CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761049Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES - MEMO

NDA/BLA #:	BLA 761049
Drug Name:	BAVENCIO ® (avelumab)
Indication(s):	For the treatment of patients with metastatic Merkel cell carcinoma
Applicant:	EMD Serono
Date(s):	Submitted: 07/06/2016, 09/02/2016, 09/23/2016 (rolling submission)
	Review Completion: 02/23/2017
	PDUFA goal: 05/23/2017
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Pallavi Mishra-Kalyani, Ph.D.
Concurring Reviewers:	Kun He, Ph.D., Statistical Team Leader
	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Office of Hematology and Oncology Products, Division of Oncology Products 2
Clinical Team:	Denise Casey, M.D., Clinical Reviewer
	Suzanne Demko, PA-C, Clinical Review Team Leader
	Patricia Keegan, M.D., Division Director
Project Manager:	Idara Udoh, M.S.
Keywords:	Single arm trial, Response rate

The statistical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. From a statistical standpoint, the BLA is acceptable to support accelerated approval.

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

/s/

PALLAVI S MISHRA-KALYANI
02/23/2017

KUN HE
02/23/2017

RAJESHWARI SRIDHARA
02/23/2017

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	BLA 761049
Supplement #:	NA
Related IND #:	IND number associated with the drug, if applicable.
Product Name:	Bavencio (avelumab)10 mg/kg IV Q2W
Indication(s):	Treatment of patients with unresectable or metastatic Merkel cell carcinoma
Applicant:	EMD Serono
Dates:	Date of Receipt: 10/23/2016 Filing Date: 11/22/2016 PDUFA Date: 05/23/2017
Review Priority:	Standard
Biometrics Division:	DBV
Statistical Reviewer:	Pallavi Mishra-Kalyani
Concurring Reviewers:	Kun He (Team Leader) Rajeshwari Sridhara (Division Director)
Medical Division:	OHOP, DOP2
Clinical Team:	Denise Casey (Clinical Reviewer) Suzanne Demko -*(Team Leader) Patricia Keegan (Division Director)
Project Manager:	Idara Udoh

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
T-003A	SA, OL trial	N = 88	Primary: ORR Key Secondary: DOR	ORR: 31.8%, 95% CI (21.9%, 43.1%)

* MC: multi-center, SA: single-arm, R: randomized, OL: open-label, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments

Designs utilized are appropriate for the indications requested.	Study design is adequate
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Relevant endpoints and analysis plan are specified
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	Interim analysis plan is specified
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	NA
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Investigation of missing data is adequate

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	P:\BLAs\BLA761049\Clinical\emr100070-003\Datasets\Tabulations\SDTM
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	SDTM
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	RS
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols,	X			

Content Parameter	Yes	No	NA	Comments
subsequent amendments, etc.).				
Safety and efficacy were investigated for gender, racial, and geriatric subgroups.	X			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			
Application appears to be free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements.	X			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE? Yes

5. Comments to be conveyed to the Applicant

5.1. Refuse-to-File Issues

None

5.2. Information Requests/Review Issues

None at this time.

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

/s/

PALLAVI S MISHRA-KALYANI
11/21/2016

KUN HE
11/21/2016