CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761041Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	761041
Supporting document/s:	1, 2
Sponsor's letter date:	February 19, 2016
CDER stamp date:	February 19, 2016
Product:	Tecentriq (atezolizumab)
Indication:	Tecentriq is indicated for patients with locally advanced or metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Tecentriq.
Sponsor:	Genentech, Inc. 1 DNA Way South San Francisco, CA
Review Division:	Division of Hematology Oncology Toxicology (Division of Oncology Products 1)
Reviewer:	Tiffany K. Ricks, PhD
Supervisor/Team Leader:	Todd Palmby, PhD
Division Director:	John Leighton, PhD, DABT (DHOT) Geoffrey Kim, MD (DOP1)
Project Manager:	Sakar Wahby, PharmD

EXECUTIVE SUMMARY

Tecentriq (atezolizumab) is a humanized, Fc-engineered, IgG1, monoclonal antibody targeting programmed death-ligand 1 (PD-L1). PD-L1 is an immune checkpoint inhibitor that negatively regulates immune responses by binding to PD-1 and B7.1 receptors[1, 2]. PD-L1 is constitutively expressed on immune cells, including T cells, B cells, dendritic cells, and macrophages. PD-L1 is also expressed on a number of non-hematopoietic cells, and its expression can be induced upon stimulation. PD-L1 signaling dampens lymphocyte activation to preserve immune tolerance and prevent immune-mediated tissue injury. On tumor cells and tumor infiltrating lymphocytes, PD-L1 can inhibit T cell proliferation and function, leading to evasion of immune surveillance. Blocking the PD-L1 pathway releases inhibition of the immune response, including immune-mediated anti-tumor activity and peripheral tolerance.

The US FDA recently approved Tecentriq under accelerated approval for the treatment of patients with locally advanced or metastatic urothelial carcinoma. To support the current BLA 761041, the Applicant submitted new clinical data for use of Tecentriq in patients with locally advanced or metastatic non-small cell lung cancer, who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy prior to receiving Tecentriq. The Applicant also submitted nonclinical pharmacology and toxicology data, which was reviewed previously under BLA 761034 for the urothelial carcinoma indication. There were no changes to the prescribing information in sections pertaining to nonclinical information. From the nonclinical perspective, Tecentriq is recommended for approval for the proposed indication.

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[1] Francisco, LM, PT Sage, and AH Sharpe, 2010, The PD-1 Pathway in Tolerance and Autoimmunity, Immunol Rev, 236:219-42.

[2] Keir, ME, MJ Butte, GJ Freeman, and AH Sharpe, 2008, PD-1 and its Ligands in Tolerance and Immunity, Annu Rev Immunol, 26:677-704.

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/s/

TIFFANY RICKS
08/25/2016

TODD R PALMBY
08/26/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA

BLA Number: 761041 **Applicant: Genentech Inc.** **Stamp Date: February 19, 2016**

Drug Name: atezolizumab (MPDL3280A) **BLA Type: BLA (351 a)**

On **initial** overview of the BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The Applicant's proposed labeling will be reviewed during the BLA review.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		Acceptability of the Applicant's proposed specification will be determined during the BLA review.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time.

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/s/

TIFFANY RICKS
03/18/2016

TODD R PALMBY
03/21/2016