



BLA 761034/S-009

**SUPPLEMENT APPROVAL**

Genentech, Inc.  
Attention: Andrew Chia, Pharm.D., M.S.  
Regulatory Program Management  
1 DNA Way  
South San Francisco, CA 94080-4990

Dear Dr. Chia:

Please refer to your supplemental Biologics License Application (sBLA) dated March 2, 2018, submitted under section 351(a) of the Public Health Service Act for Tecentriq (atezolizumab), injection, 1200 mg/20 mL (60 mg/mL).

We also refer to our approval letter dated December 6, 2018, which contained the following error: the milestone for postmarketing commitment (PMC) 3549-3 for the submission of the OAK and IMpower150 was incorrectly titled "Final Reports Submission (OAK and IMpower150)." This letter contains the correct title for these submissions "Interim Study Report Submission" for the OAK and the IMpower150 studies.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain December 6, 2018, the date of the original approval letter.

We also acknowledge receipt of your August 23 and August 27, 2018, submissions which together constituted a major amendment and extended the goal date by three months.

This Prior Approval supplemental biologics application provides for a new indication for Tecentriq, in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of patients with metastatic non-squamous, non-small cell lung cancer (NSq NSCLC), with no EGFR or ALK genomic tumor aberrations.

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

## **WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS**

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), 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>, that is identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **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 are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because non-squamous non-small cell lung cancer is rare in the pediatric population.

### **POSTMARKETING COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

Conduct an assessment of the effect of atezolizumab anti-drug antibodies (ADA) on pharmacokinetics and key efficacy endpoints including overall survival (OS), progression-free survival (PFS), and overall response rate (ORR) in non-small cell lung cancer (NSCLC) Studies POPLAR, OAK, IMpower150, IMpower130, IMpower131, and IMpower132. The final report will include the datasets and the following analyses:

- Individual trial analyses assessing the effects of ADA on the pharmacokinetics (PK) as geometric and arithmetic mean changes in drug clearance (CL) and Cmin with corresponding standard deviation and statistical significance between ADA-negative and treatment-emergent ADA-positive patients.
- The ADA rate; median time to detection of ADA; median duration of ADA positivity in months, and the numbers of doses (before/after first detection of ADA and total) received in patients with treatment-emergent ADA.
- Effect of “early” ADA (e.g., based on ADA at Week 4 or at another early visit with adequate justification) on efficacy outcome measures (OS, PFS, and ORR) in individual trials using the following three approaches:
  - 1) Propensity score matching approach. The propensity score matching criteria are expected to be consistent across all trials. The categorical PD-L1 variable with a consistent cutoff will be included in the analysis as applicable. Comparison of the demographic distribution of each covariate used in propensity score matching for the ITT population and for the ADA- positive (ADA+), ADA-negative (ADA-), and control subgroups before propensity score matching for each clinical trial should be provided using tables. Distribution of covariates between the ADA subgroups (ADA+ and ADA-) for the treatment arm and their corresponding matching subgroups for the control arm after propensity score matching should also be compared to demonstrate that matching is acceptable.
  - 2) Inversed probability of treatment weight (IPW) approach. The factors included in the IPW are expected to be consistent across all trials as applicable and be consistent to the propensity score matching approach.
  - 3) Tumor growth inhibition-overall survival (TGI-OS) modeling approach for individual trials.

For all analyses performed, include the following information in the final study report: the model codes and output listings; all datasets as a SAS transport files (\*.xpt); and a description of each data item in a define.xml file.

The timetable you submitted on December 4, 2018, states that you will conduct this study according to the following schedule:

Draft Analysis Plan Submission: 11/2018  
Final Analysis Plan Submission: 12/2018  
Final Reports Submission: 03/2019

**PMC 3549 - 2**

Conduct an assessment of the effect of atezolizumab anti-drug antibodies (ADA) on pharmacokinetics and key efficacy endpoints including overall survival (OS), progression free survival (PFS), and overall response rate (ORR) in IMvigor211 (UC), IMmotion151 (1L RCC), IMpower133 (SCLC), and IMpassion130 (TNBC) and data from all other relevant, randomized clinical trials that will be analyzed as of a specific date (e.g., September 1, 2018). The final report will include datasets and the following analyses:

- Individual trial and pooled analyses assessing the effects of ADA on the pharmacokinetics (PK) as geometric and arithmetic mean changes in drug clearance (CL) and Cmin with corresponding standard deviation and statistical significance between ADA-negative and treatment-emergent ADA-positive patients. The pooled analyses will include all studies listed in PMCs #1 and #2 (IMpassion130 will be included where applicable).
- The ADA rate, median time to detection of ADA; median duration of ADA positivity in months; and the numbers of doses (before/after first detection of ADA and total) received in patients with treatment-emergent ADA.
- Effects of “early” ADA (e.g., based on ADA at Week 4 or at another early visit with adequate justification) on efficacy outcome measures (OS, PFS, and ORR) in individual trials using the following three approaches:
  - 1) Propensity score matching approach. The propensity score matching criteria are expected to be consistent across all trials. The categorical PD-L1 variable with a consistent cutoff will be included in the analysis as applicable. Comparison of the demographic distribution of each covariate used in propensity score matching for the ITT population and for the ADA- positive (ADA+), ADA-negative (ADA-), and control subgroups before propensity score matching for each clinical trial should be provided using tables. Distribution of covariates between the ADA subgroups (ADA+ and ADA-) for the treatment arm and their corresponding matching subgroups for the control arm after propensity score matching should also be compared to demonstrate that matching is acceptable.
  - 2) Inversed probability of treatment weight (IPW) approach. The factors included in the IPW are expected to be consistent across all trials as applicable and be consistent to the propensity score matching approach.
  - 3) Tumor growth inhibition-overall survival (TGI-OS) modeling approach for individual trials.

- The results of integrated efficacy analyses that incorporate the results of each of the individual studies listed in PMC #1 and #2. In the analysis plan for each integrated analysis, clarify how the results of each individual study will be weighted or adjusted and provide the assessment of the interpretation of this integrated analysis for each of the analyses described above.

For all analyses performed, include the following information in the final study report: the model codes and output listings; all datasets as a SAS transport files (\*.xpt); and a description of each data item in a define.xml file.

The timetable you submitted on December 4, 2018, states that you will conduct this study according to the following schedule:

Draft Analysis Plan Submission: 11/2018  
Final Analysis Plan Submission: 12/2018  
Final Reports Submission: 03/2019

### **PMC 3549 – 3**

Conduct an assessment of the effect of atezolizumab neutralizing antibodies (NAb) on pharmacokinetics and key efficacy endpoints including overall survival (OS), progression-free survival (PFS), and overall response rate (ORR) in NSCLC studies POPLAR, OAK, IMpower150, IMpower130, IMpower131, IMpower132, as well as IMvigor211 (UC), IMmotion151 (1L RCC), IMpower133 (SCLC), IMpassion130 (TNBC) and data from all other relevant, randomized clinical trials that will be analyzed as of a specific date (e.g., September 1, 2018). The final report will include datasets and the following analyses:

- Individual trial and pooled analyses (IMpassion130 included where applicable) assessing the effects of NAb on the pharmacokinetics (PK) as geometric and arithmetic mean changes in drug clearance (CL) and C<sub>min</sub> with corresponding standard deviation and statistical significance between NAb-negative and treatment-emergent NAb positive patients.
- The NAb rate, median time to detection of NAb, and the numbers of doses (before/after first detection of NAb and total) received in patients with treatment-emergent NAb.
- Effects of “early” NAb (e.g., based on NAb at Week 4 or at another early visit adequate justification) and at other appropriate timepoints relevant to the development of NAb on efficacy outcome measures (OS, PFS, and ORR) in individual trials using the following three approaches:
  - 1) Propensity score matching approach. The propensity score matching criteria are expected to be consistent across all trials. The categorical PD-L1 variable with a consistent cutoff will be included in the analysis as applicable. Comparison of the demographic distribution of each covariate used in propensity score matching for the ITT population and for the NAb-positive (NAb+), NAb-negative (NAb-), and

control subgroups before propensity score matching for each clinical trial should be provided using tables. Distribution of covariates between the NAb subgroups (NAb+ and NAb-) for the treatment arm and their corresponding matching subgroups for the control arm after propensity score matching should also be compared to demonstrate that matching is acceptable.

- 2) Inversed probability of treatment weight (IPW) approach. The factors included in the IPW are expected to be consistent across all trials as applicable and be consistent to the propensity score matching approach.
  - 3) Tumor growth inhibition-overall survival (TGI-OS) modeling approach for individual trials.
- The results of integrated efficacy analyses that incorporate the results of each of the individual studies listed in PMC #1 and #2. In the analysis plan for each integrated analysis, clarify how the results of each individual study will be weighted or adjusted and provide the assessment of the interpretation of this integrated analysis for each of the analyses described above.

For all analyses performed, include the following information in the final study report: the model codes and output listings; all datasets as a SAS transport files (\*.xpt); and a description of each data item in a define.xml file.

The timetable you submitted on December 4, 2018, states that you will conduct this study according to the following schedule:

|  |         |
|--|---------|
| Final Analysis Plan Submission:                                      | 12/2018 |
| Interim Study Report for the OAK study                               | 03/2019 |
| Interim Study Report for the IMpower150 study                        | 03/2019 |
| Final Reports Submission (all other studies and integrated analyses) | 09/2019 |

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 117296 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,” or “Postmarketing Commitment Correspondence.”

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
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> ).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above, by fax to 301-847-8444, or 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> ).

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Gina Davis, Senior Regulatory Health Project Manager,  
at (301) 796-0704.

Sincerely,

*{See appended electronic signature page}*

Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

PATRICIA KEEGAN  
12/06/2018 12:00:00 AM