CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761038Orig1s000

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: October 17, 2016

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

SUBJECT: Division Director Summary Review

TO: BLA 761038

Refer to the Integrated Multidisciplinary Review for additional details

I concur with the review team's and consultants' recommendation that the BLA for olaratumab should be approved under the provisions of 21 CFR 601.41. My recommendation is based on the totality of the evidence, including treatment effects on secondary endpoints, safety issues, and the size and quality of the trial. The data supporting approval consist of the results of a single, small, randomized, multicenter clinical trial demonstrating statistically significant treatment effect on the primary endpoint, progression-free survival, at the pre-specified level of significance (0.2, two-sided), a highly statistically significant effect on overall survival that is clinically meaningful but uncertain in magnitude given large confidence intervals around the observed estimate, and incremental risks from the addition of olaratumab to doxorubicin, which do not outweigh the benefit of an improvement in overall survival. I note that the treatment effects on progression-free survival and overall response rate were not clinically meaningful and that the robustness of the effect on progression-free survival was influenced by the observer (investigator vs. independent review) and statistical test method (e.g., stratified vs. unstratified log-rank vs. re-randomization) employed. Limitations of the application are reliance on a trial with a small sample size where treatment effects may be overestimated and assessment of effects in a heterogeneous patient population, based on the number of subtypes of soft tissue sarcoma enrolled.

As a condition of accelerated approval, clinical trials will be required to further verify and describe the clinical benefit of olaratumab by obtaining a more precise estimate of the treatment effect on survival.

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/s/

PATRICIA KEEGAN
10/19/2016

MEMORANDUM

DATE: October 17, 2016
FROM: Marc Theoret
TO: File for BLA 761038 Olaratumab
Re: CDTL Review for BLA 761038

Eli Lilly and Company submitted BLA 761038 for olaratumab (LARTRUVO) in combination with doxorubicin for the treatment of patients with advanced soft tissue sarcoma (STS) not amenable to curative treatment with surgery or radiotherapy. The cross-discipline team leader (CDTL) review is complete and has been added to the BLA Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. This reviewer recommends accelerated approval (21 CFR 601, subpart E) of olaratumab for the following indication:

> in combination with doxorubicin, for the treatment of patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.

Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

MARC R THEORET
10/17/2016

MEMORANDUM

DATE: July 29, 2016
FROM: Meredith Chuk, Leslie Doros
THROUGH: Marc Theoret
TO: File for BLA 761038 Olaratumab
Re: Clinical Review for BLA 761038

Eli Lilly and Company submitted BLA 761038 for olaratumab (LARTRUVO) in combination with doxorubicin for the treatment of patients with soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery. The clinical review of safety and efficacy is complete and has been added to the NDA/BLA Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. The clinical reviewers recommend the accelerated approval (21 CFR part 601, subpart E) of olaratumab in combination with doxorubicin, for the treatment of patients with soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery and with a histologic subtype for which an anthracycline-containing regimen is appropriate. Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

MEREDITH K CHUK
07/29/2016

LESLIE A DOROS
07/29/2016

MARC R THEORET
07/29/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 761038 | **Applicant: Eli Lilly and Company** | **Stamp Date: 2/24/2016**

Drug Name: Olaratumab (Lartruvo) | **NDA/BLA Type: NME**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			All documents are submitted in English
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			As agreed to in the Meeting Preliminary Comments communicated to the Applicant on August 14, 2015 (Type B administrative meeting for planned BLA), the ISS cross-references the text portion of Section 2.7.4 and contains additional safety data from other studies to support the safety review
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			As agreed to in the above administrative meeting prior to submission, the ISE cross-references Section 2.7.3
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).			X	The application is a BLA [351(a)]
505(b)(2) Applications					
13.	If appropriate, what is the relied upon listed drug(s)?			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: IMCL CP15-0601 Study Title: Phase 1 Study of Anti-Platelet Derived Growth Factor Receptor Alpha (PDGFRα) Monoclonal Antibody IMC-3G3 in Patients With Advanced Solid Tumors Who No Longer Respond to Standard Therapy or For Whom No Standard Therapy Is Available Sample Size: 20 Arms: 1 Location in submission: 5.3.3.2	X			
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #JGDG: A Phase 1b/2 Randomized Phase 2 Study Evaluating the Efficacy of Doxorubicin With or Without a Human Anti-PDGFRα Monoclonal Antibody (IMC-3G3) in the Treatment of Advanced Soft Tissue Sarcoma Indication: Patients with advanced unresectable or metastatic sarcoma.	X			Adequate for the severe and life-threatening nature of the indication.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	There was no previous Agency commitment/agreement as trial JGDG was not designed as a registration trial.
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			Trial was conducted entirely in the US
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			Adequate for the severe and life-threatening nature of the indication
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 17.1 was used
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			This is a first-in-class drug
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Provided in Section 14.3.5
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Granted orphan drug designation for sarcoma
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical 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.

Meredith K. Chuk and Leslie Doros — 3/21/2016

Reviewing Medical Officer — Date

Clinical Team Leader — Date

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/s/

LESLIE A DOROS
03/22/2016

MEREDITH K CHUK
03/23/2016

MARC R THEORET
03/23/2016