Our STN: BL 125773/0

LATE-CYCLE MEETING MEMORANDUM
December 20, 2023

Iovance Biotherapeutics, Inc.
Attention: Guy C. Ruble, PharmD, RAC
825 Industrial Road
San Carlos, CA 94070

Dear Dr. Ruble:

Attached is a copy of the memorandum summarizing your November 20, 2023 Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact Catherine Tran at Catherine.Tran@fda.hhs.gov.

Sincerely,

Beatrice Kallungal, MS
Director
Division of Review Management and Regulatory Review 1
Office of Review Management and Regulatory Review
Office of Therapeutic Products
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time:	November 20, 2023, 11:00 AM - 12:00 PM EST
Meeting Location:	Zoom
Application Number:	BLA 125773/0
Product Name:	Lifileucel
Proposed Indications:	Treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor
Applicant Name:	Iovance Biotherapeutics, Inc.
Meeting Chair:	Karin Knudson, PhD
Meeting Recorder:	Catherine Tran, MS

FDA ATTENDEES

Marie Anderson, PhD, CBER/OCBQ/DBSQC
Peter Bross, MD, CBER/OTP/OCE
Hector Carrero, CBER/OCBQ/DMPQ
Benjamin Cyge, CBER/OCBQ/DCM
Tianjiao Dai, PhD, CBER/OBPV/DB
Asha Das, MD, CBER/OTP/OCE
Jaikumar Duraiswamy, PhD, CBER/OTP/OCTHT
Char-Dell Edwards, BS, MT, CBER/OCBQ/DIS
Melanie Eacho, PhD, RAC, CBER/OTP/OCTHT
Iain Farrance, PhD, CBER/OTP/OCTHT
Qianmiao Gao, PhD, CBER/OBPV/DB
Varsha Garnepudi, MS, RAC, CBER/OCBQ/DBSQC
Christine Harman, PhD, OCBQ/DMPQ
Jana Highsmith, CBER/OCBQ/DMPQ
Lianne Hu, PhD, MD, MPH, MS, CBER/OTP/OCE
Christopher Jason, MD CBER/OBPV/DPV
Sukhanya Jayachandra, PhD, CBER/OTP/OCTHT
Beatrice Kallungal, MS, CBER/OTP/ORMRR
Saravanan Karumbayaram, M Pharm, PhD, CBER/OTP/OCTHT
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Karin Knudson, PhD, CBER/OTP/OCTHT
Carolyn Laurencot, PhD, CBER/OTP/OCTHT
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Shiowjen Lee, PhD, CBER/OBPV/DB
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Elizabeth Lessey-Morillon, PhD, CBER/OTP/OCTHT
Heather Lombardi, PhD, CBER/OTP/OCTHT
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Steven Oh, PhD, CBER/OTP/OCTHT

Lori Peters, CBER/OCBQ/DMPQ
Douglas Rouse, MD, MPH, CBER/OBPV/DPV
Andrey Sarafanov, PhD CBER/OTP/OPPT
Ramani Sista, PhD, CBER/OTP/ORMRR
Lisa Stockbridge, PhD, CBER/OCBQ/DCM
Million Tegenge, PhD, CBER/OTP/OCE
Wojtek Tutak, CBER/OTP/OCTHT
Catherine Tran, MS, CBER/OTP/ORMRR
Nadia Whitt, MS, CBER/OTP/ORMRR
Yongjie Zhou, PhD, MD, CBER/OTP/OPT

APPLICANT ATTENDEES
Michelle Abelson, PhD, Executive Director, Research
Igor Bilinsky, PhD, Chief Operating Officer
Erwin Cammaart, MS, Executive Director, Process Development
Jeff Chou, MD, Senior Vice President, Clinical Science
Tanya Cope, MPH, Senior Director, Clinical Quality Assurance
Jamie Crawford, MS, Vice President, iCTC Manufacturing
Iain Dukes, DPhil, Director
Ulrich Ernst, PhD, Senior Vice President, Technical Operations
Brian Gastman, MD, Executive Vice President, Medical Affairs
Michele Fernandes, PMP, Senior Vice President, Portfolio Management
Friedrich Graf Finckenstein, MD, Chief Medical Officer
Malou Gemeniano, PhD, Vice President, CMC Regulatory
Angela Holton, PhD, Executive Director, Analytical Development
Anneliese Jameson, MA, Vice President, Clinical Operations
Andrew Jones, BECP, Vice President, Commercial Quality
Andrea Karpinecz, MS, Vice President, Quality Control
Huiling Li, PhD, Senior Vice President, Biostatistics
Marcus Littman, MBA, Vice President, Patient Safety
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Arvind Natarajan, PhD, MBA, Senior Vice President, Process & Analytical Development
Himani Parikh, MS, Senior Director, Regulatory Affairs
Bruce Phillips, MBA, Senior Vice President, Internal Manufacturing
Peter Prieto, MD, Senior Vice President, Medical Affairs
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Steve Rabin, PhD, Senior Director, CMC Regulatory Affairs
Ramona Repaczki-Jones, Executive Director, ATC Operations
Leslie Rosati, MS, Director, Analytical Services & Analytical Technology
Guy Ruble, PharmD, RAC, Vice President, Regulatory
Jonathan Rubin, PhD, Director, Process Development
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Kevin Smyth, MS, Senior Vice President, Quality
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Michael Weiser, MD, PhD, Director
Renee Wu, PhD, Executive Director, Biostatistics
Joe Wypych, MBA, Senior Vice President, MSAT & EM
Hequn Yin, PhD, Senior Vice President, Research
Ryan Yamagata, PhD, Senior Director, CMC Biostatistics

BACKGROUND
BLA 125773/0 was submitted on March 27, 2023, for lifileucel (AMTAGVI).

Proposed indication: Treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor

PDUFA goal date: February 24, 2024

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on November 9, 2023.

DISCUSSION

1. Discussion of Substantive Review Issues

   The Agency has listed the remaining Chemistry, Manufacturing, and Control (CMC) issues under the substantive review issues header. Some of the issues are now considered minor issues or have been resolved based on the Applicant's responses to information requests.

   i. Product specifications
   The Agency summarized concerns previously communicated at an informal teleconference and in CMC information request (IR) #16 (both dated November 9, 2023) and indicated that revision of the product specifications is necessary to provide reasonable assurance of product quality and control. The Agency also noted that the relevance of the potency/identity matrix critical quality attributes (CQAs) for product quality and potency remains unclear due to the overlapping distribution of the product attributes across lots that displayed or did not display clinical efficacy. The Agency, however, acknowledged that determining clinically meaningful CQAs is difficult because, while the manufacturing process is fairly simple, the product is highly complex, variable, and currently not well-defined. In CMC IR #16, the Agency proposed revisions to the commercial product release acceptance criteria (AC) for the potency/identity matrix based on product lots administered to subjects resulting in objective clinical responses. The Agency acknowledged the Applicant's response to CMC IR #16 (received on November 15, 2023) in which the Applicant argued that lots received by subjects with stable disease (SD) for a duration of (b) (4) should also be included in the dataset used to determine the release AC for the potency/identity matrix, but indicated that the more permissive AC proposed by the Applicant were under review and the CMC review team did not have additional comments at this time.

   The Agency is reviewing the Applicant's November 20, 2023 email response to Clinical IR #12 regarding dosing in subjects who achieved SD. While the Agency has not made a final determination on the recommended lifileucel dose, the Agency noted that the responders in the C-144-01 clinical study all received a product dose of greater than (b) (4) cells.

   The Applicant reiterated their justification for using lots received by subjects with (b) (4) SD to determine product dosing and release AC, stating that this length of SD is not part of the natural course of the disease and is longer than progression-free durations experienced by patients treated with chemotherapy. The Applicant noted that disease is confirmed by imaging and verified by a radiologist, and must be progressing upon enrollment. Patients receiving (b) (4) cells have the same SD outcome. The

Agency acknowledged the complexity in identifying clinically meaningful outcome and agreed to review the IR response and follow-up as needed.

The Agency also addressed two statements from the Applicant's response to CMC IR #16. First, the Applicant requested clarification of the Agency's estimate that proposed updates to the release AC would lead to approximately (b) (4) of commercial lots failing to meet specifications. The Agency clarified that this statement did not refer to the cumulative failure rate, but to the number of lots that would fail per release specification, with the highest failure rate observed in the revision to the product dose. The Agency, however, indicated that both the individual and cumulative specification failure rates will be considered during review of the Applicant's response. Second, the Applicant stated in their response to CMC IR #16 that FDA had agreed with the proposed AC for viability, (b) (4) and (b) (4) (b) (4) However, the Agency clarified that no such agreement had been communicated for any of the proposed release AC. The Agency stated that comments provided in CMC IR #16 focused on specific attributes in the potency/identity matrix, but additional proposed revisions to these and other release AC may be forthcoming.

In addition, the Agency reiterated that if the BLA were approved, (b) (4) (b) (4) The Applicant stated that release of a (b) (4) (b) (4) commercially will impact commercial sustainability. Additionally, (b) (4) lots may be confusing to patients and clinicians, and patients (b) (4)

ii. Comparability

The Agency requested reanalysis of the (b) (4)/iCTC comparability study using an alternative reference population at an informal teleconference and in CMC IR #16 (both dated November 9, 2023). The Agency acknowledged that the Applicant had provided this reanalysis and that the results demonstrated that all in-process and release attributes assessed in the (b) (4)/iCTC comparability study met the equivalence AC or quality ranges. As such, the Agency stated that the (b) (4)/iCTC analytical comparability assessment based on product testing appears reasonable and this is no longer considered a major review issue.

However, the Agency reiterated the limitations surrounding the CQAs assessed in this comparability protocol for a (b) (4) The Agency emphasized that it will be very challenging to complete a convincing comparability exercise to support future major manufacturing changes without additional (b) (4) The Agency

recommended that the Applicant perform extensive (b) (4) (b) (4) and stressed that additional clinical studies may be required after a (b) (4) if product comparability cannot be established through analytical product testing alone. The Applicant acknowledged this advice and indicated that they intended to conduct additional (b) (4) their product.

iii. Process control

The Agency acknowledged that the additional in-process controls proposed by the Applicant in response to CMC IR #11 (received August 28, 2023) likely provide better control of the manufacturing process, but indicated that additional clarification of the resulting actions for lots that do not meet the proposed action limits was needed. In CMC IR #17 (sent November 16, 2023), the Agency noted some discrepancies found in the CMC section regarding the process control strategy and asked the Applicant to clarify if lots that do not meet IPC but meet release specifications would be able to be released commercially. The Agency also asked the Applicant to establish AC for the new in-process control evaluating the frequency of (b) (4) on (b) (4) based on the manufacturing campaign data provided in REP-0370 (submitted on August 17, 2023), or explain why these data are not appropriate for establishing an AC for this IPC.

The Applicant stated they will provide response to CMC IR #17 as requested. The Applicant explained that the available in-process data for frequency of (b) (4) was collected with a different (b) (4) specifically the (b) (4) instead of the current (b) (4) machine, and that this instrument change requires a redefined assay. The Applicant proposed to establish an interim AC for this in-process control until enough commercial lots can be evaluated to establish a relevant AC and asked if the Agency agreed with this approach. The Agency agreed to consider the proposal but deferred any additional comment until after reviewing the pending IR response.

iv. Flow cytometry assay control

The Agency acknowledged the Applicant's response to CMC IR #14 (received September 19, 2023,) but noted that unaddressed concerns with the (b) (4) strategy and control of the flow cytometry assay were communicated in CMC IR #17 (dated November 16, 2023). The Applicant stated they intend to address all of the flow cytometry (b) (4) issues by adopting the (b) (4) strategies proposed by the Agency in CMC IR #17, and will submit a response to CMC IR #17 on November 22, 2023. The Agency stated they will review the pending IR response and follow-up as needed.

v. Cumulative leachables assessment

The Agency referred to CMC IR #6 (dated July 21, 2023) notifying the Applicant that a real-time study assessing cumulative leachables should be

performed, noting that the Applicant had agreed to conduct such a study in their response to CMC IR #6 (dated July 25, 2023). The Agency stated that a future communication will further address topics surrounding the cumulative leachables study protocol and completion of this study.

The Agency asked three clarifying questions to the Applicant about their future cumulative leachables assessment. First, the Agency asked whether the Applicant plans to perform a simulated cumulative leachables assessment. The Applicant confirmed they will perform a simulated cumulative leachables assessment. Second, the Agency asked for the specific process step from which the cumulative leachables assessment will start. The Applicant stated they will start the cumulative leachables study at high-risk (b) (4) The Agency agreed that starting from (b) (4) is most critical and that all subsequent processing steps should be included in the study. The Agency also stated that the full shelf-life of the product should also be evaluated in the study, and the maximum process time and temperature ("in-use" conditions) according to the final specification should be tested. In addition, both organic and elemental leachables should be assessed in the cumulative leachables assessment, and the Applicant should use a (b) (4) safety margin. The Applicant confirmed inclusion of all of the Agency's recommendations in the future cumulative leachables study.

2. Discussion of established Pharmacologic Class

   The Applicant's proposal of pharmacologic class is "autologous T cell immunotherapy." The Agency's review of the pharmacological class is ongoing.

3. Discussion of Minor Review Issues

   There were no minor review issues discussed in this meeting.

4. Additional Applicant Data

   The Applicant did not have additional data in this meeting. The Applicant is available for informal teleconferences as the review continues.

5. Information Requests

   Response to the CMC IR #16 sent November 9, 2023, has been received on November 15, 2023 and is pending review. Response to CMC IR #17 is projected for November 22, 2023. Response to CMC IR #18 and a partial response to Clinical IR #12 were both received on November 20, 2023 and are pending review. The Agency may send additional information requests as warranted as the review continues.

6. Risk Management Actions (e.g., REMS, the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk)

   The Agency does not anticipate a REMS at this time.

7. Postmarketing Requirements/Postmarketing Commitments

   a. CMC
      The review of the CMC information is ongoing. The Agency's determination on PMR/PMCs is pending at this time.

   b. Pharmacovigilance
      The review of the pharmacovigilance plan is ongoing. The Agency's determination on postmarketing safety study(ies) is pending at this time. The Applicant asked for Agency comments to the pharmacovigilance plan. The Agency's review is ongoing and any comments will be provided after the review.

8. Major Labeling Issues

   The label review is ongoing. The Agency does not have any major labeling issues to communicate at this time.

9. Review Plans

   The Agency plans to send any labeling comments by January 25, 2024. The Applicant requested an earlier notice of labeling comments. The Agency can provide a notice of upcoming labeling comments when the labeling review is near completion.

10. Applicant Questions

    The Applicant asked when the review of the (b) (4) will be completed. The Agency will complete the (b) (4) (b) (4)

11. Wrap-up and Action Items

    The Late Cycle Meeting Summary will be sent by December 20, 2023.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.