Our STN: BL 125773/0

MID-CYCLE COMMUNICATION SUMMARY
August 25, 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 summary of your July 27, 2023, Mid-Cycle Communication Teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to STN 125773 in your future submissions related to lifileucel.

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

Sincerely,

Melanie Eacho, PhD
Director
Division of Cell Therapy 1
Office of Cellular Therapy and Human Tissue
Office of Therapeutic Products
Center for Biologics Evaluation and Research

Mid-Cycle Communication Teleconference Summary

Application Type and Number:	BLA 125773/0
Product Name:	lifileucel
Proposed Indication for Use:	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:	Iovance Biotherapeutics, Inc.
Meeting Date & Time:	July 27, 2023, 11:00 - 11:50 AM EST
Committee Chair:	Karin Knudson, PhD
Regulatory Project Manager:	Catherine Tran, MS

Attendees:

FDA Attendees:

Meghna Alimchandani, MD, CBER/OBPV/DPV
Katherine Barnett, MD, CBER/OTP/OCE
Peter Bross, MD, CBER/OTP/OCE
Hector Carrero, CBER/OCBQ/DMPQ
Dennis Cato, CBER/OCBQ/DIS
Elin Cho, MS, CBER/OBPV/DB
Monique Cortez, MS, CBER/OTP/ORMRR
Benjamin Cyge, CBER/OCBQ/DCM/APLB
Tianjiao Dai, PhD, CBER/OBPV/DB
Asha Das, MD, CBER/OTP/OCE
Heba Degheidy, MD, PhD, CBER/OTP/OCTHT
Jaikumar Duraiswamy, PhD, CBER/OTP/OCTHT
Char-Dell Edwards, BS, MT, CBER/OCBQ/DIS
Melanie Eacho, PhD, RAC, CBER/OTP/OCTHT
Chaohong Fan, MD, PhD, CBER/OTP/OCE
Qianmiao Gao, PhD, CBER/OBPV/DB
Varsha Garnepudi, PhD, CBER/OCBQ/DBSQC
Jana Highsmith, CBER/OCBQ/DMPQ
Lianne Hu, PhD, MD, MPH, MS, CBER/OTP/OCE
Christopher Jason, MD CBER/OBPV/DPV
Timothy Kamaldinov, CBER/OTP/OGT
Hosna Keyvan, CBER/OTP/ORMRR
John Khuu, MD, CBER/OTP/OCE
Karin Knudson, PhD, CBER/OTP/OCTHT
Shiowjen Lee, PhD, CBER/OBPV/DB
Peter Lenahan, DC, PhD, MPH, CBER/OCBQ/DIS
Elizabeth Lessey-Morillon, PhD, CBER/OTP/OCTHT
Wei Liang, PhD, CBER/OTP

Anthony Lorenzo, CBER/OCBQ/DMPQ
Carrie Mampilly, MPH, CBER/OCBQ/DIS
Leyish Minie, MSN, RN, CBER/OTP/ORMRR
Tyree Newman, MDiv, CBER/OTP/ORMRR
Brian Niland, PhD, CBER/OTP/OCTHT
Steven Oh, PhD, CBER/OTP/OCTHT
Carolyn Renshaw, CBER/OCBQ/DMPQ
Douglas Rouse, MD, MPH, CBER/OBPV/DPV
Seth Schulte, CBER/OCBQ/DBSQC/
Ramani Sista, PhD, CBER/OTP/ORMRR
Melek Sunay, PhD, CBER/OTP/OPT
Million Tegenge, PhD, CBER/OTP/OCE
Catherine Tran, MS, CBER/OTP/ORMRR
Lori Tull, CBER/OTP/ORMRR
Ramjay Vatsan, PhD, CBER/OTP/OGT
Nadia Whitt, MS, CBER/OTP/ORMRR

Applicant Attendees:

Michelle Abelson, PhD, Executive Director, Research
Igor Bilinsky, PhD, Chief Operating Officer
Erwin Cammaart, MS, Executive Director, Process Development
Iain Dukes, DPhil, Director
Ulrich Ernst, PhD, Senior Vice President, Technical Operations
Friedrich Graf Finckenstein, MD, Chief Medical Officer
Malou Gemeniano, PhD, Vice President, Regulatory - CMC
Andrea Karpinecz, MS, Vice President, Quality Control
Huiling Li, PhD, Senior Vice President, Biostatistics
Sandy Mohan, PhD, Vice President, Quality
Matthew Morrison, MS, Senior Director, MSAT and EM
Arvind Natarajan, PhD, Senior Vice President, Process & Analytical Development
Himani Parikh, MS, Senior Director, Regulatory
Bruce Phillips, MBA, Senior Vice President, Internal Manufacturing
Steve Rabin, PhD, Senior Director, Regulatory - CMC
Leslie Rosati, MS, Director, Analytical Services & Analytical Technology
Guy Ruble, PharmD, RAC, Vice President, Regulatory
Jonathan Rubin, PhD, Director, Process Development
Wen Shi, MD, PhD, Vice President, Clinical Science
Kevin Smyth, MS, Senior Vice President, Quality
Binh Truong, MS, Senior Director, Regulatory - CMC
Fred Vogt, PhD, JD, Interim CEO
Michael Weiser, MD, PhD, Director
Joe Wypych, MBA, Senior Vice President, MSAT & EM
Hequn Yin, PhD, Senior Vice President, Research
Ryan Yamagata, PhD, Senior Director, CMC Biostatistics

Discussion Summary:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.

   Meeting Discussion:
   FDA communicated the following Chemistry, Manufacturing, and Controls (CMC) concerns to the Applicant. The Applicant was informed that items #a-d are considered major review issues and items #e-h are considered minor review issues that will only be discussed briefly to provide an update on our review.

   a. We have concerns that the current release specifications are not sufficient to ensure manufacturing consistency/control and distinguish a quality and potent drug product lot. The release specifications are integral to the evaluation of process validation, comparability, and release assay validations. We plan to send CMC information requests (IRs) after the midcycle meeting regarding the identified critical quality attributes (CQAs), the release specifications and proposed acceptance criteria, and correlation of product attributes and clinical response.

      The Applicant did not have comments or questions related to this item and communicated they look forward to the IR and will respond accordingly.

   b. As communicated in CMC IR #5, it is unclear whether the current in-process controls are sufficient to ensure manufacturing consistency and control. The Applicant's response to CMC IR #5 is under review. We plan to send additional IRs after the midcycle meeting requesting additional justification for the current in-process controls and ability of the manufacturing process controls to detect a failed manufacturing run prior to release testing.

      The Applicant did not have comments or questions related to this item and communicated they look forward to the IR and will respond accordingly.

   c. The process performance qualification (PPQ) studies performed at iCTC (b) (4) using tumor starting material are under review. We have concerns that the (b) (4) may not be an appropriate starting material for PPQ studies, as the process used for the PPQ studies is not representative of the commercial Gen 2 manufacturing process. The PPQ studies performed at iCTC (b) (4) using tumor starting material are under review and will also depend on the outcomes of items #a-b.

The Applicant did not have comments or questions related to this item and communicated they look forward to the IR and will respond accordingly.

d. We have concerns that the Applicant has not established comparability between the manufacturing sites (i.e., (b) (4) iCTC). As communicated in CMC IR #1, comparability will need to be established between (b) (4) iCTC to use iCTC as a commercial manufacturing site for launch. We informed the Applicant that the comparability review will depend on the outcomes of items #a-b.

   The Applicant asked us about the details of the specific comparability method concerns. We provided a summary of two concerns, specifically (1) Tier 2 attributes evaluated by a quality range in the study and (2) the exclusion of failed comparability runs from the statistical analysis. The Applicant did not have additional comments or questions related to this item and communicated they look forward to the IR and will respond accordingly.

e. We have concerns with the assessment of cumulative leachables from all high-risk process components, which should be performed in a (b) (4) (b) (4) study that covers the manufacturing process, the entirety of the product shelf life, and in-use conditions of the drug product. We communicated this to the Applicant in CMC IR #6.

   The Applicant did not have any comments or questions related to this item and no additional discussion occurred.

f. We informed that Applicant that they have not provided sufficient validation of the release appearance/visual inspection method. We communicated this to the Applicant in CMC IR #6.

   The Applicant did not have any comments or questions related to this item and no additional discussion occurred.

g. We informed the Applicant that their response to CMC IR #3 regarding the flow cytometry validation is under review. We may be requesting additional clarification via IR.

   The Applicant did not have any comments or questions related to this item and no additional discussion occurred.

h. We informed the Applicant that their response to CMC IR #5 concerning the (b) (4) is under review. We may be requesting additional information via IR.

The Applicant did not have any comments or questions related to this item and no additional discussion occurred.

2. Information regarding major safety concerns.

   Meeting Discussion:
   We did not communicate any major safety concerns.

3. Preliminary Review Committee thinking regarding a.) risk management, b) the potential need for any post-marketing requirement(s) (PMRs), and c.) the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk.

   Meeting Discussion:
   We communicated that at the present time, none have been identified. There was no additional discussion.

4. Any information requests sent, and responses not received.

   Meeting Discussion:
   We informed the Applicant that the responses to the CMC IR #6 were received on July 26, 2023, and are under review. In addition, we received responses to Clinical IR #4 on July 26, 2023, by email. The Applicant is planning a formal submission for July 27, 2023. There was no additional discussion.

5. Any new information requests to be communicated.

   Meeting Discussion:
   We communicated that as the review continues, new IRs will be conveyed as warranted and as noted under item #1. The Applicant requested a timeline for the receipt of the IRs concerning the CMC issues identified under item #1. We responded that the IRs will be sent within a few weeks. The Applicant asked whether we would be open to informal teleconferences to discuss the CMC issues after they receive the IR noted under item #1. We stated that we are open to informal teleconferences to discuss the CMC issues.

6. Proposed date for the Late-Cycle meeting (LCM).

   Meeting Discussion:
   We informed the Applicant that the LCM is currently scheduled for September 11, 2023, 2:00 PM-3:30 PM. The LCM meeting materials will be provided approximately 10 calendar days in advance of the LCM, and if these timelines change, updates will be communicated during the course of the review. There were no questions or concerns about this scheduled meeting.

7. Updates regarding plans for the Advisory Committee (AC) meeting.

Meeting Discussion:
We informed the Applicant that, at this time, no AC meeting is anticipated. There was no additional discussion.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates, and notification of intent to inspect manufacturing facilities.

   Meeting Discussion:
   We informed the Applicant that the pre-license inspection of Iovance Biotherapeutics is scheduled and confirmed for Monday, August 21 through Friday, August 25, 2023. Pre-license inspection of (b) (4) is scheduled and confirmed for (b) (4) (b) (4) A teleconference is scheduled and confirmed for August 1, 2023, 1:00 PM EST. There was no additional discussion.