for these studies.

***Section 3.2.P.5.2, Analytical Procedures***

18. Update Section 3.2.P.5.2 to include brief descriptions of the [redacted] bioburden testing method and DP release test methods, such as the sterility test and endotoxin method. The [redacted] bioburden test method should include the sample volumes tested, [redacted]. The sterility test method description should include the number of units and the total sample volume tested, [redacted] and the acceptance criteria for passing the sterility test. The endotoxin test method description should include identification of the LAL test method, preparation of the samples and standards, the dilutions(s) used for routine testing, the maximum valid dilution, the conditions for assay validity (negative control, positive controls, etc.), and the acceptance criteria for recovery.

***Section 3.2.P.5.3, Validation of analytical procedures***

19. Provide the results of the [redacted] testing for durvalumab DP, as discussed in report VX-604300, PQP, R1. Please summarize the results and provide a brief narrative in the BLA. Update Section 3.2.P.5.3 of the BLA according.

20. Indicate the supplier of the [redacted] for the endotoxin recovery studies.

21. The rabbit pyrogen test summary and validation report should be provided in Section 3.2.P.5.3. Please update the BLA accordingly.

***Section 3.2.P.5.6, Justification of specifications***

22. The drug product endotoxin release specification of ≤ [redacted] EU/mg based on the maximum dose of 50 mg/kg does not allow for a minimum 2-fold safety. Please adjust the endotoxin specification to allow for the minimum 2-fold safety factor, or alternatively provide a justification.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly Ballard

Digitally signed by Kelly Ballard
Date: 2/02/2017 03:10:01PM
GUID: 57e29be6020b38ae4817a9d8118b31c1

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, February 02, 2017 10:02 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you're the following information request for your BLA 761069 in regards to your container label and carton labeling:

1. The strength per total volume should be the primary and prominent expression on the principal display panel.[1] Reduce the prominence of the strength per mL (50 mg/mL) either by reducing the font size or de-bolding the "(50 mg/mL)" statement to minimize the risk of confusion where users fail to determine the total amount of the drug in the container.

2. (b) (4)

Reference: [1] 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

Please submit a response by Friday, February 10, 2017 with the **revised container labels and carton labeling** 1) by email to facilitate review 2) and by official submission to your BLA.

Regards,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**

**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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janice.kim@fda.hhs.gov

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/s/

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JANICE H KIM
02/02/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, February 02, 2017 11:00 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request from our review team for your BLA 761069:

The following six patients had a radiographic progression on the PDL1 high group.

CD1108/2000133952
CD1108/20000421521
CD1108/20002212430
CD1108/20002282396
CD1108/20004391842
CD1108/20011902357

There were 26 patients in this group that had a response (PR/CR) which implies that 20 patients have an ongoing response. Please clarify as to why 19 patients are mentioned with ongoing response in Table 14.2_1.1.6.3.1

Please submit a response by Monday, February 6, 2017 by 2pm 1) by email to facilitate review 2) and by official submission to your BLA.

Regards,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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Fax: 301-796-9845
janice.kim@fda.hhs.gov

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JANICE H KIM
02/02/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, February 02, 2017 1:38 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request for BLA 761069:

1. Please provide a dataset indicating the date of disease progression following prior therapy for the 2nd-line post-platinum cohort.

Please submit a response by 2pm February 6, 2017 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
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JANICE H KIM
02/02/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, February 02, 2017 2:55 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request for your BLA 761069:

**Carton Labeling**:

1. The display of the manufacturing information is incorrect. The Applicant on the Form FDA 356h is considered the licensed manufacturer. Therefore, the labeling must show "Manufactured by: Applicant name, address, license number" per 21 CFR 610.61(b)". For example: Manufactured by: AstraZeneca UK Limited, 1 Francis Crick Ave, Cambridge England CB2 0AA, US License number xxxx.

   If this is fulfilled, then you have the option of labeling a distributor per 21 CFR 610.64. For example "Manufactured for AstraZeneca Pharmaceutics LP, Wilmington DE 19850."

**Container Label**

1. See manufacturer information above. Because this is a partial label per 21 CFR 610.60(c), only the manufacturer name is required. If space permits, you can label the manufacturer name, address, and license number as explained above.

Please submit a response by 2 pm on February 10, 2017 1) by email to facilitate review and 2) by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
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JANICE H KIM
02/02/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, February 01, 2017 5:33 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA761069 Clinical information request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following clinical information request for your BLA 761069:

1. There are discrepancies between the sites of disease at baseline in the BASE2LPP dataset and the TU dataset. In the BASE2LPP dataset, there are 78 patients with liver lesions, 99 with lung lesions, and 54 with bone lesions. However, in the TU dataset, setting TUACPTFL =Y and VISIT = BASELINE, there are only 181 patients with baseline results (missing patient 20002282528). There are only 62 patients documented as having a liver lesions (63 if biliary tract location is added). There are only 79 patients with lung lesions (87 if pleural and pleural fluid lesions are included). There are only 34 patients with bone lesions (64 if pelvis lesions are included). Please reconcile these discrepancies and indicate how the flags for site of disease in the BASE2LPP dataset were created.
2. The nature of the protocol violation for patient CD1108/20010902512 is unclear. Please provide the patient's prior therapies and dates relative to enrollment.

Please submit a response by February 3, 2017 by 2pm EST 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
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JANICE H KIM
02/01/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Friday, January 27, 2017 3:50 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Durvalumab Clinical Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request from our clinical review team:

1. Seven patients in the ISS ADAE dataset are reported as experiencing “endocrinopathy” under AEDECOD without further specification. Please provide granularity as to what disorders these events represent.

Please submit a response by February 1, 2017 by 2pm EST 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
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JANICE H KIM
01/31/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**MID-CYCLE COMMUNICATION**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Imfinzi (durvalumab) Injection.

We also refer to the teleconference between representatives of your firm and the FDA on January 25, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-9628.

Sincerely,

*{See appended electronic signature page}*

Janice Kim, PharmD, MS
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MID-CYCLE COMMUNICATION

**Meeting Date and Time:** January 25, 2017; 9:00AM – 10:00AM

**Application Number:** BLA 761069
**Product Name:** durvalumab
**Indication:** Treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4)
**Applicant Name:** AstraZeneca UK Limited
**Meeting Chair:** V. Ellen Maher, MD
**Meeting Recorder:** Janice Kim, PharmD, MS

## FDA ATTENDEES

Geoffrey Kim, MD, Director, DOP1
Ellen Maher, MD, Cross Discipline Team Leader, DOP1
Daniel Suzman, MD, Clinical Reviewer, DOP1
Laura Fernandes, PhD, Biostatistics Reviewer, DBV
Stacy Shord, PharmD, Clinical Pharmacology, DCPV
Yuhong Chen, PhD, Clinical Pharmacology Reviewer, DCPV
William Pierce, PharmD, CAPT, USPHS, Associate Director Labeling, DOP1
Janice Kim, PharmD, MS, Regulatory Project Manager, DOP1

## APPLICANT ATTENDEES

Hesham Abdullah, MD, MSc, RAC, VP, Regulatory Affairs, Oncology
Alex Batkhan, MS Associate Director, Statistical Programming
Yong Ben, MD, MBA, Global Clinical Lead, Immuno-Oncology
Jamie Gillette, MSc, RAC, Regulatory Affairs Director, Oncology
Ashok Gupta, MD, PhD, VP Immune-Mediated Therapy, Oncology
Tony Ho, MD, Global Medicines Leader, Durvalumab
Robert Iannone, MD, MSCE, Global Head, Immuno-oncology
Praveen Marapaka, PhD, Senior Director, Regulatory Affairs, Oncology
Pralay Mukhopadhyay, PhD, Senior Director and Biometrics Team Lead
Rajesh Narwal, PhD, Principal Scientist, Clinical Pharmacology and DMPK
Ajay Parashar, BPharm, MDD, MS, RAC, Associate Director, Labeling Strategy
Lorin Roskos, Vice President, R&D
Li Shi, PhD, Senior Director, Clinical Statistics
Magdalena Zajac, PhD, Associate Diagnostic Expert
Wenmei Huang, PhD, Principal Statistician
Marlon Rebelatto, DVM, PhD, Principal Pathologist

## 1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 2.0 SIGNIFICANT ISSUES

The indication statement you submitted is not consistent with the indication statement for atezolizumab in an identical population. Please provide your rationale for your indication statement and discuss possible changes to the indication statement to conform to other approved products.

**Meeting Discussion:**

- The Applicant agreed to an indication statement identical to that of atezolizumab.
- To provide data from all 182 second-line post-platinum patients.
- Clinical Pharmacology to consider AstraZeneca's proposal of fixed dose of (b) (4) mg every 2 weeks

## 3.0 INFORMATION REQUESTS

A number of information requests have been communicated to the Applicant. It is likely that additional information requests will be sent.

## 4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns and there is no plan for a REMS. Postmarketing requirements/commitments to submit long term safety and efficacy data may be needed.

## 5.0 ADVISORY COMMITTEE MEETING

No plans at this time for an AC Meeting.

## 6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for March 6, 2017.

We intend to send the briefing package to you approximately 2 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of the review. You may choose altogether to cancel the Late Cycle Meeting, if you feel it is not needed, given our continued and regular communications. The PDUFA Action Date is June 13, 2017.

APPEARS THIS WAY ON ORIGINAL

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JANICE H KIM
01/31/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Tuesday, January 31, 2017 1:35 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Clinical Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following clinical information request:

1. Please indicate whether there were any patients in the primary efficacy population without IRC-confirmed measureable disease who were treated. Additionally, please indicate whether the radiologists who assessed the baseline disease assessment were the same as those who performed the on-treatment assessments.
2. Patient 20011902357 does not have measureable disease at baseline per the IRC. Please indicate if this patient was considered a responder in your analyses.
3. Provide additional details regarding Grade 2 myositis in patient 20022522574 and Grade 1 arthritis in patient 13711011923, particularly concerning the timing, outcome, imaging, and use of corticosteroids.

Please submit a response by February 5, 2017 by 2pm 1) by email to facilitate review 2) and by official submission to you BLA.

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
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JANICE H KIM
01/31/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Friday, January 27, 2017 11:58 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Clinical Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following clinical information request:

1. Your ISS dataset ADIMAE.xpt reports 7 patients with immune-mediated adrenal insufficiency. However, the ADAE.xpt dataset notes 14 patients with adrenal insufficiency, including 7 patients in the 1108 dataset that received steroids. The ADCM dataset for ATLANTIC has not been provided. Please provide a justification for why these additional 7 patients were not considered to have experienced immune-mediated adrenal insufficiency. Additionally, please provide an integrated summary dataset of concomitant medications.

Please submit a response by February 1st 2017 by 2pm EST 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice Kim

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
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JANICE H KIM
01/27/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, January 26, 2017 6:56 AM
**To:** 'Gillette, Jamie'
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request:

Please indicate if an IDMC was in place and if so, submit the IDMC reports and meeting minutes for this application.

Please respond by 2pm 1/27/2017 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

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JANICE H KIM
01/26/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Friday, January 13, 2017 10:57 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Clinical Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following clinical information request based on your previous response on November 26, 2016 to our information request:

Thank you for previously providing data on patients with autoimmune diseases who were enrolled in clinical trials across the durvalumab development program.
We are collecting these data in an effort to potentially allow for clinicians to treat patients with autoimmune diseases with durvalumab, as to date little data has been known on the safety of doing so.

Please provide the following data for each of these patients:

1. Name of autoimmune disease
2. Active/corticosteroid-dependent at baseline?
3. Duration of dosing with durvalumab
4. Any irAEs while on durvalumab
5. Worsening of underlying autoimmune disease while on study?
6. Requirement for steroids for AEs while on study?
7. Patient outcome (disposition)

Please provide a response by January 23, 2017 by 4pm 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice Kim

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
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JANICE H KIM
01/13/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, January 11, 2017 5:16 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Clinical Information Request

Dear Ms. Gillette,

The purpose of this email is to convey the following information request from the clinical review team:

1. Please clarify the column "TXTYPE" in the ADCM dataset; indicate whether "PRIMARY" refers to de novo metastatic disease and "RECURRENCE LOCALLY ADVANCED OR METASTATIC" refers to disease that was previously treated in the non-metastatic setting.
2. Patient 10025012482 has missing entries for TXTYPE in ADCM, but is listed as having received carboplatin and gemcitabine as well as having received radiation therapy with an unknown date. However, the administration of prior chemotherapy and radiation therapy is not documented anywhere in this patient's CRF and the "Prior Cancer Treatments" section appears to be missing. "Prior Cancer Treatments" appears to be missing from the CRF of several other UC patients as well. Please indicate the source documentation for prior cancer therapies for all other patients in the UC cohort.

Please submit a response by January 18, 2017 by 2pm 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
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JANICE H KIM
01/12/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Monday, January 09, 2017 6:20 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 671069 Information Request

Dear Ms. Gillette,

The purpose of this email is to request you to resend SDTM TR dataset from the 90 day update, as it is not present or loading correctly.

Please re-submit the dataset by Monday January 9, 2017 by 5pm EST 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
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JANICE H KIM
01/09/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Monday, January 09, 2017 10:17 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Clinical Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following clinical information request:

1. Patient CD1108/13717012466 is documented as having PR despite a new lesion occurring on Disease Assessment 1. Provide additional detail on this new lesion marked as “equivocal” to justify why this represents a PR.

Please submit a response by January 11, 2017 2pm EST 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
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JANICE H KIM
01/09/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, January 05, 2017 1:30 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 IR

Dear Ms. Gillette,

The purpose of this email is to convey to you the following clinical information request:

1. Patient CD1108/13717011648 is classified as being in PR at Disease Assessment 1, but has a new lesion at Disease Assessment 4. Additionally, this patient is classified as being in CR at Disease Assessment 6. Please provide an explanation for characterizing the new lesion at Disease Assessment 4 as not representing progressive disease.

Please submit a response by January 10th 2017 by 2pm 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
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JANICE H KIM
01/05/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, January 05, 2017 1:43 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** RE: BLA 761069 Information Request

Dear Ms. Gillette,

We received your submission to the responses to our comments. However, you did not submit the revised container labels with the "Must dilute before use. See prescribing information." on side panel of the container label. Can you submit a revised container label?

Thank you,

Janice Kim

---

**From:** Gillette, Jamie [mailto:Jamie.Gillette@astrazeneca.com]
**Sent:** Wednesday, January 04, 2017 3:37 PM
**To:** Kim, Janice
**Cc:** Kacuba, Alice
**Subject:** RE: BLA 761069 Information Request

Dear Janice,
Please find attached our response to the information request below. We are submitting this response officially to the BLA today.
If you need any additional information, please let me know.
Best regards,
Jamie

**Jamie Gillette, MSc, RAC**
Regulatory Affairs Director, Oncology

**AstraZeneca** | Global Medicines Development | GRAPSQA
200 Orchard Ridge Drive, Gaithersburg, MD 20878
T: (301) 398-5510 F: (301) 398-4018 (b) (6)
**jamie.gillette@astrazeneca.com**

---

**From:** Kim, Janice [mailto:Janice.Kim@fda.hhs.gov]
**Sent:** Thursday, December 29, 2016 5:25 PM
**To:** Gillette, Jamie <Jamie.Gillette@astrazeneca.com>
**Cc:** Kacuba, Alice <Alice.Kacuba@fda.hhs.gov>
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey the following information request from our labeling team:

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

**a. Replace the statement "IMFINZI is a trademark of the AstraZeneca group of companies © AstraZeneca XXXX" with "Must dilute before use. See prescribing information." on the side panel to minimize the risk of the product administered without dilution.**

**b. Clarify what the (b) (4) box is on the side panel.**

Please provide a response by January 4th by 2 pm 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice Kim

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
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JANICE H KIM
01/05/2017

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, January 04, 2017 8:29 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Clinical Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request for BLA 761069 (durvalumab) from our clinical review team:

1. Your submission includes 38 patients who were positive for post-baseline ADAs out of 1163 evaluable patients. However, using the adza.xpt file from the 90-day update, there were 1153 patients treated with 10 mg/kg durvalumab with a post-baseline ADA result, of whom 1111 had a negative baseline result. There were additionally 6 patients with a positive baseline ADA who had an increase in titer with therapy. In the dose escalation cohort, 38 patients with a negative titer at baseline and a post-baseline ATA level. Of these 1155 patients (1111+6+38), there were 43 patients with a positive post-baseline ADA titer (including 5 with a positive titer at baseline, but increase in titer on follow-up). Please indicate the methodology by which you determined the numerator and denominator for your ADA frequency.
2. Provide additional data regarding the patients with neutralizing antibodies including response and toxicity. Please provide the result of the renal biopsy and additional information regarding the infusion reaction in patient D4191C00003/E6002035.

Please submit a response by January 9, 2017 by 2pm 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
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JANICE H KIM
01/04/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**INFORMATION REQUEST**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated and received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for durvalumab.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB January 18, 2017 in order to continue our evaluation of your application.

1. The DP release and stability acceptance criteria for Appearance-Visible Particles is the product [redacted] (b) (4) There is a concern that this may allow for release of DP that contains impurities that pose a risk to patient safety. The BLA contains no justification or characterization results for these potential impurities. Update the BLA to provide an assessment for the risk [redacted] (b) (4) impurities may pose to the patients. Also provide a summary of the frequency [redacted] (b) (4) are observed in DP vials.

2. The DP Extractable Volume specification is ≥ [redacted] (b) (4) ml for the 500 mg/vial and ≥ [redacted] (b) (4) ml for the 120 mg/vial. The upper limit of the Extractable Volume is needed to prevent excessive overfills for a single use vial. Update the DP release acceptance criteria to include an upper limit for Extractable Volume. For additional information please see the FDA 2015 Guidance - Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products.

3. The proposed DP stability specifications do not include a method for Osmolality, Extractable Volume, or Total Protein. This DP stability control strategy is deficient because there are no specifications to monitor the [redacted] (b) (4) Update the DP stability specifications to include a method to monitor for [redacted] (b) (4)

4. The DP release and stability testing strategy in Table P.5.1-1 does not contain a test to monitor [redacted] (b) (4) This control strategy is deficient because there is a risk

[redacted] Update the DP release and stability control strategy [redacted]

5. The DP comparability results in the section P 2.3 (Manufacturing Process Development) [redacted] rovide an assessment of [redacted] characterization results [redacted]

6. The DP release and stability specifications include a method to quantify Sub-Visible Particles ≥ [redacted] µm and ≥ [redacted] µm. However there is no commitment in the BLA to include a method to monitor for the levels of Sub-Visible Particles [redacted] m. Update the BLA to contain a commitment to monitor for Sub-Visible Particles ≥ [redacted] µm. These particles can adversely affect product quality because they may increase the risk of immune response. A specification for Sub-Visible Particles should be established after sufficient results become available.

7. The BLA indicates that some DS release and stability testing methods have been validated and transferred to the DS manufacturing facility at Frederick. However, the method transfer reports are not provided in the BLA to support the method validation. Provide a summary table and indicate which methods were validated at the Frederick Facility or validated at somewhere else. For the methods not validated at the Frederick facility update the BLA and submit the method transfer reports.

8. Table S.3.2.2.1-2 in Characterization section indicates that the method for host cell DNA (HCD) was validated [redacted] validation lots. There is no description of the HCD method in the BLA. Provide a summary of the HCD method and the method validation report. This information is need for the FDA to better evaluate the HCD levels reported in Table S.3.2.2.1-2.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly Ballard

Digitally signed by Kelly Ballard
Date: 1/04/2017 03:12:53PM
GUID: 57e29be6020b38ae4817a9d8118b31c1

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, January 04, 2017 2:07 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 IR

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request from the clinical review team for your BLA 761069:

1. Please provide a dataset and analysis of AEs that began prior to 7/24/2016, were not included in the dataset with 7/24/2016 DCO, but were included in the 90-day safety update.

Please submit a response by January 9, 2017 by 2 pm by 1) email to facilitate review and 2) by official submission to your application.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@fda.hhs.gov

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/s/

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JANICE H KIM
01/04/2017

## Kacuba, Alice

**From:** Kacuba, Alice
**Sent:** Thursday, December 29, 2016 1:01 PM
**To:** Gillette, Jamie (Jamie.Gillette@astrazeneca.com)
**Cc:** Kim, Janice
**Subject:** 12-29-16----- Clinical Information Request for Durvalumab BLA

**Importance:** High

Dear Jamie,

The purpose of this email is to communicate the following Clinical Information Request for your application. Please provide a response by 1 pm Jan. 6, 2017 by 1) email to facilitate review and 2) by official submission to the official application..

1. The following patients had a date of last platinum chemotherapy administration greater than 1 year prior to their first dose of durvalumab. Please provide confirmation that these patients met your eligibility criteria for 2nd-line post-platinum status.
    a. CD1108/20000421521
    b. CD1108/20000891013
    c. CD1108/20010231897

2. Provide a death narrative for patient CD1108/20010902512. The current narrative describes an event of sepsis but not the patient's death. Clarify whether classification as progressive disease was based on radiographic or clinical parameters.

Thank you.
Alice

**Alice Kacuba, RN, MSN, GWCPM, RAC**
*Chief, Project Management Staff*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
Tel: 301-796-1381
Fax: 301-796-9845
alice.kacuba@fda.hhs.gov

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/s/

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ALICE KACUBA
12/29/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, December 29, 2016 5:25 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Dear Ms. Gillette,

The purpose of this email is to convey the following information request from our labeling team:

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

**a. Replace the statement "IMFINZI is a trademark of the AstraZeneca group of companies © AstraZeneca XXXX" with "Must dilute before use. See prescribing information." on the side panel to minimize the risk of the product administered without dilution.**

**b. Clarify what the (b) (4) box is on the side panel.**

Please provide a response by January 4th by 2 pm 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice Kim

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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janice.kim@fda.hhs.gov

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/s/

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JANICE H KIM
12/29/2016

## Kacuba, Alice

**From:** Kacuba, Alice
**Sent:** Wednesday, December 28, 2016 12:16 PM
**To:** Gillette, Jamie (Jamie.Gillette@astrazeneca.com)
**Cc:** Kim, Janice
**Subject:** 12-28-16 Clinical IR

**Importance:** High

Dear Jamie,

The purpose of this email is communicate an Information Request from Clinical. Please respond by 1/5/17 by 1) an email to facilitate review and 2) by an official submission to your BLA.

1. There are several discrepancies in the progressive disease results. For example, patient CD1108/20001342423 is listed in the ADRS dataset as having PD at the first visit due to a new lesion and a 13.1% increase in tumor size from baseline. However, in the 90 day safety update, this patient is listed as having PD at the first visit due to a 103.9% change from baseline with no new lesion. Patient CD1108/20002211906 is listed in the ADRS dataset as having PD at the first visit despite no new lesions and a 30% decrease in tumor size from baseline. However, in Table 16.2_6.5.2.2, this patient is listed as having a PR with a 40% decrease in tumor size from baseline. In the 90 day safety update, this patient is listed as having PD with a 30% decrease in tumor size from baseline and no new lesions. You should provide an explanation of these discrepancies and perform a systematic analysis to ensure that any discrepancies are resolved.

2. Provide the number of patients remaining on therapy as of the three DCO dates (7/24, 10/24, and the January cut-off). Additionally, provide a breakdown for each of these three dates of the number of patients who are being treated beyond progression.

Thank you.
Alice (for Janice Kim)

**Alice Kacuba, RN, MSN, GWCPM, RAC**
*Chief, Project Management Staff*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
Tel: 301-796-1381
Fax: 301-796-9845
alice.kacuba@fda.hhs.gov


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/s/

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ALICE KACUBA
12/28/2016

## Kacuba, Alice

**From:** Kacuba, Alice
**Sent:** Tuesday, December 27, 2016 12:32 PM
**To:** Gillette, Jamie (Jamie.Gillette@astrazeneca.com)
**Cc:** Kim, Tamy (Tamy.Kim@fda.hhs.gov)
**Subject:** FW: Durvalumab IR

**Importance:** High

Hi, Happy Holidays.

Here is a Clinical Information Request. We request a response by 2 pm Jan. 4, 2017 by 1) email to facilitate review and 2) an official submission to your application.

1. The Independent Review Charter states that the independent radiologist will perform a global radiology review following the primary review. Please comment whether any tumor responses required adjudication and, if so, which patients this occurred in. Additionally, Section 8.2 of the Charter states that re-review may be conducted under exceptional circumstances. Please state whether this occurred and, if so, what the circumstances were.

Thank you.
Alice (for Janice Kim)

**Alice Kacuba, RN, MSN, GWCPM, RAC**
*Chief, Project Management Staff*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
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alice.kacuba@fda.hhs.gov

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/s/

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ALICE KACUBA
12/27/2016

## Kacuba, Alice

**From:** Kacuba, Alice
**Sent:** Tuesday, December 27, 2016 2:26 PM
**To:** 'Jamie.Gillette@astrazeneca.com'
**Cc:** Kim, Janice
**Subject:** Clinical Information Request for Durvalumab BLA

**Importance:** High

Good afternoon,

The purpose of this email is to communicate with you a 2nd round of Clinical Information Requests. Please response by 2 pm Jan 4, 2017 by 1) email and 2) official submission to the application.

1. Indicate whether the global radiology review resulting in any changes in tumor measurements or the status of new lesions and if so, what these changes were.
2. Indicate whether there were any lesions that met RECIST criteria for PD, but were not recorded as PD.
3. Clarify which patients had their baseline scans assessed for measurable disease prior to treatment. Clarify what the procedure was if the radiologist reviewing the baseline scan disagreed with the radiologist assessing response.

Thank you.
Alice (for Janice Kim)

**Alice Kacuba, RN, MSN, GWCPM, RAC**
*Chief, Project Management Staff*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
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alice.kacuba@fda.hhs.gov

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/s/

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ALICE KACUBA
12/27/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, December 21, 2016 12:20 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 durvalumab information request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following clinical information request:

1. There are five patients with baseline tumor measurement by investigator but not by IRC. Additionally, there are two patients with null baseline tumor measurement values by IRC. Please indicate the reasons for lack of IRC-reviewed tumor baseline measurements in these 7 patients. These patients are listed below:
   CD1108/20001122360
   CD1108/20001242380
   CD1108/20002282391
   CD1108/20002282412
   CD1108/20006782366
   CD1108/20001131668
   CD1108/20002092413

2. Please update the baseline analysis dataset (including provided as per the response submitted December 19th to include all 182 2nd-line post-platinum patients.

Please respond to this request by December 28, 2016 by 1) email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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janice.kim@fda.hhs.gov


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/s/

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JANICE H KIM
12/21/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**INFORMATION REQUEST**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated and received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for durvalumab.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB January 10, 2017 in order to continue our evaluation of your application.

1. The efficacy of durvalumab in urothelial cancer is based on the results provided in clinical trial CD-ON-MEDI4736-1108 (1108). Table S.2.6.3.1-1 (Genealogy and Use of the Durvalumab Lots) in the Manufacturing Process Development section indicates that multiple DS lots (b) (4) were used in clinical trial 1108. Clinical trial 1108 evaluated the product for treatment of a variety of different types of solid tumors and used 10 DP lots derived from 10 different DS lots. DS lots YL5034, BJ5070, BK5014, BJ5013, and BJ5017 were used in the physicochemical comparability studies (b) (4) . It is unclear in the BLA which urothelial patients in clinical trial 1108 received which of the 10 DS lots. Provide a table and list all the DS lots and corresponding DP lots that have been in clinical trial 1108 for the urothelial cancer indication and the other cancer indications. Indicate what percentage of the total urothelial cancer patients received the DP lots derived from the DS lots that were evaluated in the comparability studies (lots YL5034, BJ5070, BK5014, BJ5013, and BJ5017). This information is important to evaluate the comparability strategy and analytical results

2. The Batch Analysis section of the BLA contains tables that list the release results for the DS and DP. However, the results are not graphically trended. A graphical trend analysis will help the FDA better determine if changes have occurred in any product attribute during development. Provide the batch analysis results graphically in control charts for the drug substance and product release results for reducing and non-reducing gel electrophoresis peaks, HPSEC peaks, cIEF peaks, and the AP-1 Reporter Gene Bioassay. On the control charts indicate the lot disposition (b) (4)

[redacted] the mean, three standard deviations, 95/99% confidence interval, and the proposed release specifications. Also indicate the lots evaluated in urothelial cancer patients. The information is required to determine if the proposed release specifications are supported by clinical and manufacturing experience.

3. The BLA indicates that a new working cell bank (WCB) was created for the manufacture [redacted] material. The BLA does not provide a reason or justification for creating a new working cell bank late in development. Provide a summary of the reasons the new WCB was created. This information will better help the FDA evaluate the impact of the process change on product quality.

4. The DS and DP release and stability acceptance criteria for Charge Heterogeneity by cIEF for % total basic peak is "report result". The acceptance criterion is not appropriate because it does not adequately control product quality. Update the BLA to specify a numerical range.

5. The DS and DP release and stability acceptance criterion for the AP-1 Reporter Gene Bioassay is [redacted]% of reference standard activity. The acceptance criterion range is too wide. Tighten the acceptance criterion to better reflect clinical and manufacturing experience.

6. The DS and DP release and stability acceptance criteria for HPSEC, cIEF (Charge Heterogeneity), reducing and non-reducing gel electrophoresis are deficient because they do not control for new peaks. Up the BLA to revise the specifications to include an acceptance criterion for no new peaks above the method limit of detection.

7. The introduction in section S.3.1.1 on page 1 states that reference standard PRS4736A is derived from [redacted] DS lot CF2289-01. However, in the batch analysis section Table S.4.4-3, on page 8, indicates that lot CF2289-01 is derived from the clinical [redacted] DS. Reference standard section indicates that the first lot working reference standard (WRS4736-1) was derived from [redacted] DS lot CF2289-01. Explain this discrepancy regarding the process used to manufacture DS lot CF2289-01. Update the BLA to accurately reflect the origin of DS lot CF2289-01.

8. Provide all the DS and DP stability results that were not provided in the original BLA. The stability updates will better help the FDA evaluate the proposed DS and DP expiries.

9. Table P.5.4-1 in the Batch Analysis section 3.2.P.5.4 for [redacted] product is labeled 500 mg/vial. However the Manufacturing section P.2.3, page 2, indicates the [redacted] clinical lots are [redacted] mg/vial. Update the BLA to reflect the correct strength of the [redacted] clinical lots.

**Immunogenicity**

10. The cut points for the anti-drug antibody (ADA) screening and confirmatory assays are too high and the results may not reflect the actual incidence and titer of ADAs in patients.

The immunogenicity screening cut point is based on a 1% false positive rate, which instead should use a 5% false positive rate. In addition, the confirmatory immunogenicity assay cut point uses a 0.1% false positive rate, which instead should use a 1% false positive rate. Provide the new cut points for each assay and reevaluate the clinical data based on a 5% false positive rate for the screening assay and 1% false positive rate for the confirmatory assay. The BLA should be updated with the results. Additional information can be found in the 2016 FDA draft guidance – Assay Development and Validation for Immunogenicity Test of Therapeutic Protein Products.

11. The validation report (V-IM-0077) for the Screening Detection assay, the Confirmation assay, and Titration of the Anti-MEDI4736 Antibodies in Human Serum is provided in the BLA. However, the standard operating procedure for the methods is not provided. Provide the SOPs in order for the FDA to better evaluate the methods used in the immunogenicity analysis.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly Ballard

Digitally signed by Kelly Ballard
Date: 12/20/2016 03:26 01PM
GUID: 57e29be6020b38ae4817a9d8118b31c1

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**PROPRIETARY NAME REQUEST**
**CONDITIONALLY ACCEPTABLE**

AstraZeneca UK Limited
c/o AstraZeneca Pharmaceuticals LP
One MedImmune Way
Gaithersburg, MD 20878

ATTENTION: Jamie Gillette, MSc., RAC
Director, Global Regulatory Affairs

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated October 13, 2016, received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for Durvalumab, 50 mg/mL.

We also refer to your October 17, 2016, correspondence, received October 17, 2016, requesting review of your proposed proprietary name, Imfinzi.

We have completed our review of the proposed proprietary name, Imfinzi and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your October 17, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-0942. For any other information regarding this application, contact Janice Kim, Regulatory Project Manager in the Office of New Drugs, at 301-796-9628.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

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DANIELLE M HARRIS on behalf of TODD D BRIDGES
12/16/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, December 15, 2016 6:57 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 (durvalumab) clinical information request

Dear Ms. Gillette,

The purpose of this email is to convey to you the following information request from the clinical team:

1. Please provide data from Tables #1-6 in your regulatory response document dated 11/11/2016 as XPT datasets.
2. Provided updated data from all information requests once the IRC-reviewed data is available for all 182 2nd-line post-platinum patients.

Please submit a response by December 20, 2016 by 2pm 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you.

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@fda.hhs.gov

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JANICE H KIM
12/15/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**FILING COMMUNICATION –**
**NO FILING REVIEW ISSUES IDENTIFIED**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated October 13, 2016, received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for Imfinzi (durvalumab) Injection.

We also refer to your amendments dated July 29, 2016 and August 12, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is June 13, 2017. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

In addition, the planned date for our internal mid-cycle review meeting is January 13, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

We request that you submit the following Clinical Pharmacology Information Request:

Amend your proposed package insert (subsection 12.2) to include information on exposure-response relationships (e.g., concentration-response, dose-response) and time course of pharmacodynamic response (including short term clinical response), if known. If this information is unknown, this subsection must contain a statement about the lack of information.

## PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

## PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf ).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Janice Kim, Regulatory Project Manager, at (301) 796-9628.

Sincerely,

*{See appended electronic signature page}*

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology
Center for Drug Evaluation and Research

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/s/

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GEOFFREY S KIM
12/15/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Tuesday, December 13, 2016 2:00 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Durvalumab Clinical Information Request

Dear Jamie,

The purpose of this email is to convey the following clinical information request to you:

1. Regarding patient 20023712474, provide details regarding the patient's disease progression, including site of disease progression and absolute and percent change of the target lesions.
2. Provide the data from the IRC-reviewed results from the additional 52 patients with follow-up as of the DCO of 7-13 weeks.
3. When available, provide the investigator-reviewed and IRC-reviewed results from all 182 2$^{nd}$-line post-platinum patients once they have had at least 13 weeks of follow-up.

Please submit a response to this information request by December 20, 2016 by 2pm 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
Tel: 301-796-9628
Fax: 301-796-9845
janice.kim@fda.hhs.gov

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/s/

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JANICE H KIM
12/14/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**INFORMATION REQUEST**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated and received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for durvalumab.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB December 14, 2016 in order to continue our evaluation of your application.

Provide an updated manufacturing schedule for durvalumab drug substance at the MedImmune LLC Frederick Manufacturing Center (FMC), including details on the (b) (4) between January and February 2017.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly Ballard

Digitally signed by Kelly Ballard
Date: 12/12/2016 03:50 26PM
GUID: 57e29be6020b38ae4817a9d8118b31c1

## Kim, Janice

**From:** Kim, Janice
**Sent:** Friday, December 09, 2016 10:01 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 (durvalumab): clinical information request

Dear Ms. Gillette,

The purpose of this meeting is to convey to you an information request from the clinical review team:

1. Provide an analysis of steroid or other systemic immunosuppressive medication use in the 2nd line post-platinum UC patients (n = 182) and in the overall safety population consisting of all durvalumab-treated patients on Studies 1108 and ATLANTIC. Indicate the total number of patients in each population that:
    a. Received steroids (indicate ≥10mg/day and ≥40mg/day prednisone equivalent) or other systemic immunosuppressive medication (Provide subject ID for 182 UC patients only)
    b. Received steroids (as noted above) or other systemic immunosuppressive medication for an immune-mediated adverse event (Provide subject ID for 182 UC patients only). Indicate infusion-related/hypersensitivity events separately.
    c. In the UC cohort only, indicate which patients received hormone replacement therapy either with or without steroids/immunosuppressants.

Please provide a response by December 16, 2016 at 2pm by 1) email to facilitate review 2) as well as an official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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/s/

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JANICE H KIM
12/09/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, December 08, 2016 10:39 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 (durvalumab) Clinical Pharmacology Information Request

Dear Ms. Gillette,

The purpose of this email is to convey to you an information request from our clinical pharmacology review team for your BLA 761069:

“Provide bioanalytical report for durvalumab concentration measured in Study 1108.”

Please provide a response by Friday December 9, 2016 at 2pm EST 1) by email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
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/s/

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JANICE H KIM
12/08/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**PRIORITY REVIEW DESIGNATION**

AstraZenenca, UK Limited
Attention: Jamie Gillette, MSc, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated October 13, 2016, received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for Imfinzi (durvalumab) Injection.

We also refer to your submissions dated July 29, 2016, August 12, 2016, and October 13, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 601.2(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is June 13, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 23, 2017.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before December 26, 2016.

If you have any questions, call Janice Kim, Regulatory Project Manager, at (301) 796-9628.

Sincerely,

*{See appended electronic signature page}*

Geoffrey Kim, MD
Division Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

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GEOFFREY S KIM
12/08/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, December 07, 2016 9:35 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 (durvalumab): Clinical Information Request

Dear Ms. Gillette,

The purpose of this email to convey the following clinical information request for your BLA 761069:

1. Please provide a laboratory analysis dataset that contains only the 182 2nd-line post-platinum patients.

Please submit a response by December 9, 2016 by 1) email to facilitate review and 2) by official submission to your BLA.

Thank you,

Janice Kim

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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/s/

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JANICE H KIM
12/07/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Friday, December 02, 2016 1:41 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 durvalumab - Pharmacometrics information request

Dear Ms. Gillette,

The purpose of this email it to request your response to the following information request from the pharmacometrics review team:

1) The following analysis programs and output listings cannot be located under section 5.3.3.5: run6.mod, run6.lst, run65.mod, run65.lst, run94max0.mod, and run94max0.lst. Please submit these files or specify the locations.
2) Please evaluate the potential time-varying clearance of durvalumab given similar findings in previously approved PD1/PDL1 targeting treatments (see section 12.3 in the labels of TECENTRIQ (atezoliaumab) BLA 761041, OPDIVO (nivolumab) BLA 125544, and KEYTRUDA (pembrolizumab) BLA 125514). The following model structure can be used to describe the time-dependent PK. Submit the analysis results along with model codes and datasets for FDA's review.

   Time-varying PK model structure:

$$CL_{TDPKi} = TVCL \cdot e^{\frac{(T_{\max} + \eta_{T_{\max}}) \cdot Time^{\gamma}}{T50^{\gamma} + Time^{\gamma}}} \cdot Cov \cdot e^{\eta_i}$$

Please submit part 1 Wednesday, December 7, 2016 and part 2 by Friday, December 22, 2016 by 1) email and 2) by official submission to your BLA.

Thank you.

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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janice.kim@fda.hhs.gov

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/s/

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JANICE H KIM
12/02/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Friday, December 02, 2016 1:57 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 durvalumab: Clinical Information Request

Dear Ms. Gillette,

The purpose of this email it to request your response to the following clinical information request from the clinical review team:

1. Patient 20001672526 is documented as experiencing acute respiratory failure on Day 14 leading to death. Provide additional detail regarding rule out of pneumonitis in this patient including radiographic studies. Additionally, discuss whether progression of disease occurred in this patient; if so, provide additional radiographic and/or clinical justification.
2. Patient 12455011922 is documented as experiencing death due to progressive disease. However, the patient experienced Grade 3 autoimmune hepatitis leading to treatment discontinuation 3 weeks prior to death. Provide additional detail regarding disease progression in this patient.
3. Patient 13711012235 is documented as experiencing death due to progressive disease. The patient experienced acute cholangitis one week prior to death that lead to discharge to hospice. Provide additional detail regarding disease progression in this patient, including results of MRCP and hepatobiliary scan.
4. Patient 20002282412 is documented as experiencing "unspecified cardiac arrest due to rapid disease progression." Provide additional detail regarding disease progression in this patient.
5. Provide additional detail regarding nature of disease progression for Patient 20006782366
6. Provide additional detail for Patient 20023712474 regarding disease progression in the liver given later radiographic findings suggestive of acute hepatitis.
7. Patient 13717012048 is documented as experiencing death due to general health deterioration, however the narrative states that the patient experienced concomitant disease progression. Please reconcile this discrepancy and provide additional data regarding the timing and nature of disease progression.

Please respond to this IR by December 12, 2016 by 1) email and by 2) official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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/s/

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JANICE H KIM
12/02/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, December 01, 2016 8:40 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 for durvalumab: Clinical Information Request

Dear Ms. Gillette,

The purpose of this email is to request a response to the following clinical information request from the review team:

*Please submit analysis datasets of concentration-QT analyses for both Study D4191C00003 and CD-ON-MEDI4736-1108. We are unable to merge datasets transposed from ADEG and ADPK well due to difficulty in understanding the analysis time-point descriptions from both ADEG and ADPK datasets.*

*Furthermore, please upload all related ECG waveforms with annotations for both studies to the ECG warehouse (www.ecgwarehouse.com).*

Please submit your response by 2pm December 5, 2016 by 1) email to facilitate review 2) and by official submission to your BLA.

Thank you,

Janice Kim

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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JANICE H KIM
12/01/2016

# Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

**BACKGROUND**

**Please check all that apply:** ☒ **Full Waiver** ☐ **Partial Waiver** ☐ **Pediatric Assessment** ☐ **Deferral/Pediatric Plan**

**BLA/NDA#: 761069**

**PRODUCT PROPRIETARY NAME: Imfinzi**
**ESTABLISHED/GENERIC NAME: durvalumab**

**APPLICANT/SPONSOR: AstraZeneca**

**PREVIOUSLY APPROVED INDICATION/S:**
*(1)* _____
*(2)* _____
*(3)* _____
*(4)* _____

**PROPOSED INDICATION/S:**
*(1)* _____*urothelial cancer* _____
*(2)* _____
*(3)* _____
*(4)* _____

**BLA/NDA STAMP DATE: October 13, 2016**

**PDUFA GOAL DATE: June 13, 2017, TARGET DATE: MARCH 13, 2017**

**SUPPLEMENT TYPE:**

**SUPPLEMENT NUMBER:**

***Does this application provide for (If yes, please check all categories that apply and proceed to the next question):***

***NEW*** ☒ ***active ingredient(s) (includes new combination);*** ☐ ***indication(s);*** ☐ ***dosage form;*** ☐ ***dosing regimen; or*** ☐ ***route of administration?***

***Did the sponsor submit an Agreed iPSP? Yes*** ☒ ***No*** ☐

***Are there any changes to the Agreed iPSP that are different than the sponsor's current pediatric plan? Yes*** ☐ ***No*** ☒

***Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)***

***Yes*** ☐ ***No*** ☒

***Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes*** ☐ ***No*** ☒

***If Yes, PMR #*** _____ ***NDA #*** _____

***Does the division agree that this is a complete response to the PMR? Yes*** ☐ ***No*** ☐

***If Yes, to either question Please complete the Pediatric Assessment Template.***

***If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.***

**WAIVER REQUEST**

***Please attach:***

☒ ***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change.***

***If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***

☐ ***Pediatric Record***

1 Pediatric age group(s) to be waived. 0-17

2 Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

☒ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.

☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **<u>and</u>** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. ***(This reason is for Partial Waivers Only)***

*3 Provide justification for Waiver:* durvalumab has limited applicability to pediatric patients because the pathophysiology of urothelial balder cancer occurs for the most part in the adult population

*4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:* None at this time

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

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/s/

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JANICE H KIM
11/28/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, November 23, 2016 11:42 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request
**Attachments:** Highlights of ClinPharm and Cardiac Safety_20150923.doc

Good afternoon,

In reference to BLA 761069, the review team has the following information request: Please complete the attached ClinPharm and Cardiac Safety Table.

Please respond to this request by Tuesday November 29, 2016 2PM 1) by email 2) as well as an official submission to your BLA.

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
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/s/

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JANICE H KIM
11/23/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, November 17, 2016 2:37 PM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069

Good afternoon Jamie,

In reference to BLA 761069, the clinical review team has the following information request:

1. Please provide a narrative for patient 20007442265.
2. Two patients (20001992509 and 20000891660) are listed in the AE dataset as deceased due to disease under treatment, however per the narratives they appear to be alive. Please clarify the status of these patients.

Please respond by November 22, 2016 by 2pm 1) by email 2) as well as an official submission to your BLA>

Thank you,

Janice

**Janice Kim, PharmD, MS**
*Regulatory Project Manager*

**Division of Oncology Products 1**
**Office of Hematology and Oncology Products**
**Center for Drug Evaluation and Research**
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JANICE H KIM
11/17/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Tuesday, November 15, 2016 7:48 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Clinical Information Request

Good morning Jamie,

In reference to BLA 761069 the clinical review team has the following information request:

With the increasing availability of immune based therapies targeting the PD-1/PD-L1 pathway for solid tumors, we note that the registrational trials for these patients often excluded patients with autoimmune disease. As this class of agents is increasingly being used in the post marketing space and in non-clinical trial settings, we are interested in collecting data on patients with pre-existing autoimmune diseases who were treated with these agents.
Please provide any information from your database on patients with autoimmune disease and patients with positive autoimmune serology who were treated with these agents. This may include patients across your clinical development program, and is not specific to urothelial cancer.

Responses due by Monday, November 28th at 2pm EST 1) by email as well as 2) as an official submission to your BLA.

**********

Janice Kim, PharmD, MS
Regulatory Project Manager/DOP 1
Office of Hematology & Oncology Products (OHOP) / CDER / FDA
10903 New Hampshire Avenue / Bldg 22, Room 2329 / Silver Spring, MD 20993
Janice.kim@fda.hhs.gov
(P): 301-796-9628

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JANICE H KIM
11/15/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**INFORMATION REQUEST**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologics License Application (BLA) dated and received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for durvalumab.

We are reviewing your submission and have the following request for information. We request a prompt written response by COB November 18, 2016 in order to continue our evaluation of your application.

1. Rabbit pyrogen test data as required in 21 CFR 610.13(b) was not provided for the drug product. Please provide rabbit pyrogen test data for three different lots of the drug product to demonstrate that the drug product does not contain pyrogenic substances other than bacterial endotoxin.

2. Sterilization validation data (b) (4) was not provided. Please update section 3.2.P.3.5 to include sterilization validation data (b) (4) If the information is located in the supplier's Drug Master File, provide a Letter of Authorization which clearly indicates the location of the information within the Drug Master File. If applicable, justify the use of a product family approach for dose setting, dose mapping, and dose audits by explaining why the representative product is worst-case. Section 3.2.P.3.5 should be updated with the following information for the (b) (4)
    a. Provide a copy of the Certificate of Analysis (b) (4)
    b. Provide a diagram (b) (4)
    c. Summarize dose establishment data (b) (4), describe how the dose establishment study was performed, and provide the dose establishment report.
    d. Summarize dose mapping data (b) (4) and describe how the dose mapping studies were performed. Indicate the number of runs performed. Describe the load composition, density, and dosimeter placement within the load.

Compare the dose mapping [redacted] (b) (4) used for production.

e. Summarize data from the last three quarterly dose audits performed at the sterilization site and provide the dose audit reports.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly Ballard

Digitally signed by Kelly Ballard
Date: 11/10/2016 08:49:18AM
GUID: 57e29be6020b38ae4817a9d8118b31c1

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, November 09, 2016 8:03 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Clinical Information Request

Good morning,

In reference to BLA 761069, the clinical review team has the following information request:

1. Please provide an adverse event dataset and analysis (including incidence of all treatment-emergent AEs, Grade 3-4 AEs, AESIs, and immune-mediated events) for two cohorts (indicate the 94 patient population with a flag):
    a. The 94 patient 2nd-line post-platinum patients followed for at least 13 weeks
    b. The 182 patient 2nd-line post-platinum patients followed for any amount of time

Please respond by November 15, 2016 2pm 1) by email as well as 2) as an official submission to your BLA.

Thank you,

Janice Kim

**********

Janice Kim, PharmD, MS
Regulatory Project Manager/DOP 1
Office of Hematology & Oncology Products (OHOP) / CDER / FDA
10903 New Hampshire Avenue / Bldg 22, Room 2329 / Silver Spring, MD 20993
Janice.kim@fda.hhs.gov
(P): 301-796-9628

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JANICE H KIM
11/09/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, November 09, 2016 11:39 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 IR

Good afternoon,

In reference to BLA 761069, the clinical review team has the following IR:

1. Please provide two PDFs of the death and adverse event narratives, one containing all patients with bladder cancer treated on Study 1108 and the other containing only the 2nd-line post-platinum bladder cancer patients.

Please respond by November 15, 2016 2pm 1) by email as well as 2) as an official submission to your BLA.

**********

Janice Kim, PharmD, MS
Regulatory Project Manager/DOP 1
Office of Hematology & Oncology Products (OHOP) / CDER / FDA
10903 New Hampshire Avenue / Bldg 22, Room 2329 / Silver Spring, MD 20993
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JANICE H KIM
11/09/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Tuesday, November 08, 2016 10:48 AM
**To:** 'Gillette, Jamie'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Clinical Information Request

Good morning Jamie,

In reference to BLA 761069, the clinical review team has the following information request:

1. Please provide a breakdown of baseline demographics between the three enrollment cohorts of UBC patients (initial PD-L1 unselected, PD-L1 selected, and PD-L1 unselected expansion cohort). Please organize this by Subject ID and include baseline disease characteristics including MSKCC and Bellmont risk group scores, PD-L1 biomarker status (using the TC/ IC ≥25% scoring), and BICR sum of tumor diameters.
2. Please comment on whether site of biopsy is available for each patient. If so, please provide this in the baseline demographic table requested above.

Please respond by November 15, 2016 2pm 1) by email as well as 2) as an official submission to your BLA.

Thank you,

Janice Kim

**********

Janice Kim, PharmD, MS
Regulatory Project Manager/DOP 1
Office of Hematology & Oncology Products (OHOP) / CDER / FDA
10903 New Hampshire Avenue / Bldg 22, Room 2329 / Silver Spring, MD 20993
Janice.kim@fda.hhs.gov
(P): 301-796-9628

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JANICE H KIM
11/08/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**PROPRIETARY NAME ACKNOWLEDGEMENT**

AstraZeneca UK Limited
c/o AstraZeneca Pharmaceuticals LP
One MedImmune Way
Gaithersburg, MD 20878

ATTENTION: Jamie Gillette, MSc, RAC
Director, Global Regulatory Affairs

Dear Mr. Gillette:

Please refer to your Biologics License Application (BLA) dated and received October 13, 2016, submitted under section 351(a) of the Public Health Service Act for Durvalumab, 500mg/10 mL and 120mg/2.4 mL.

We acknowledge receipt of your correspondence dated and received October 17, 2016, requesting a review of your proposed proprietary name, Imfinzi.

If the application is filed, the user fee goal date will be January 15, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Janice Kim, Regulatory Project Manager, in the Office of New Drugs at (301) 796-9628.

Sincerely,

*{See appended electronic signature page}*

Frances Fahnbulleh, PharmD, RPh.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

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FRANCES G FAHNBULLEH
11/04/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Thursday, November 03, 2016 6:53 AM
**To:** 'Jamie.Gillette@astrazeneca.com'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Clinical Information Request

Good morning,

In reference to BLA 761069, when do you expect to have BICR data available for the 52 patients followed for 7-13 weeks?

Send us your response by Friday November 4, 2016 at 2 pm 1) by email as well as 2) as an official submission to your BLA.

Thank you,

Janice

**********

Janice Kim, PharmD, MS
Regulatory Project Manager/DOP 1
Office of Hematology & Oncology Products (OHOP) / CDER / FDA
10903 New Hampshire Avenue / Bldg 22, Room 2329 / Silver Spring, MD 20993
Janice.kim@fda.hhs.gov
(P): 301-796-9628

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JANICE H KIM
11/03/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Wednesday, November 02, 2016 6:47 AM
**To:** 'Jamie.Gillette@astrazeneca.com'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Good morning,

In reference to your BLA 761069, our review team has the following information request:

Please provide a reanalysis of the ORR for study 1108 where you stratify both on PD-L1 status and whether or not the patient was included in the data used to support Breakthrough designation status (n=39) versus those addition patients (n=64). Please provide the analysis in the following (or similar) format.

| All patients (n=103) | | |
|---|---|---|
| | n/total n | ORR (95% CI) |
| PD-L1 High* | | |
| PD-L1 Low* | | |

| Training set (n=39) which includes patients with efficacy data and PD-L1 data that were included in breakthrough designation request using the November 15, 2015 data cutoff. | | |
|---|---|---|
| | n/total n | ORR (95% CI) |
| PD-L1 High* | | |
| PD-L1 Low* | | |

| Validation set (n=64) which includes patients that were not included in the data that was submitted for breakthrough designation request using the November 15, 2015 cutoff (n=64) | | |
|---|---|---|
| | n/total n | ORR (95% CI) |
| PD-L1 High* | | |
| PD-L1 Low* | | |

*PD-L1 status is considered high if either TC≥25% or IC≥25%
*PD-L1 status is considered low if TC<25% and IC<25%

Send us your response by Tuesday November 8, 2016 at 2 pm 1) by email as well as 2) as an official submission to your BLA.

**********

Janice Kim, PharmD, MS
Regulatory Project Manager/DOP 1
Office of Hematology & Oncology Products (OHOP) / CDER / FDA
10903 New Hampshire Avenue / Bldg 22, Room 2329 / Silver Spring, MD 20993
Janice.kim@fda.hhs.gov
(P): 301-796-9628

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JANICE H KIM
11/02/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**BLA ACKNOWLEDGMENT**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: durvalumab, injection, 500 mg/vial and 120 mg/vial

Date of Application: October 13, 2016

Date of Receipt: October 13, 2016

Our Reference Number: BLA 761069

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight

mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (301) 796-9628.

Sincerely,

*{See appended electronic signature page}*

Janice Kim, PharmD, MS
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

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JANICE H KIM
11/01/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Tuesday, November 01, 2016 7:03 AM
**To:** 'Jamie.Gillette@astrazeneca.com'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Information Request

Good morning,

In reference to BLA 761069, the review team has the following information request: "Please revise the datalistings. In the current file structure for the datalisting submitted for bimo inspections (bimo_1108_Sites A_I_Final and bimo_1108_J_Final) the listings are not aggregated by clinical site, but instead by datalisting category. Please ensure that all datalistings (a-j) for each clinical site be collated by site; a-j. For example, the PDF file for each Clinical Site should have datalistings a-j in the same file and each datalisting bookmarked as appropriate. 1 bimo datalisting pdf file for each clinical site for study 1108."

Send us your revisions by Thursday November 3, 2016 at 2 pm 1) by email as well as 2) as an official submission to your BLA.

Let me know if you have any questions.

Thank you,

Janice Kim

**********

Janice Kim, PharmD, MS
Regulatory Project Manager/DOP 1
Office of Hematology & Oncology Products (OHOP) / CDER / FDA
10903 New Hampshire Avenue / Bldg 22, Room 2329 / Silver Spring, MD 20993
Janice.kim@fda.hhs.gov
(P): 301-796-9628

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/s/

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JANICE H KIM
11/01/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Monday, October 31, 2016 7:13 AM
**To:** 'Jamie.Gillette@astrazeneca.com'
**Cc:** Kacuba, Alice
**Subject:** BLA 761069 Clinical Information Request

Good morning,

In reference to BLA 761069, the clinical review team has the following information request:

1. We are interested in reviewing the response data on the 50 additional post-platinum patients with only one on-study tumor assessment. Please provide this dataset and indicate whether these responses have been IRC-reviewed.
2. Please indicate the number of screen-fails during the 40-patient enrollment period where inclusion criteria mandated tumor PD-L1 positive status. In patients with a screen-fail during this period, indicate how many patient had tumors that were PD-L1 positive or negative by TC or IC >25% criteria.

Send us your response by Wednesday November 2, 2016 at 2 pm 1) by email as well as 2) as an official submission to your IND.

Thank you and please let me know if you have any questions.

Janice Kim

**********

Janice Kim, PharmD, MS
Regulatory Project Manager/DOP 1
Office of Hematology & Oncology Products (OHOP) / CDER / FDA
10903 New Hampshire Avenue / Bldg 22, Room 2329 / Silver Spring, MD 20993
Janice.kim@fda.hhs.gov
(P): 301-796-9628

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/s/

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JANICE H KIM
10/31/2016

## Kim, Janice

**From:** Kim, Janice
**Sent:** Tuesday, October 25, 2016 12:35 PM
**To:** 'Jamie.Gillette@astrazeneca.com'
**Cc:** Kacuba, Alice
**Subject:** Clinical IR - BLA 761069

Good afternoon,

In reference to BLA 761069, our clinical team has the following information request:

- Please provide an integrated summary of safety dataset.

Please respond by November 2, 2016 at 2:00 PM via email as well an official submission to your application.

Thank you,

Janice

**********

Janice Kim, PharmD, MS
Regulatory Project Manager/DOP 1
Office of Hematology & Oncology Products (OHOP) / CDER / FDA
10903 New Hampshire Avenue / Bldg 22, Room 2329 / Silver Spring, MD 20993
Janice.kim@fda.hhs.gov
(P): 301-796-9628

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/s/

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JANICE H KIM
10/25/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND (b) (4)

**MEETING REQUEST-
WRITTEN RESPONSES**

AstraZeneca Pharmaceuticals, LP
Attention: Jamie Gillette, MS, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for durvalumab (MEDI4736).

We also refer to your submission dated July 15, 2016, containing a Type B Pre-BLA meeting request. The purpose of the requested meeting is to reach agreement with the Agency on the pivotal clinical results that will support a marketing application under the accelerated approval regulatory pathway.

Further reference is made to our Meeting Granted letter dated July 28, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your August 12, 2016, background package.

If you have any questions, contact Tracy Cutler, Regulatory Health Project Manager at (301) 796-9608.

Sincerely,

*{See appended electronic signature page}*

Tracy L. Cutler, MPH, CCRP, CIP
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

*{See appended electronic signature page}*

V. Ellen Maher, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

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**WRITTEN RESPONSES**

| | |
|---|---|
| **Meeting Type:** | B |
| **Meeting Category:** | Pre-BLA |
| **Application Number:** | IND (b) (4) |
| **Product Name:** | Durvalumab (MEDI4736) |
| **Indication:** | Treatment of patients with locally advanced or metastatic urothelial cancer (b) (4) |
| **Sponsor/Applicant Name:** | AstraZeneca Pharmaceuticals LP |
| **Regulatory Pathway:** | 505(b)(1) |

## 1.0 BACKGROUND

AstraZeneca is seeking accelerated approval for durvalumab in the treatment of patients with locally advanced/metastatic urothelial cancer (b) (4) On July 12, 2016, the Agency met with the Sponsor in a Breakthrough Therapy meeting to discuss the development program and the Agency recommended, based on the Sponsor's estimation of the number of patients who had received durvalumab and been followed for at least two rounds of subsequent imaging, that the study cut-off date for submission of a BLA should be at least July 14, 2016. This would allow approximately 100 patients to have undergone 2 tumor assessments and 169 patients to have received durvalumab and been followed for at least 30 days. The proposed application will be based on efficacy data from 96 patients with urothelial cancer treated on Study CD-ON-MEDI4736-1108 (Study 1108; IND 112249) with a data cutoff of July 24, 2016. Study 1108 is an ongoing phase 1-2 study evaluating durvalumab monotherapy in various solid tumors with multiple cohorts. Patients in the dose-expansion phase were treated with durvalumab 10 mg/kg every 2 weeks and an urothelial carcinoma cohort with no limitations on prior lines of therapy initiated under Amendment 5. Study 1108 enrolled 20 patients with urothelial carcinoma who were enrolled regardless of PD-L1 expression, 40 patients whose tumors contained ≥5% tumor cells staining for PD-L1, and 132 patients enrolled regardless of PD-L1 expression. Efficacy was assessed via evaluation of the response rate and duration of response by independent review as well as response rate by PD-L1 staining (PD-L1 high is defined as tumor or immune cell staining ≥25% and PD-L1 low is defined as tumor or immune cell staining <25%).

The Sponsor also plans to submit the Ventana PD-L1 (SP263) diagnostic assay for complementary use based on a cut-off where:

- Tumor cell ≥25% OR immune cell ≥25% = PD-L1 high, and
- Tumor cell <25% AND immune cell <25% = PD-L1 low.

The application will also include safety data from 185 patients with urothelial cancer and 1223 patients with other solid tumors. This includes data from Study 1108 (which had multiple cohorts and enrolled 779 patients with solid tumors other than urothelial cancer) and Study D4191C00003 (ATLANTIC), a phase 2 open-label study of durvalumab monotherapy which enrolled 444 patients with non-small cell lung cancer who had received at least 2 prior systemic regimens. The ATLANTIC data will include >12 months of follow-up for 265 patients and >6 months of follow-up for 177 patients. In the 90-day safety update, the Sponsor plans not to revise existing patient narratives that were included in the initial application. The Sponsor does plan to provide updated data for overall response and duration of response in the update.

The Sponsor also has an ongoing study (DANUBE) which is intended to support regular approval. DANUBE will randomize 1005 patients with newly diagnosed Stage IV urothelial cancer to:

1) Durvalumab 1.5 g IV every 4 weeks
2) Durvalumab + tremelimumab
3) Standard of care with cisplatin/gemcitabine or carboplatin/gemcitabine.

The primary analyses are:

- Overall survivial (OS) of durvalumab vs. the standard of care in patients whose tumor staining (both tumor cells and immune cells) is PD-L1 high using an alpha of 0.025; and
- Progression free survival (PFS) and OS of durvalumab/tremelimumab vs. the standard of care regardless of PD-L1 status using an alpha of 0.01 for PFS and 0.015 for OS.

This meeting will discuss the content and format of the proposed BLA.

## 2.0 QUESTIONS AND RESPONSES

**Question 1:** Based on the top-line pivotal efficacy and safety results from Study 1108, and the fact that a confirmatory trial (Study D419BC00001 [DANUBE]) is well underway, does the Agency agree that the benefit-risk profile of durvalumab, for the treatment of patients with locally advanced or metastatic UC (b) (4) is supportive of a BLA submission under the accelerated approval pathway?

> **FDA Response: This decision will be made at the time of filing. While the number of patients available for the evaluation of efficacy is small, it is likely to be sufficient for filing. Whether this data will be sufficient for approval will be a review issue.**

**Question 2:** Does the Agency agree with the Sponsor's proposed timing and content of the Day 90 update?

> **FDA Response: No. Please also include narratives for immune-related adverse events from your entire safety database with the October 24, 2016, cutoff. Revised narratives should be provided in the safety update if additional relevant data becomes available. Additional efficacy data should not be included in the safety update.**

**Question 3:** Does the Agency agree with the proposed format and content of the product labelling (Target Product Profile [TPP], Appendix A)?

**FDA Response: The wording of the package insert will be a review issue. With regards to Section 5, note that this section may include adverse events that do not meet the criteria for immune-mediated adverse events, such as infection, depending on the safety profile of durvalumab. You should submit multiple draft package inserts for durvalumab that reflect each of the potential uses of the Ventana PD-L1 (SP263) Assay, as either a complementary diagnostic, companion diagnostic, and for the possibility that the assay will not be used at all (i.e., one draft label using the assay as complementary, one draft label using the assay as a companion diagnostic, and one draft label without use of the assay).**

**Question 4:** Does the Agency agree with the Sponsor's proposal for content and timing of the complete BLA application for durvalumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4) ?

**FDA Response: Yes.**

**Question 5:** Does the Agency agree with the proposed content and format of the technical data package, including Office of Scientific Investigations (OSI) and Module 5 datasets, as well as proposal for an application orientation meeting in support of the BLA application for durvalumab?

**FDA Response: The proposed content and format appear to be acceptable. If your application is filed, you will be contacted concerning the scheduling of an Application Orientation Meeting.**

**Additional Comment**

- **Please include an analysis of infection, including broad pooling of preferred terms, in your CSR.**

## 3.0 OTHER IMPORTANT MEETING LANGUAGE

### 3.1 Discussion of the Content of a Complete Application

- The content of a complete application was discussed.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend

to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting is planned. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

### 3.2 PREA Requirements

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

### 3.3 Prescribing Information

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

### 3.4 Submission Format Requirements

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

### 3.5 Secure Email Communications

Secure email is required for all email communications from FDA to sponsors when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

### 3.6 Manufacturing Facilities

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

| Site Name | Site Address | Federal Establishment Indicator (FEI) or Registration Number (CFN) | Drug Master File Number (if applicable) | Manufacturing Step(s) or Type of Testing [Establishment function] |
|---|---|---|---|---|
| 1. | | | | |
| 2. | | | | |

Corresponding names and titles of onsite contact:

| Site Name | Site Address | Onsite Contact (Person, Title) | Phone and Fax number | Email address |
|---|---|---|---|---|
| 1. | | | | |
| 2. | | | | |

### 3.7 Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

**I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is

maintained. As above, this is the actual physical site where documents would be available for inspection.

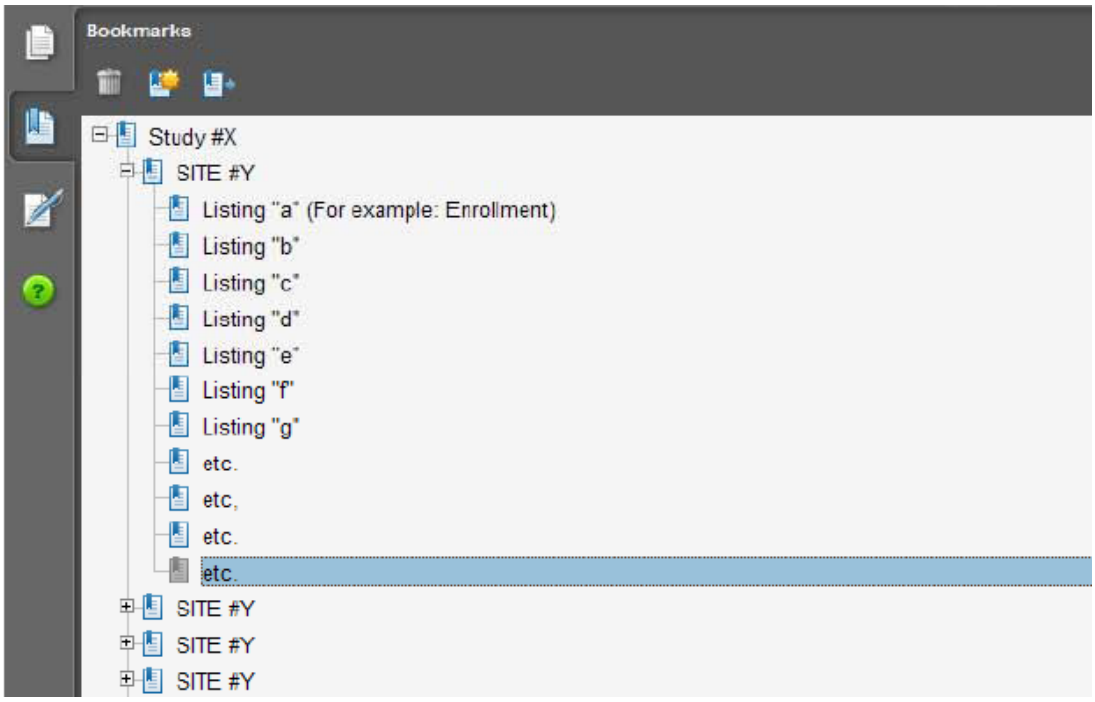
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

## II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:




## III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf ) for the structure and format of this data set.

## Attachment 1
## Technical Instructions:
## Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

| DSI Pre-NDA Request Item[1] | STF File Tag | Used For | Allowable File Formats |
|---|---|---|---|
| I | data-listing-dataset | Data listings, by study | .pdf |
| I | annotated-crf | Sample annotated case report form, by study | .pdf |
| II | data-listing-dataset | Data listings, by study (Line listings, by site) | .pdf |
| III | data-listing-dataset | Site-level datasets, across studies | .xpt |
| III | data-listing-data-definition | Define file | .pdf |

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:


C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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TRACY L CUTLER
09/13/2016

VIRGINIA E MAHER
09/13/2016

## Benton, Sandra J

**From:** Benton, Sandra J
**Sent:** Tuesday, February 09, 2016 7:17 AM
**To:** Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Moscicki, Richard; Marcus, Kendall; Kehoe, Theresa
**Cc:** Jarow, Jonathan; Hinton, Denise; Sacks, Leonard V; Raggio, Miranda; Wedlake, Lauren; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Balcazar, Pamela; Cutler, Tracy; Suzman, Daniel; Maher, Virginia E.; Ibrahim, Amna; Kim, Geoffrey
**Subject:** RE: February 10, 2016 Medical Policy Council – Breakthrough Therapy Designation - IND (b) (4)

As the Council agrees with DOP1's recommendation to grant AstraZeneca's breakthrough therapy designation request and does not believe a Council discussion is needed, this request will be cancelled from the February 10, 2016 meeting agenda.

Please let me know if you have any questions. Thanks!

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

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**From:** Benton, Sandra J
**Sent:** Thursday, January 28, 2016 1:28 PM
**To:** Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Moscicki, Richard; Marcus, Kendall; Kehoe, Theresa
**Cc:** Jarow, Jonathan; Hinton, Denise; Sacks, Leonard V; Raggio, Miranda; Wedlake, Lauren; Benton, Sandra J; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Balcazar, Pamela; Cutler, Tracy; Suzman, Daniel; Maher, Virginia E.; Ibrahim, Amna; Kim, Geoffrey
**Subject:** February 10, 2016 Medical Policy Council – Breakthrough Therapy Designation - IND (b) (4)

Hi! OMP has scheduled a Medical Policy Council discussion on February 10, 2010 regarding the breakthrough therapy designation request from AstraZeneca for its IND (b) (4) MEDI4736 (Durvalumab) for the treatment of patients with PD-L1-positive, inoperable or metastatic, urothelial bladder cancer after treatment failure on standard platinum-based regimens.

DOP1 recommends that this breakthrough therapy request be granted. Attached is DOP1's background on the breakthrough therapy designation with its rationale for granting the request.

DOP1 has asked if this request can be reviewed by email.

Would you please review DOP1's recommendation and let me know by COB Friday, February 5 if –

- You agree with DOP1's recommendation regarding this breakthrough therapy request and you do not believe a Council discussion is needed.
- You agree with DOP1's recommendation regarding this breakthrough therapy request. However, you would like a Council discussion regarding any questions you have.

- You agree with DOP1's recommendation regarding this breakthrough therapy request. However, you would like to have a discussion of the development plan and what FDA will recommend, if appropriate.
- You disagree with DOP1's recommendation regarding this breakthrough therapy request.

If the Council agrees with bullet 1, I will cancel the discussion for this IND.

Please let me know if you have any questions. Thank you.

Sandy Benton
Senior Policy Analyst
CDER/Office of Medical Policy
301-796-1042
sandra.benton@fda.hhs.gov

<< File: Durvalumab BTDR.DOC >> << File: INd (b) (4) BTDR.PDF >>

# CDER Breakthrough Therapy Designation Determination Review Template

| | |
|---|---|
| **IND/NDA/BLA #** | (b) (4) |
| **Request Receipt Date** | 12-18-15 |
| **Product** | MEDI4736 (Durvalumab) |
| **Indication** | Treatment of patients with PD-L1-positive, inoperable or metastatic, urothelial bladder cancer after treatment failure on standard platinum-based regimens |
| **Drug Class/Mechanism of Action** | Human IgG1-kappa monoclonal antibody directed against PD-L1 |
| **Sponsor** | AstraZeneca |
| **ODE/Division** | OHOP/DOP1 |
| **Breakthrough Therapy Request Goal Date (within 60 days of receipt)** | 2-16-2016 |

*Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.*

**Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs***

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   Patients with PD-L1-positive inoperable or metastatic urothelial bladder cancer whose tumor has progressed during or after at least one prior line of therapy, which must include a standard platinum-based regimen

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

***If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:***

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

***If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:***

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?
      - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - ☐ Undetermined
      - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

**4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:**

***If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.***

**5. Clearance and Sign-Off (no MPC review)**

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

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**Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.**

**6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.**

Urothelial bladder cancer is a serious and life-threatening disease without FDA-approved treatment options available in the 2nd line setting following platinum-based therapy. Overall response rates for commonly-used 2nd line therapies including gemcitabine and taxanes are poor, with overall response rates ranging from 6-25% and overall survival rates of 5-12 months in small Phase 2 studies. Per standard practice guidelines, no standard therapy exists in the 2nd line setting and participation in clinical trials of new agents is recommended, while a single-agent taxane or gemcitabine are preferred for palliation.

MEDI4736 (durvalumab) is a human IgG1-kappa monoclonal antibody directed against PD-L1. There are currently no PD-L1-targeted therapies for bladder cancer that have been approved by the FDA, however there has been clinical

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

activity noted using other agents. For example, the Roche/Genentech anti-PD-L1 agent, MPDL3280A (atezolizumab) was granted Breakthrough Therapy Designation for metastatic urothelial bladder cancer based on a confirmed response rate of 50% in 20 patients with PD-L1 positive tumors (47% ORR in 19 patients with prior platinum therapy) with preliminary evidence of high durability. This response rate declined to 27% (95% CI:18.6%, 36.8%) in 100 patients on independent review.

**7. Information related to endpoints used in the available clinical data:**

The primary endpoint of the study was safety with dose expansion cohorts evaluating response rate, PFS, and overall survival.

**8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

There are no therapies approved specifically for this population. The only phase 3 trial in the 2nd line setting compared vinflunine to best supportive care. The ORR was 8.6% (95% CI: 5.0, 13.7) with a mPFS of 3 vs 1.5 months and median OS of 6.9 vs 4.6 months (p = 0.03). Multiple agents, including gemcitabine, taxanes, vinflunine, and irinotecan as well as doublet chemotherapies have demonstrated limited activity in the second-line setting with ORRs of 5-40%. PFS for singlet chemotherapy has been short (mPFS apprxomately 2-3 months). Moreover, the greater response rates seen with doublet chemotherapy do not translate into dramatically longer PFS (mPFS approximately 4-6 months) (Table 1). Combination chemotherapies have not demonstrated significant improvements in OS compared to single-agent therapy and carry greater toxicity (Table 2). Thus, singlet chemotherapy(generally a taxane or gemcitabine) is typically recommended by consensus guidelines for palliation in this setting.

| Study selection | ORR | | PFS | | OS | |
|---|---|---|---|---|---|---|
| | No. of evaluable arms of studies | Probability % (95% CI) | No. of evaluable arms of studies | Median PFS (95% CI) | No. of evaluable arms of studies | Median OS (95% CI) |
| Single-agent chemotherapy | 22 | 14.2 (11.1–17.9) | 18 | 2.69 (2.25–3.12) | 20 | 6.98 (6.19–7.78) |
| Vinflunine | 3 | 11.7 (6.2–20.9) | 3 | 2.92 (2.55–3.29) | 3 | 7.20 (6.30–8.10) |
| Paclitaxel or docetaxel | 5 | 10.5 (6.9–15.8) | 3 | 2.20 (1.36–3.04) | 4 | 7.35 (6.16–8.55) |
| Doublet chemotherapy | 24 | 31.9 (27.3–36.9) | 15 | 4.05 (3.54–4.57) | 23 | 8.50 (7.35–9.64) |
| Doublet with cisplatin | 2 | 40.4 (28.5–53.5) | 1 | 6.20 (3.95–8.45) | 2 | 10.39 (7.53–13.26) |
| Doublet without cisplatin | 22 | 30.9 (26.1–36.3) | 14 | 3.79 (3.40–4.17) | 21 | 8.35 (7.15–9.55) |
| Doublet with carboplatin | 4 | 25.4 (17.9–34.7) | 4 | 3.86 (3.20–4.51) | 4 | 8.14 (5.76–10.52) |

**Table 1: Meta-analysis of 2nd line chemotherapy. Note that there are only two study arms evaluating response rate in doublets with cisplatin and only one evaluating PFS, thus the confidence intervals are wide. Raggi et al, Ann Oncol 2016**

| | Single-agent | | Doublet | | *P* value* |
|---|---|---|---|---|---|
| | Number of evaluable arms of studies | Probability % (95% CI) | Number of evaluable arms of studies | Probability % (95% CI) | |
| Anemia | 22 | 9.7 (5.6–16.1) | 24 | 14.5 (10.1–20.3) | 0.438 |
| Neutropenia | 22 | 11.6 (5.5–23.3) | 24 | 16.8 (9.0–29.3) | 0.531 |
| Thrombocytopenia | 22 | 7.5 (4.3–12.6) | 24 | 8.9 (5.5–14.1) | 0.781 |
| Peripheral neuropathy | 15 | 3.6 (1.9–6.7) | 16 | 5.5 (3.0–9.7) | 0.431 |
| Nephrotoxicity | 13 | 3.0 (1.3–6.7) | 13 | 3.1 (1.6–5.8) | 0.699 |

**Table 2: Pooled estimates of Grade 3-4 toxicities in single-agent and doublet studies. Raggi et al, Ann Oncol 2016**

**9. A brief description of any drugs being studied for the same indication, or very similar indication, that**

**requested breakthrough therapy designation[3].**

Atezolizumab (MPDL-3080A) is Roche/Genentech anti-PD-L1 monoclonal antibody that was granted BTD for patients with metastatic bladder cancer expressing PD-L1. Breakthrough therapy was granted based on a 47% response rate among 19 patients who have progressed after prior cisplatin based therapy. The company is currently submitting a rolling NDA for this indication based on a single-arm study with a response rate of 27.0% (18.6, 36.8).

**10. Information related to the preliminary clinical evidence:**

MedImmune originally filed IND 112249 for durvalumab on 6/13/2012 containing Study CD-ON-MEDI4736-1108 (Study 1108) entitled "A Phase ½ study to evaluate the safety, tolerability, and pharmacokinetics (PK) of MEDI4736 in subjects with advanced solid tumors." Protocol Amendment 5 was filed on 5/27/2014 to evaluate the 10 mg/kg Q2week dose of durvalumab in a dose-expansion cohort of patients with urothelial bladder cancer. Patients in this cohort had either progressed, were intolerant to, were ineligible for, or had refused approved standard first-line therapy with no limit placed on the number of prior therapies received. Based on this cohort, a preliminary BTD request was submitted on 11/12/2015 with a teleconference between the FDA and AstraZeneca taking place on 12/2/2015.

This BTDR is supported by data from the UBC cohort of the ongoing Study CD-ON-MEDI4736-1108 based on a data cut-off date of 11/20/2015. Sixty-one patients received durvalumab 10 mg/kg Q2W of whom PD-L1 status was available for 42 patients. Thirty-nine of these patients had received at least 1 prior line of therapy, had measureable disease at baseline, and had at least one on-treatment scan or had died; these patients were included as the evaluable population. Among the population that had progressed following therapy with a platinum-containing regimen, 26 had received one prior therapy, 12 had received two prior therapies, and 19 had received three or more prior therapies. The PD-L1+ population was defined as patients whose tumors had ≥25% tumor cell membrane positivity for PD-L1 or whose tumor-associated immune cells had any PD-L1 staining above background. Twenty-seven (69.2%) patients were PD-L1+ and twelve (30.8%) were PD-L1-. The median followup among evaluable patients was 6.34 months (min 0.8, max 14.8 months).

The clinical activity of durvalumab is noted in Table 3. The confirmed ORR for the PD-L1+ group was 13/27 (48.1%) with two additional unconfirmed responses, compared to no confirmed responses in the PD-L1- population and one unconfirmed response. The sponsor is seeking breakthrough designation for PD-L1+ patients. In the PD-L1+ group, the median time to response was 6.9 weeks (range 5.6-31.7 weeks) and 14/15 (93.3%) of the responders have an ongoing response. The median duration of response was not yet reached, however the minimum duration of response was 36 weeks, four responses have lasted ≥12 weeks and three additional responses have lasted ≥24 weeks, including the longest ongoing response of 49.3 weeks. Duration of response is shown in the swimmer's plot in Figure 1. Median PFS in the PD-L1+ group is 11.1 months (1.6-NA) while the median OS has not been reached.

Of note, the prognostic significance of PD-L1 is unclear. PD-L1 in tumors cells has been associated with a more aggressive phenotype and reduced survival (Huang et al), however other reports have not found an association with survival (Bellmunt et al, Faraj et al). Positive PD-L1 expression in tumor-infiltrating mononuclear cells has been associated with improved survival (Bellmunt et al.)

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

| | PD-L1$^{+}$ N=27 | PD-L1$^{-}$ N=12 | Total N=39 |
|---|---|---|---|
| **CR+PR (ORR)** | **15 (55.6%)** | **1 (8.3%)** | **16 (41.0%)** |
| **95% CI** | **35.3, 74.5** | **0.2, 38.5** | **25.6, 57.9** |
| Confirmed CR+PR | 13 (48.1%) | 0 | 13 (33.3%) |
| 95% CI | 28.7, 68.1 | 0.0, 26.5 | 19.1, 50.2 |
| Ongoing CR+PR, awaiting confirmation by scan | 2 (7.4%) | 1 (8.3%) | 3 (8.0%) |
| CR+PR+SD ≥12 weeks (DCR12); | 16 (59.3%) | 4 (33.3%) | 20 (51.3%) |
| 95% CI | 38.8, 77.6 | 9.9, 65.1 | 34.8, 67.6 |

**Table 3: Overall response rate by PD-L1 status**

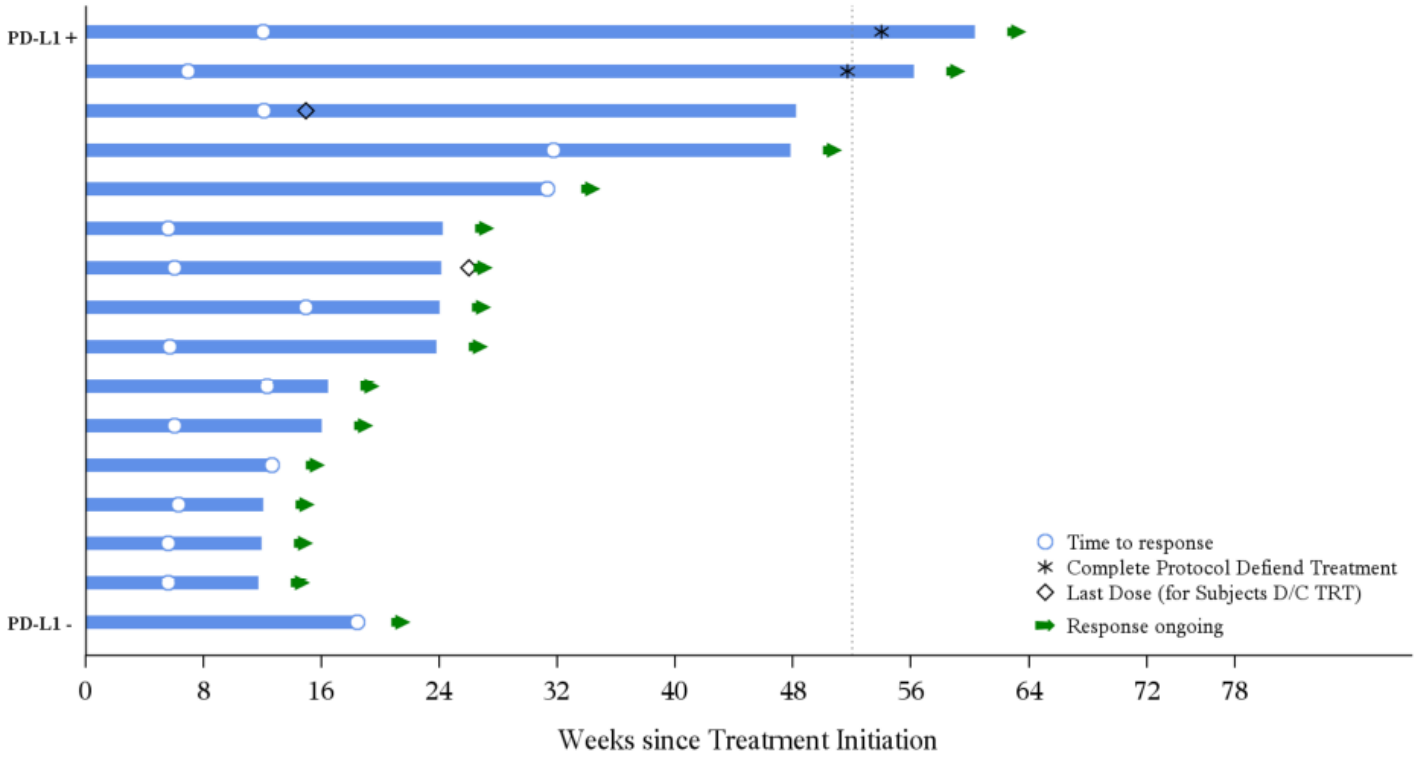


**Figure 1: Swimmer's plot of response duration**

These data provide preliminary evidence of clinical efficacy of durvalumab in the PD-L1+ population which is a substantial improvement over available therapies. A radiologic response rate of 48% represents a greater than 3-fold improvement over available single agents. This response rate is also greater than combination chemotherapies, although these are not recommended by consensus guidelines over single agents due to increased toxicity and lack of improved overall survival. While the median duration of follow-up is currently short, there is preliminary evidence of remarkable durability of the responses as compared to those seen with existing chemotherapy.

In the UBC cohort, 33 of 61 (54.1%) patients experienced a Grade 3 or greater adverse event, of which 3 (4.9%) were judged as related. Eight (13.1%) patients discontinued durvalumab. The most common Grade 3 or greater events regardless of causality were: hyponatremia (9.8%), acute kidney injury (8.2%), urinary tract infection (8.2%), abdominal pain (4.9%), and anemia (4.9%). Grade 3 or greater immune-mediated advese events were reported in 4 (6.6%) patients. The most frequent of these was acute kidney injury (4.9%). All-grade immune-mediated adverse events occurred in 9 (14.8%) patients. The most common was acute kidney injury (4.9%), increased creatinine (3.3%) and diarrhea (3.3%). The safety profile is well-characterized in other cancer types. In the overall Study 1108 population, Grade 3 or greater adverse events occurred in 55% of patients and the safety profile was similar to the UBC cohort.

Overall, these safety data compared favorably to those of single-agent chemotherapy. These regimens are limited by severe hematologic and non-hematologic toxicities, including neutropenia (G3-4:12%), anemia (G3-4: 10%), thrombocytopenia (G3-4: 8%), peripheral neuropathy (G3-4: 4%), and nephrotoxicity (G3-4: 3%) (see Table 2). These toxicities are frequently poorly tolerated by fragile patients in the 2$^{nd}$ line UBC setting.

**11. Division's recommendation and rationale (pre-MPC review):**

☒ GRANT :

Provide brief summary of rationale for granting:

The data from Study 1108 provide preliminary evidence of a substantial improvement in clinical efficacy compared with available therapy for a population with high unmet need: patients with metastatic urothelial bladder cancer who are PD-L1+ and have progressed on first-line platinum-containing chemotherapy. Available therapies for these patients include single-agent or doublet chemotherapy, which have a disappointing duration of response and short PFS and OS, while being associated with considerable toxicity in a fragile patient population. The duration of response and effect on overall survival for durvalumab are also compelling while the safety profile is well-characterized and compares favorably to that of available chemotherapy.

☐DENY:

**12. Division's next steps and sponsor's plan for future development:**

The Sponsor has amended the protocol to increase the size of the UBC cohort in Study 1108 to 120 patients (estimated to include 70 PD-L1+ and 50 PD-L1- patients) to further evaluate the current PD-L1 selection criteria. The Sponsor may consider this a registrational trial based on the magnitude of benefit. A Phase 1 study evaluating the combination of durvalumab with a CTLA-4 inhibitor (tremelimumab) is ongoing. Lastly, a Phase 3 randomized trial (D419BC0001) is planned in treatment-naïve patients with unresectable metastatic UBC comparing durvalumab, durvalumab plus tremelimumab, and standard of care chemotherapy.

**13. List references, if any:**

Albers, P., et al. "Randomized phase III trial of 2nd line gemcitabine and paclitaxel chemotherapy in patients with advanced bladder cancer: short-term versus prolonged treatment [German Association of Urological Oncology (AUO) trial AB 20/99]." *Annals of Oncology* 22.2 (2011): 288-294.

Beer, Tomasz M., et al. "Southwest Oncology Group phase II study of irinotecan in patients with advanced transitional cell carcinoma of the urothelium that progressed after platinum-based chemotherapy." *Clinical genitourinary cancer* 6.1 (2008): 36-39.

Bellmunt, J., et al. "Association of PD-L1 Expression on Tumor Infiltrating Mononuclear Cells and Overall Survival in Patients with Urothelial Carcinoma." *Annals of Oncology* (2015): mdv009.

Choueiri, Toni K., et al. "Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer." *Journal of Clinical Oncology* 30.5 (2012): 507-512.

Culine, S., et al. "A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen." *British journal of cancer* 94.10 (2006): 1395-1401.

Faraj, Sheila F., et al. "Assessment of Tumoral PD-L1 Expression and Intratumoral CD8+ T Cells in Urothelial Carcinoma." *Urology* 85.3 (2015): 703-e1.

Huang, Yide, et al. "The prognostic significance of PD-L1 in bladder cancer."*Oncology reports* 33.6 (2015): 3075-3084.

Ko, Yoo-Joung, et al. "Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicentre, phase 2 study." *The lancet oncology* 14.8 (2013): 769-776.

Petrylak, Daniel Peter, et al. "Interim results of a randomized phase 2 study of docetaxel with ramucirumab versus docetaxel in second-line advanced or metastatic urothelial carcinoma." *ASCO Annual Meeting Proceedings*. Vol. 33. No. 7_suppl. 2015.

Raggi, D., et al. "Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: a systematic review and meta-analysis." *Annals of Oncology* 27.1 (2016): 49-61.

Sternberg, Cora N., et al. "Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy." *Cancer* 92.12 (2001): 2993-2998.

Vaughn, David J., et al. "Vinflunine in platinum-pretreated patients with locally advanced or metastatic urothelial carcinoma." *Cancer* 115.18 (2009): 4110-4117.

**14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?** YES ☒ NO ☐

**15. Clearance and Sign-Off (after MPC review):**

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: Daniel Suzman {See appended electronic signature page}
Team Leader Signature: V. Ellen Maher {See appended electronic signature page}
Division Director Signature: Geoffrey Kim {See appended electronic signature page}

**5-7-15/M. Raggio**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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SANDRA J BENTON
02/18/2016

GEOFFREY S KIM
02/18/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND (b) (4)

**GRANT –**
**BREAKTHROUGH THERAPY DESIGNATION**

AstraZeneca Pharmaceuticals LP
Attention: Jamie Gillette, MSc, RAC
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for durvalumab (MEDI4736).

We also refer to your December 18, 2015, request for Breakthrough Therapy designation. We have reviewed your request and have determined that durvalumab (MEDI4736) for the treatment of patients with programmed death-ligand 1 (PD-L1) positive inoperable or metastatic urothelial bladder cancer whose tumor has progressed during or after one standard platinum-based regimen, meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of durvalumab (MEDI4736) for the treatment of patients with PD-L1 positive inoperable or metastatic urothelial bladder cancer whose tumor has progressed during or after one standard platinum-based regimen, to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.*[1]

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics,* Attachment 1, for potential topics for discussion at

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

this initial breakthrough therapy meeting[2]. Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*[3] for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If you have any questions, contact Tracy Cutler, Regulatory Health Project Manager, at (301) 796-9608 or Tracy.Cutler@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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[2] http://www fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm

[3] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

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/s/

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GEOFFREY S KIM
02/16/2016

# LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**LATE-CYCLE MEETING MINUTES**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Imfinzi (durvalumab) 500 mg/vial and 120 mg/vial

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on March 6, 2017.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Janice Kim, Regulatory Project Manager at (301) 796-9628.

Sincerely,

*{See appended electronic signature page}*

V. Ellen Maher, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM OF LATE-CYCLE MEETING MINUTES

**Meeting Date and Time:** March 6, 2017; 1:00 PM – 2:00 PM
**Meeting Location:** White Oak Building 22; Room 1313

**Application Number:** BLA 761069
**Product Name:** durvalumab
**Applicant Name:** AstraZeneca

**Meeting Chair:** V. Ellen Maher, MD
**Meeting Recorder:** Janice Kim, PharmD, MS

**FDA ATTENDEES**
Geoffrey Kim, MD, Director, DOP1
Amna, Ibrahim, MD, Deputy Director, DOP1
Julia Beaver, MD, Supervisory Associate Director, DOP1
V. Ellen Maher, MD, Cross Discipline Team Leader, DOP1
Daniel Suzman, MD, Clinical Reviewer, DOP1
Gideon Blumenthal, MD, Associate Director for Precision Therapeutics, OHOP
Sundeep Agrawal, MD, Clinical Reviewer, DOP1
Harpreet, Singh, MD, Clinical Reviewer, DOP1
Chana Weinstock, MD, Clinical Reviewer, DOP1
Shenghui Tang, PhD, Biostatistics Team Leader, DBV
Laura Fernandes, PhD, Biostatistics Reviewer, DBV
Stacy Shord, PharmD, Clinical Pharmacology Team Leader, DCPV
Yuhong Chen, PhD, Clinical Pharmacology Reviewer, DCPV
William Pierce, PharmD, CAPT, USPHS, Associate Director Labeling, DOP1
Howard Anderson, PhD, Product Quality Team Leader, OBP
Michael Di, PhD, Product Quality Reviewer, OBP
Davinna Ligons, PhD, Product Quality Reviewer, OBP
Patricia Hughes, PhD, Lead Consumer Safety Officer, OPQ
Monica Commerford, PhD, Microbiology Reviewer, OPQ
Maria Cruz-Fisher, PhD, Microbiology Reviewer, OPQ
Diane Raccasi, PhD, Microbiology Reviewer, OPQ
Maria Jose Lopez-Barragan, PhD, Microbiology Reviewer, OPQ
Lynne Ensor, PhD, Microbiology Reviewer, OPQ
Peter Qiu, PhD, Facilities Team Leader, OPQ
Kelly Ballard, MS, Regulatory Business Process Manager, OPQ
Todd Palmby, PhD, Pharmacology/Toxicology Team Leader, DOP1
Eias Zahalka, PhD, Pharmacology/Toxicology Reviewer, DOP1
Aaron Schetter, PhD, MPH, Scientific Reviewer, CDRH
Alice Kacuba, RN, MSN, GWCPM, RAC, Chief Project Management Staff

Janice Kim, PharmD, MS, Regulatory Project Manager, DOP1

**APPLICANT ATTENDEES**
Hesham Abdullah, MD, MSc, RAC, VP, Regulatory Affairs, Oncology
Yong Ben, MD, MBA, Global Clinical Lead, Immuno-Oncology
Sean Bohen, MD, PhD, EVP, Head, Global Medicines Development (GMD)
Jennifer Eck, Director, Regulatory Affairs CMC
Jamie Gillette, MSc, RAC, Regulatory Affairs Director, Oncology
Raymond Godlewski, VP Quality and Compliance, Biologics Operations-Colorado
Ashok Gupta, MD, PhD, VP Immune-Mediated Therapy, Oncology
Tony Ho, MD, Global Medicines Leader, Durvalumab
Robert Iannone, MD, MSCE, Head, Immuno-oncology, Global Medicines Development
Praveen Marapaka, PhD, Senior Director, Regulatory Affairs, Oncology
Pralay Mukhopadhyay, PhD, Senior Director and Biometrics Team Lead
Rajesh Narwal, PhD, Principal Scientist, Clinical Pharmacology and DMPK
Ajay Parashar, BPharm, MDD, MS, RAC, Associate Director Labeling Strategy
Susan Powers, VP Quality and Compliance Biologics Operations
Andrew D. Skibo, Head, AZ Biologics Operations
William Wang, Senior Director, R&D
Pascal Soriot, Chief Executive Officer
Lolke de Haan, Senior Director, R&D
Loris Roskos, Vice President, R&D
Jill Walker, Executive Director, Diagnostics
(b) (4)

## 1.0 BACKGROUND

AstraZeneca submitted BLA 761069 on October 13, 2016 for durvalumab.

Sponsor's proposed indication: Treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4)

PDUFA goal date: June 13, 2017

FDA issued a Background Package in preparation for this meeting on March 1, 2017.

## 2.0 DISCUSSION

1. Introductory Comments

   Welcome, Introductions, Group Rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

   Facilities inspection findings:

   ***Discussion:*** [redacted] will respond to the 483 on Friday, March 10, 2017. The FDA Facilities Inspection group will review these responses and reply to [redacted]. The Facilities Inspection group may have additional requests as they review that submission.

3. Information Requests

   ***Discussion:*** Facilities will provide additional information requests to [redacted]

4. Major Labeling Issues

   ***Discussion:*** The Applicant expressed concern about inclusion of the data on the response rate by PD-L1 status in 128 patients in their package insert. The Agency stated that we will discuss this further internally. The Agency also explained why they had not included data on the response rate by PD-L1 status in all 182 patients.

5. Review Plans

   ***Discussion:*** FDA awaits the response from [redacted] to address the 483. FDA will review. FDA may have additional requests during that review.

6. Wrap-up and Action Items

   This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

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JANICE H KIM
03/21/2017

VIRGINIA E MAHER
03/21/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761069

**LATE CYCLE MEETING**
**BACKGROUND PACKAGE**

AstraZeneca UK Limited
Attention: Jamie Gillette, MS, RAC
Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Gillette:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Imfinzi (durvalumab) 500 mg/vial and 120 mg/vial.

We also refer to the Late-Cycle Meeting (LCM) scheduled for March 6, 2017. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Janice Kim, Regulatory Project Manager, at (301) 796-9628.

Sincerely,

*{See appended electronic signature page}*

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package
FDA Foreign Visitor Request Form

# LATE-CYCLE MEETING BACKGROUND PACKAGE

| | |
|---|---|
| **Meeting Date and Time:** | March 6, 2017; 1:00 – 2:00 PM |
| **Meeting Location:** | White Oak Building 22, Room 1313 |
| **Application Number:** | 761069 |
| **Product Name:** | durvalumab |
| **Indication:** | Treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4) |
| **Applicant Name:** | AstraZeneca UK Limited |

**FDA ATTENDEES (tentative)**
Geoffrey Kim, MD, Director, DOP1
Ellen Maher, MD, Cross Discipline Team Leader, DOP1
Daniel Suzman, MD, Clinical Reviewer, DOP1
Shenghui Tang, PhD, Biostatistics Team Leader, DBV
Laura Fernandes, PhD, Biostatistics Reviewer, DBV
Stacy Shord, PharmD, Clinical Pharmacology Team Leader, DCPV
Yuhong Chen, PhD, Clinical Pharmacology Reviewer, DCPV
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Michael Di, PhD, Product Quality Reviewer, OBP
Davinna Ligons, PhD, Product Quality Reviewer, OBP
Todd Palmby, PhD, Pharmacology/Toxicology Team Leader, DOP1
Eias Zahalka, PhD, Pharmacology/Toxicology Reviewer, DOP1
Janice Kim, PharmD, MS, Regulatory Project Manager, DOP1
Alice Kacuba, RN, MSN, GWCPM, RAC, Chief Project Management Staff

**APPLICANT ATTENDEES**
TBD

## INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal

date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

## BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

### 1. Discipline Review Letters

No Discipline Review letters have been issued to date.

### 2. Substantive Review Issues

The following substantive review issues have been identified to date:

- **The inspection findings at (b) (4) are a potential approvability issue.**
  - A lack of sterility assurance was observed on the (b) (4) during the media fill program. This issue may extend to the (b) (4) and affect sterility assurance of durvalumab.
  - Acceptable resolution of facility inspection findings of deficiencies are necessary for the approval of your BLA.

## ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

## REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

## LCM AGENDA

1. Introductory Comments – 5 minutes (Janice Kim/V. Ellen Maher)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 10 minutes

   Each issue will be introduced by FDA and followed by a discussion.

   - Facilities inspection findings

3. Discussion of Minor Review Issues – 5 minutes

In future submissions, please provide:

a. Flags in your adverse event dataset for events which occurred on study drug or within 30 days of discontinuation of study drug and for events which occurred on study drug or within 90 days of discontinuation of study drug;
b. An analysis dataset which contains the duration of exposure in each patient;
c. In the dataset define file, an explanation of all categories (column names) and results within the column; and
d. An integrated laboratory dataset that includes all patients in the safety database.
e. An integrated summary of safety dataset including only treatment emergent events.
f. An adverse event dataset in which Grade 5 events of the underlying disease being treated have been removed. That is, a protocol which stipulates that death due to disease progression would not be reported as an adverse event and removal of this adverse event during monitoring would be helpful. Additionally, you should attempt to differentiate the PT "general physical health deterioration."
g. An ADSL dataset in which baseline sites of disease are as per ICR evaluation.
h. In your ADSL dataset, columns indicating timing between last therapy to both progressive disease and start of study drug.
i. In your immune-mediated adverse events dataset, a flag indicating retreatment with study drug after corticosteroid administration.

4. Additional Applicant Data – 0 minutes (Applicant)

   N/A

5. Information Requests – 5 minutes

   We are awaiting your response to several information requests. (Clinical and Product Quality)

6. Discussion of Upcoming Advisory Committee Meeting – 0 minutes

   N/A

7. REMS or Other Risk Management Actions – 0 minutes

   N/A

8. Postmarketing Requirements/Postmarketing Commitments – 15 minutes

You have been notified of a post-marketing requirement to complete the Danube study and to submit study reports and datasets.

We have also asked that you commit to the following post marketing commitments:

- Provide data from Danube concerning PD-L1 status and patient outcome to Ventana to update the device label.
- Provide the median and updated information on the range of the duration of response in the 182 patients in the urothelial cancer cohort of Study 1108 who have received prior platinum-based therapy. This should be provided for all patients, patients with PD-L1 high tumor staining, and patients with PD-L1 low tumor staining.
- Reevaluate the ADA confirmatory and triple mutation assay cut points using a 1.0% false positive rate.
- Conduct drug tolerance studies for the screening, confirmatory, titering, and triple mutation assays that are in the range of the Ctrough of 182 ug/mL to better demonstrate that the assay can detect ADA in the presence of drug.
- Confirm that there is no significant growth of organisms at 2 - 8°C in the drug product diluted with 0.9% sodium chloride and 5% dextrose by performing microbiological challenge studies with diverse microorganisms to support the 24 hour storage time. Your study should include Gram-negative microorganisms (such as *E. coli* and/or *E. cloacae*) which are known to proliferate in these solutions. The challenge studies should include at a minimum time points at twice the label claim storage time. These studies can be completed as a post-marketing commitment.

9. Major labeling issues – 0 minutes

   None at this time

10. Review Plans – 5 minutes

    Complete labeling negotiations and PMC negotiations

11. Wrap-up and Action Items – 5 minutes (TBD following LCM)

# FDA Foreign Visitor Request

| | |
|---|---|
| VISITORS FULL NAME (First, Middle, Last) | |
| GENDER | |
| COUNTRY OF ORIGIN/CITIZENSHIP | |
| DATE OF BIRTH (MM/DD/YYYY) | |
| PLACE OF BIRTH (city and country) | |
| PASSPORT NUMBER:<br>COUNTRY THAT ISSUED PASSPORT:<br>ISSUANCE DATE:<br>EXPIRATION DATE: | |
| VISITOR ORGANIZATION/EMPLOYER | |
| | |
| MEETING START DATE AND TIME | |
| MEETING ENDING DATE AND TIME | |
| PURPOSE OF MEETING | |
| BUILDING(S) & ROOM NUMBER(S) TO BE VISITED | |
| WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED? | |
| POINT OF ENTRY<br>(This is the building that the foreign visitor will enter) | |
| HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number) | |
| ESCORT INFORMATION (If different from Hosting Official) | |

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/s/

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JANICE H KIM
03/01/2017

GEOFFREY S KIM
03/01/2017