CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761334Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 139181

MEETING PRELIMINARY COMMENTS

Incyte Corporation
Attention: Michael J. McGraw, Pharm.D., M.S.
Executive Director, Global Regulatory Affairs
1801 Augustine Cut-Off
Wilmington, DE 19803

Dear Dr. McGraw:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for retifanlimab (INCMGA00012).

We also refer to your correspondence, received September 2, 2021, requesting a meeting to discuss the top-line efficacy results from Study POD1UM-201 to support a BLA submission for retifanlimab as monotherapy for the treatment of adult (b) (4) patients (b) (4) with metastatic or recurrent locally advanced Merkel cell carcinoma, and to obtain the Agency's feedback on the content and format of the proposed BLA.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call me at (240) 402-5913.

Sincerely,

{See appended electronic signature page}

Autumn Zack-Taylor, M.S.
Regulatory Health Project Manager
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: October 27, 2021
Meeting Location: 3:00PM-4:00PM EST

Application Number: IND 139181

Product Name: Retifanlimab (INCMGA00012)
Indication: For the treatment of adult (b) (4) patients (b) (4) with metastatic or recurrent locally advanced Merkel Cell Carcinoma

Sponsor Name: Incyte Corporation
Regulatory Pathway: 351(a) of the Public Health Service Act

FDA ATTENDEES (tentative)

Steven Lemery, M.D., M.H.S., Director (Acting), OOD/DO3
Leslie Doros, M.D., Clinical Team Leader (Acting), OOD/DO3
Vaibhav Kumar, M.D., Clinical Reviewer, OOD/DO3
Joyce Cheng, Ph.D., Statistics Team Leader, OB/DBV
Jiaxin Fan, Ph.D., Statistics Reviewer, OB/DBV
Jeanne Fourie Zirkelbach, Ph.D., Clinical Pharmacology Team Leader, OCP/DCPII
Miao Zhao, Ph.D., Clinical Pharmacology Reviewer, OCP/DCPII
Matthew Thompson, Ph.D., Nonclinical Team Leader, OOD/DHOT
Emily Place, Ph.D., Nonclinical Reviewer, OOD/DHOT
Bazarragchaa Damdinsuren, Ph.D., Product Quality Team Leader, OBP/DBRRIV
Li Lu, Ph.D., Product Quality Reviewer, OBP/DBRRIV
Autumn Zack-Taylor, M.S., Regulatory Health Project Manager, ORO/DROOD

SPONSOR ATTENDEES

Farah Ali, Senior Manager, Global Regulatory Affairs, CMC
Xuejun Chen, Ph.D., Vice President, Drug Metabolism and Pharmaceutics
Mark Cornfeld, M.D., M.P.H., Vice President, Clinical Development
Scott Gangloff, Vice President, Global Biopharmaceutical Development
Kevin Hou, Ph.D., Group Vice President, Biostatistics and Programming
Elizabeth Jamme, M.D., Senior Medical Director, Global Risk Management and Safety Surveillance
Lance Leopold, M.D., Group Vice President, Clinical Development
Michael J. McGraw, Pharm.D., M.S., Executive Director, Global Regulatory Affairs
Nina Moore, M.S., Senior Manager, Global Regulatory Affairs

Mihaela Munteanu, Ed.D., M.S., Vice President, Clinical Development
Tina Nguyen, Pharm.D., Senior Manager, Global Risk Management and Safety Surveillance
Kevin O'Hayer, M.D., Ph.D., Senior Director, Clinical Development
Jennifer Pulini, Pharm.D., Executive Director, Clinical Development
Mallika Singh, Ph.D., Executive Director, Biologics CMC Project Management and Operations
Michael Smith, Ph.D., Director, Translational Science
Nithya Srinivas, Ph.D., Senior Research Investigator, Clinical Pharmacokinetics
Maxim Soloviev, M.D., Ph.D., D.S.P., Senior Director, Toxicology
Chuan Tian, Ph.D., Director, Biostatistics
Matthew Vaughn, Senior Director, Global Regulatory Affairs, CMC
Yan-ou Yang, Director, Drug Metabolism and Biopharmaceutics
Sharon Wolfe-Schwartz, Associate Director, Development Operations
Camille Varillo, Executive Director, Global Regulatory Operations

INTRODUCTION

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for October 27, 2021, 3:00PM-4:00PM between Incyte Corporation and the Division of Oncology 3. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

Regulatory

On June 8, 2018, Incyte Corporation (Incyte) submitted an Investigational New Drug (IND) Application, IND 139181, including Protocol INCMGA 0012-201 (POD1UM-201), entitled "A Phase 2 Study of INCMGA00012 in Participants With Metastatic Merkel Cell Carcinoma (MCC)." The IND went into effect on July 5, 2018.

On September 15, 2020, Incyte submitted a request for Fast Track designation for the treatment of patients with metastatic or recurrent locally advanced MCC. The Fast-Track designation request was granted on November 6, 2020.

On October 14, 2020, an End-of-Phase 2 meeting was held between representatives from Incyte and FDA to discuss the ongoing Phase 2 study in patients with locally advanced or metastatic MCC (Study POD1UM-201) and its sufficiency to support a marketing application for accelerated approval of retifanlimab in the proposed indication. FDA provided advice on the requirements to support an accelerated approval pathway based on response rate and provided guidance on the requirements to convert to regular approval which included conducting a second study or enrolling more than the proposed 60 patients in the PODIUM study with a minimum of 12 months of follow-up and that patients are followed for overall survival until at least 70% of events have occurred.

On October 26, 2020, retifanlimab was granted Orphan Drug Designation (DRU-2019-6957) for the treatment of MCC.

On March 5, 2021, Incyte submitted a Type C, Guidance meeting request to discuss and reach agreement on the proposed safety and efficacy analysis plans and content and format of the marketing application for retifanlimab for the treatment of patients with recurrent locally advanced or metastatic MCC. Specifically, the pooling strategy (i.e., specific studies to be pooled and analytic methodology), analysis of subgroups within the proposed pool, the grouping of MedDRA preferred terms to support the presentation of safety in the labeling text, participant narratives to be included in the marketing application, and other important analyses intended to support the safety assessment. The meeting request was granted as a Written Responses Only meeting on March 8, 2021.

On September 2, 2021, Incyte submission a Type B, Pre-Biologics License Application (BLA) meeting request to discuss the top-line efficacy results from Study POD1UM-201 to support a BLA submission for retifanlimab as monotherapy for the treatment of adult (b) (4) patients (b) (4) with metastatic or recurrent locally advanced Merkel cell carcinoma, and to obtain the Agency's feedback on the content and format of the proposed BLA.

Clinical

Study INCMGA 0012-201 has fully enrolled (n=107) and the final analysis is intended to provide confirmatory evidence of the clinical benefit of retifanlimab in patients with MCC to convert an accelerated approval to a regular approval as discussed during the Type B, End of Phase 2 (EOP2) meeting held on October 14, 2020. Top-line results for the final analysis of the objective response rate (ORR) endpoint are anticipated in the second quarter of 2022.

Pivotal Study INCMGA 0012-201 (PODIUM-201)

PODIUM-201 is an ongoing, single-arm, open-label, multicenter study investigating retifanlimab as a single agent for patients with treatment-naïve, locally recurrent or

metastatic MCC. The primary endpoint is ORR by independent central review as per RECIST v1.1. The trial has now fully enrolled 107 patients. Incyte provided the efficacy data for 65 evaluable patients to support the BLA.

Efficacy Results

As of the data cutoff of June 16, 2021, 65 patients were available for efficacy. Incyte states that 9 of the 65 patients have missing baseline or post-baseline tumor assessments. The reported ORR was 51% with 11 (17%) patients having a complete response. Median follow-up was 7.5 months.

Table 1: Efficacy Results in PODIUM-201

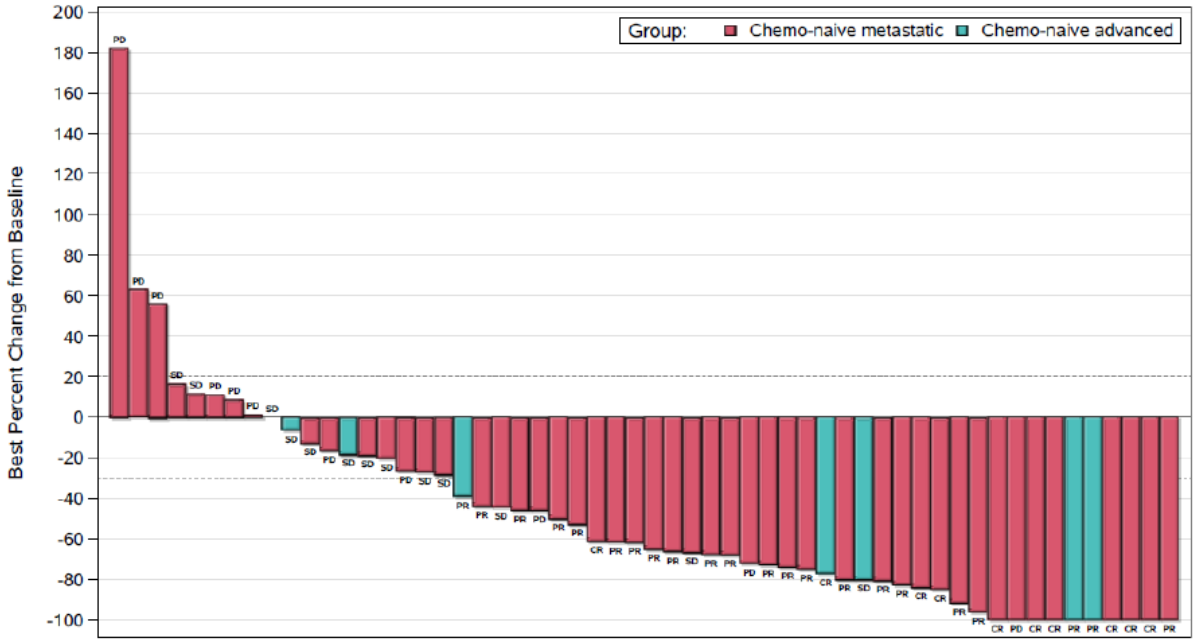
Efficacy Parameter	**Retifanlimab N = 65**
ORR (95% CI)	51% (38, 63)
Complete Response (CR)	17%
Partial response (PR)	34%
Median DoR (months) (range)[a]	Not reached (1.1, 16.6+)
Patients with DoR ≥ 6 months[b]	64%

[a] The median duration of exposure with retifanlimab was 277 days (1 day to 708 days).
[b] Observed proportion of patients with DoR over 6 months.

Source: Copied from applicant meeting package, Table 2, Page 17.

The waterfall and swimmer plots provided in the briefing package are shown below.

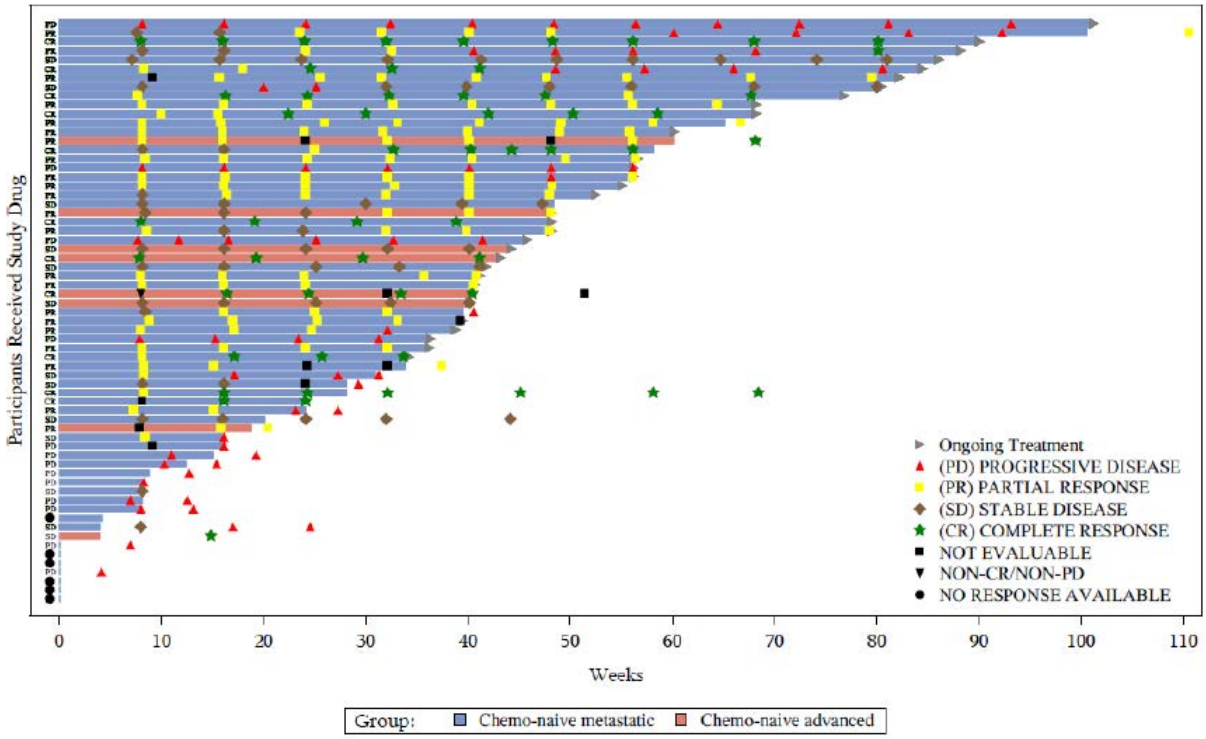
Figure 1: Waterfall Plot of Best Percentage Change in Sum of Target Lesions by ICR (Full Analysis Set)



Note: 65 chemo-naive participants enrolled in the study but 9 participants have missing baseline or post baseline target lesion assessment.

Source: Copied from applicant meeting package, Figure 2, Page 18.

Figure 2: Swimmer Plot of Duration of Treatment and Response Assessment by ICR (Full Analysis Set)



Source: Copied from applicant meeting package, Figure 3, Page 18.

DISCUSSION

1. *Does the Agency agree that the data from the primary analysis of Study INCMGA 0012 201 (POD1UM 201) support a BLA submission in the proposed indication?*

   FDA Response: The top-line data submitted may be acceptable to support filing a BLA in the proposed indication. At the time of the BLA submission, all patients with a confirmed response should have at least 6 months of follow up from the onset of response. Clarify if all patients who experienced a confirmed response as of the data cutoff of June 16, 2021 have had at least 6 months of follow-up from the onset of response. If they have not, Incyte may need to delay the submission of the proposed BLA and amend the data cutoff date to capture this data.

2. *Does the Agency agree that the Table of Contents provided constitutes a complete BLA?*

   FDA Response: The proposed Table of Contents appears acceptable. Include the report for human pharmacokinetic (PK) study INCMGA 0012-101 under Section 5.3.3.

3. *Does the Agency agree with the Sponsor's proposal to incorporate the Chemistry, Manufacturing, and Controls data and Pharmacology and Toxicology data by cross-reference to the original BLA* [redacted]

FDA Response: If Incyte will [redacted], FDA agrees with Incyte's proposal to cross-reference the proposed information. [redacted] DO3 may request that the MCC application be updated to include the Chemistry, Manufacturing, and Controls data and Pharmacology and Toxicology data.

FDA recommends conducting an animal study that will measure the effect of PD-1 inhibition on the magnitude of the primary (first vaccination) and recall (second vaccination) antibody responses to antigen challenge (e.g., tetanus toxoid or KLH). This study should evaluate the effect of PD-1 inhibition on the primary immune response once steady state plasma levels have been achieved and should reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing.

4. *Does the Agency agree with the Sponsor's plan for submitting summary level clinical site data from POD1UM 201 for inspection planning?*

FDA Response: FDA does not agree. BLA content for the Planning of Bioresearch Monitoring (BIMO) data should be submitted for all major trials used to support safety and efficacy. This would include the trials that Incyte proposes to include to support safety (INCMGA 0012-101, 0012-202, 0012-203). In addition to the referenced FDA Guidance for Industry, entitled "Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions," also refer to the FDA Technical Specifications Document, entitled "Bioresearch Monitoring Technical Conformance Guide," available at: https://www.fda.gov/media/85061/download.

5. *Does the Agency agree with the Sponsor's proposed plan for submitting clinical datasets to support the individual clinical study reports, the population pharmacokinetic analyses, and the integrated summaries?*

FDA Response: The proposed approach appears reasonable.

6. *Does the Agency agree with the proposed presentation of the safety data in the labeling?*

   FDA Response: FDA does not agree. In Section 6, include safety data from the 65 patients from Study PODIUM 201 that received at least one dose of study therapy.

7. *Does the Agency agree that the data from the primary analysis of Study INCMGA 0012-201 support a Priority Review designation?*

   FDA Response: A determination for priority review will be made during review of the original BLA submission. Incyte's request for priority review should be submitted with the original BLA. For more information, refer to the FDA Guidance for Industry, entitled "Expedited Programs for Serious Conditions – Drugs and Biologics," available at: https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf.

8. *Does the Agency agree with the proposed plan to provide the Oncology Center of Excellence's Assessment Aid for the retifanlimab BLA?*

   FDA Response: FDA agrees with the proposed plan to submit an Assessment Aid.

ADDITIONAL COMMENTS

DIVERSITY PLAN

9. The information below represents standard DO3 requests regarding the development of a Diversity Plan. Given that Study INCMGA 0012-201 has completed enrollment, in the BLA, describe steps (as indicated below) Incyte has taken to collect data to elucidate the impact of race and ethnicity on patient outcomes throughout the entire development life-cycle of retifanlimab.

   Ensure that subgroups that comprise the population with the disease in the U.S. are enrolled in sufficient numbers in the trial(s) conducted under this IND, to enable the evaluation of safety, efficacy, and dosage in these groups. Racial and ethnic minorities (REMs; American Indians or Alaska Natives, Asians, Blacks or African Americans, Native Hawaiian or Other Pacific Islander, Hispanics or Latinos) are frequently underrepresented in cancer clinical trials despite having a disproportionate disease burden for certain diseases relative to their proportional representation in the general population.

   Develop a Diversity Plan outlining the strategy to collect data to elucidate the impact of race and ethnicity on patient outcomes throughout the entire

development life-cycle of the medical product, including in early clinical development.

Discuss the Plan with the review division early in clinical development, no later than during the End-of-Phase 2 meeting. When a Diversity Plan is one of the topics intended for discussion during a milestone meeting, sponsors should alert the FDA by marking the meeting request and the briefing document submissions with "**DIVERSITY PLAN**" in large, bolded type in the cover letter.

The recommended elements of a Diversity Plan in the table below, should be included in a dedicated section of a meeting briefing document.

Domain	**Recommended Scope**
1. Overview of the disease/condition	Summarize available information on the incidence and prevalence of the disease/condition in both the overall population and in the REM subgroups. • Describe available data on the pathophysiology of the disease, methods of diagnosis, and currently available treatments and/or prevention strategies in REM subgroups. • Discuss the current understanding of and available evidence supporting any similarities and/or differences between the disease in the general population and in the REM subgroups in the U.S.
2. Target enrollment of REM subjects	Define and provide justification for the planned accrual of subjects from REM subgroups. • Specify, 'highly relevant' REM subgroups based on assessment in Domain #1. Specify target enrollment of REM subjects (e.g., based on the epidemiology of the disease and/or based on a priori information regarding important differences associated with race or ethnicity).
3. Scope of drug development program	Describe the planned studies that will support the safety, efficacy and dosage of the medical product in a future marketing application. Outline the following: • study design, study population (including study eligibility criteria), endpoints and, the expected geographic location of the studies; • clinical pharmacology assessment across studies (e.g., pharmacokinetic, pharmacodynamic, pharmacogenomics) and/or other information that is

Domain	Recommended Scope
	potentially relevant to characterizing safety and efficacy in one or more REM subgroups.
4. Measures to enroll diverse population	Describe in detail the measures that will be implemented to enroll and retain REM subjects in the planned trial(s), and the planned use of data from trials to characterize safety, efficacy, and dosage in these subjects. Describe trial accrual and retention strategy in terms of: • site location and access (e.g., language, transportation); • community engagement (e.g., community advisory boards and navigators, patient advocacy groups, etc.); • reducing burdens due to trial design/conduct (e.g., number/frequency of study-related procedures, use of local laboratory/imaging, telemedicine). Describe metrics to ensure that achieving diverse subject accrual goals and specify measures to be implemented during the conduct of the trial(s) if planned enrollment targets are not met.
5. Justification for deferral to post-approval	Describe factors precluding obtaining data in pivotal trial(s). • Describe the proposed post-approval trial(s) that will provide data on REM subjects. Provide a timeline for initiating and completing studies.

REM= Racial and ethnic minority groups

Collect and analyze pharmacokinetic (PK), pharmacodynamic (PD), and pharmacogenomic data by race and ethnicity. Ensure that the PK/PD data are of sufficient quantity and quality to permit such analyses.

Assess race and ethnicity in addition to other covariates known to affect drug PK and PD to facilitate exposure-response analyses to inform safe and effective dosing regimens across the intended patient population.

COVID-19

10. Given that enrollment and clinical trial conduct occurred during the COVID pandemic, in the BLA, include information with respect to how protocol conduct or data collection were impacted by COVID or COVID-related procedures. If helpful, include flags in datasets.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 9, 2021, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[2]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with

[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[3]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a

[3] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

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[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[7]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[8]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

[7] http://www.fda.gov/ectd
[8] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[9]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[10]: In general, the data submission should be fully CDISC-compliant

[9] https://www.fda.gov/media/85061/download
[10] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program

to facilitate efficient review.

- Assessment Aid[11]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

ADVANCING ONCOLOGY DECENTRALIZED TRIALS

FDA Oncology requests that applicants submitting data to support NDA/BLA applications to voluntarily add flags to datasets in order to discriminate between REMOTE assessments and TRIAL SITE assessments. The intent is to allow FDA to learn from trials conducted in the COVID-19 pandemic that permitted some aspects of trial conduct to be performed remote from trial sites to reduce potential COVID exposure. The FDA hopes to learn more about the opportunities and challenges of these REMOTE modifications in order to foster use of "decentralize" aspects of clinical trials prospectively in the post-COVID era.

[11] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

For details please refer to: https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials."

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AUTUMN D ZACK-TAYLOR
10/18/2021 09:10:07 AM

IND 139181

MEETING MINUTES

Incyte Corporation
Attention: Michael McGraw, Pharm.D., M.S.
Executive Director, Global Regulatory Affairs
1801 Augustine Cut-Off
Wilmington, DE 19803

Dear Dr. McGraw:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for retifanlimab (INCMGA00012).

We also refer to the teleconference between representatives of your firm and the FDA on October 14, 2020. The purpose of the meeting was to discuss the proposed development plan for retifanlimab for the treatment of adult (b) (4) patients (b) (4) with locally advanced or metastatic Merkel cell carcinoma.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-5913.

Sincerely,

{See appended electronic signature page}

Autumn Zack-Taylor, M.S.
Regulatory Health Project Manager
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

[1]We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	October 14, 2020; 1:00PM-2:00PM EST
Meeting Location:	Teleconference
Application Number:	IND 139181
Product Name:	Retifanlimab (INCMGA00012)
Indication:	Treatment of adult (b) (4) patients (b) (4) with locally advanced or metastatic Merkel cell carcinoma
Sponsor Name:	Incyte Corporation
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Steven Lemery, M.D., M.H.S.
Meeting Recorder:	Autumn Zack-Taylor, M.S.

FDA ATTENDEES

Steven Lemery, M.D., M.H.S.	Director (Acting), OOD/DO3
Lola Fashoyin-Aje, M.D., M.P.H.	Deputy Director (Acting), OOD/DO3
Denise Casey, M.D.	Clinical Team Leader (Acting), OOD/DO3
Marsha Mitchum, M.D.	Clinical Reviewer, OOD/DO3
Joyce Cheng, Ph.D.	Statistical Team Leader, OB/DBV
Abhishek Bhattacharjee, Ph.D.	Statistical Reviewer, OB/DBV
Miao Zhao, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCPII
Matthew Thompson, Ph.D., M.P.H.	Nonclinical Team Leader (Acting), OOD/DHOT
Emily Place, Ph.D.	Nonclinical Reviewer, OOD/DHOT
Bazarragchaa Damdinsuren, Ph.D.	Product Quality Team Leader, OBP/DBRRIV
Craig Long, Pharm.D.	Regulatory Health Project Manager, ORO/DROOD
Autumn Zack-Taylor, M.S.	Regulatory Health Project Manager, ORO/DROOD

SPONSOR ATTENDEES

Xuejun Chen, Ph.D.	Vice President Drug Metabolism and Pharmaceutics
Mark Cornfeld, M.D., M.P.H.	Vice President Clinical Development
Kevin Hou, Ph.D.	Group Vice President Biostatistics and Programming

Lance Leopold, M.D.	Group Vice President Clinical Development
Michael J. McGraw, Pharm.D., M.S.	Executive Director Regulatory Affairs
Mihaela Munteanu, Ed.D., M.S.	Vice President Clinical Development
Michael Smith	Director Translational Science
Jennifer Pulini, Pharm.D.	Senior Director Clinical Development
Sadhna Shankar, M.D.	Executive Director Clinical Development
Chuan Tian, Ph.D.	Director Biostatistics and Programming
Stephani Thompson, Pharm.D., M.S.	Senior Manager Regulatory Affairs
Jia Li, Ph.D.	Senior Research Investigator, Clinical Pharmacokinetics

BACKGROUND

Regulatory

On June 8, 2018, Incyte Corporation (Incyte) submitted IND 139181, including Protocol INCMGA 0012-201 (POD1UM-201) entitled “A Phase 2 Study of INCMGA00012 in Participants With Metastatic Merkel Cell Carcinoma.” The IND went into effect on July 5, 2018.

On April 14, 2020, Incyte submitted Protocol Amendment 5, which modified the protocol to exclude patients who received prior chemotherapy and revised the planned sample size from 90 total patients to 60 chemotherapy-naïve patients.

On September 15, 2020, Incyte submitted a request for Fast Track designation for the treatment of patients with metastatic or recurrent locally advanced Merkel Cell Carcinoma (MCC). The request for Fast Track designation is currently under review.

Clinical

Retifanlimab is a humanized IgG4κ monoclonal antibody (mAb) that recognizes human PD-1 expressed by T- and B-lymphocytes. Clinical experience to date is from 521 patients exposed to single agent retifanlimab across 7 ongoing studies in various solid tumors. The recommended phase 2 doses (RP2Ds) established in these studies are 3 mg/kg every 2 weeks (Q2W), 500 mg every 4 weeks (Q4W), and 375 mg every 3 weeks (Q3W).

POD1UM-201 is an ongoing single-arm, open-label, multicenter study of retifanlimab in patients with recurrent locally advanced or metastatic MCC. Patients receive retifanlimab 500 mg Q4W for up to 2 years. The primary endpoint is objective response rate (ORR) according to RECIST v1.1 as assessed by independent central review (ICR). According to Incyte, assuming a target ORR of 60%, a sample size of approximately 60 patients will have 80% power to exclude the lower 95% confidence limit of 40% with a one-sided alpha=0.025 in the chemotherapy-naïve patient

population. The primary analysis of ORR will be performed on all chemotherapy-naïve participants who receive at least one dose of retifanlimab. A supportive analysis of ORR will be performed in the subset of patients with a centrally-confirmed diagnosis of MCC and who have measurable disease at baseline and have received at least one dose of retifanlimab. Secondary endpoints or assessments include duration of response (DOR), safety, and pharmacokinetics (PK). All patients will be followed for a minimum of 6 months following onset of confirmed response.

As of April 7, 2020, approximately 20 chemotherapy-naive and 5 chemotherapy-refractory patients were enrolled. A pre-planned futility analysis was performed on the first 25 evaluable participants (defined as patients with 2 on-study response assessments or those who discontinued the study early). The analysis showed an objective response rate (ORR) according to RECIST v1.1 as assessed by blinded-independent review of 36% (8 of 21 chemotherapy-naive patients, and 1 of 4 chemotherapy-refractory patients).

DISCUSSION

1. *Does the Agency agree that the data from the ongoing Phase 2 study in patients with locally advanced or metastatic MCC (POD1UM-201) will be sufficient to support a marketing application for accelerated approval of retifanlimab in the proposed indication?*

   FDA Response: To file an application seeking accelerated approval for retifanlimab for the treatment of patients with locally advanced or metastatic MCC based on the results of POD1UM-201, the observed response rate and DOR should be of sufficient magnitude to conclude that retifanlimab is reasonably likely to provide clinical benefit and provides an advantage over available therapy in the intended use population. What constitutes available therapy will be determined at the time of the regulatory decision. The results will also be weighed against the safety risks observed.

   Since FDA does not use inferential procedures to evaluate single arm study results, the sample size should be large enough to allow for sufficient precision of the effect sizes of confirmed ORR and durability to assess the treatment effects of retifanlimab in the context of available therapy. FDA recommends following patients for at least 6 months after a confirmed response to allow for adequate evaluation of DOR. To support an application for regular approval, longer follow-up duration will be expected.

   Discussion during the meeting: Incyte Corporation acknowledged FDA's response; there was no further discussion of this item during the meeting.

2. *Does the Agency agree with the Sponsor's proposed plan to* (b) (4) *?*

FDA Response: The proposal to (b) (4) may be acceptable; however, FDA strongly recommends that Incyte evaluate retifanlimab (b) (4)

Incyte Corporation response, received via email on October 8, 2020: The Sponsor acknowledges FDA's response to Question 2, and proposes to amend (b) (4) (see Incyte's response to preliminary comments on Question 3).

Discussion during the meeting: FDA acknowledged Incyte Corporation's response; there was no further discussion of this item during the meeting.

3. *Does the Agency agree that following all patients in POD1UM-201 for OS for at least 2 years after enrollment will provide confirmatory evidence to convert the accelerated approval into a regular approval for retifanlimab in patients with recurrent locally advanced or metastatic MCC?*

FDA Response: No. FDA acknowledges that there may be challenges with conducting a randomized trial of retifanlimab in patients with MCC; however, should an accelerated approval of retifanlimab be granted on the basis of POD1UM-201 (N=60), a more robust experience with retifanlimab in MCC will be needed to support regular approval. Incyte should conduct another study or enroll additional patients with MCC in POD1UM-201 who will be followed for a minimum of 12 months from onset of response to establish the ORR and the DOR. Patients should also be followed for overall survival (OS) until at least 70% of patients have died (or an alternative agreed upon duration of time) to characterize effects on survival. Data collected in a post-marketing trial can be limited to the data necessary to achieve these goals. Although FDA will review this information for durability, FDA does not intend to make cross-trial comparisons with other therapies and acknowledges that conclusions based on time-to-event endpoints in single arm trials are limited.

Incyte Corporation response, received via email on October 8, 2020: The Sponsor acknowledges FDA's recommendations and would like to seek further

clarification during the scheduled meeting. To address these concerns, Incyte proposes to expand the ongoing study to enroll additional participants with chemotherapy naïve MCC with distant metastatic or recurrent locally advanced disease. The current sample size of 60 chemotherapy-naïve participants provides 95% CI of ±13% for objective response rates (ORRs) of 40-60% which corresponds to the published experience with pembrolizumab and avelumab in this setting (Nghiem et al 2019, D'Angelo et al 2019). In order to improve the precision of the point estimate, Incyte proposes to enroll an additional 25 participants (N=85 for the target population) to narrow the 95% CI to approximately ±11% for ORRs between 40 and 60%. Incyte has conducted exploratory analyses, and has determined that for sample sizes of 85 or 100, the reduction of the half width of the 95% CI is minimal (less than 1%) for ORRs between 40 and 60%, and hence considers 85 as an acceptable target sample size.

All the 85 participants enrolled in the study will be followed for durability of response (DOR) and overall survival (OS). The participants will be followed for a minimum of 12 months after the onset of response for assessment of ORR and DOR. The FDA has recommended follow up for OS until at least 70% of patients have died. However, the median OS for patients with metastatic MCC treated with avelumab in the JAVELIN Merkel 200 study was 20.3 months (95% CI 12.4 months to not estimable) (D'Angelo et al 2019). The survival curve for this study has plateaued after 50% of patients have died. In addition, the median OS has not been reached in the study of pembrolizumab for the treatment of advanced MCC (Nghiem et al 2019). The survival curve for this study plateaus after 35% of participants have died. This suggests that these therapies in this disease are likely to be associated with a high cure fraction. Consequently, it is likely that future deaths in these studies may be related to causes other than advanced MCC. Hence, Incyte proposes to follow study participants for OS for 2 years after the last participant is enrolled or until the median OS is observed, whichever is later. Based on the results of the JAVELIN Merkel 200 study, it is reasonable to assume that this length of follow up will provide a durable estimate of OS.

Discussion during the meeting: FDA acknowledged Incyte's rationale regarding follow-up time. FDA stated however that the BLA should include details regarding the extent of expected follow-up at the time of the proposed analyses including estimates of OS based on the proposed data cut-off dates.

FDA recommended a larger sample size for the purpose of regular approval than the proposed 85 patients. FDA recommended that Incyte consider other products approved for this indication and the data package that will support approval. The data package may also depend upon the results obtained for retifanlimab. Incyte acknowledged FDA's recommendations.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[4]
On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data*

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

Technical Conformance Guide, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg.

[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[6]

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to

[6] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[7] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[8]

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[9]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[10]

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and*

[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[8] https://www.fda.gov/media/109533/download
[9] http://www.fda.gov/ectd
[10] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[11]

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling

[11] https://www.fda.gov/media/85061/download

changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment

Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[12]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[13]

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS

Attached is Incyte Corporation's agenda, received via email on October 8, 2020, entitled "Response to October 2 2020 MCC EOP2 Meeting Preliminary Comments."

6 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

[12] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[13] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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