# FDA Briefing Document

# Oncologic Drugs Advisory Committee Meeting

# June 24, 2021

# BLA 761209
# Retifanlimab-dlwr infusion
# Incyte Corporation

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the retinfalimab BLA 761209 to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

## Table of Contents

## 1. PROPOSED INDICATION

The Applicant, Incyte Corporation (Incyte), is seeking approval for the following indication:

> *Retifanlimab is indicated for the treatment of patients with locally advanced or metastatic squamous carcinoma of the anal canal (SCAC) who have progressed on or are intolerant of platinum-based chemotherapy.*

## 2. EXECUTIVE SUMMARY

Retifanlimab is an anti-programmed cell death protein-1 (PD-1) antibody. For this Biologics License Application (BLA), Incyte submitted the results of a single trial as the primary evidence of retifanlimab's safety, efficacy, and dosage for the proposed indication and to support the request for accelerated approval (under 21 CFR 601 Subpart E).

The POD1UM-202 trial is an ongoing, open-label, single-arm clinical trial to assess the safety and efficacy of retifanlimab. A total of 94 patients with locally advanced or metastatic SCAC who progressed on, were ineligible for, or intolerant of platinum-based chemotherapy received retifanlimab 500 mg by intravenous (IV) infusion every 4 weeks. Treatment continued for up to 2 years in the absence of clinical disease progression, intolerable toxicity, or other discontinuation criteria. The primary endpoint is objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as determined by independent central radiographic review (ICR). The ORR per ICR is 14% (95% confidence interval [CI]: 8, 22); median estimated duration of response (DoR) is 9.5 months (95% CI: 4.4, not estimable).

The major review issues identified by FDA for this application are summarized below:

1. It is unclear whether the results of POD1UM-202, a small, single-arm trial where only 13 patients had an objective response per Independent Central Review (approximately half of whom had limited follow-up for durability of response), represent a reliable estimate of response and whether a response rate of 14% is reasonably likely to predict clinical benefit. Given the context of inconsistent relationships between response rate as a predictor of overall survival or progression-free survival benefit observed with immune checkpoint inhibitors, the main question for the FDA is whether to grant the Applicant's request for accelerated approval or defer action on the application until the results of a randomized trial demonstrating safety and efficacy are available.

2. Given the relatively small size of POD1UM-202 and given the demographics and baseline disease characteristics of trial participants, there is uncertainty regarding how applicable the results are to patients who will receive the drug if approved. For example, few patients with HIV-positive status or individuals who are members of racial minority groups were enrolled in POD1UM-202, increasing the uncertainty of the true treatment effect across the population in which retifanlimab will be indicated.

## 3. BACKGROUND

### 3.1 Squamous Carcinoma of the Anal Canal (SCAC)

Anal cancer is a rare cancer with 9,090 estimated new cases in 2021, which is 0.5% of estimated new cancer cases in 2021.[1] It accounts for 0.2% (estimated 1,430 deaths) of all cancer deaths in 2021.[1] Most cases of anal cancer are diagnosed as non-metastatic disease, and 13% are diagnosed with distant metastases.[1] The 5-year survival rate is 82% and 66% for patients with localized or regional disease, respectively, and decreases to 35% for patients with distant metastases.[1]

Squamous cell carcinoma of the anus is the most common type of anal cancer and is seen in 80-85% of cases.[2,3] The risk factor with the strongest association with anal cancer is infection with the human papillomavirus virus (HPV); high-risk HPV DNA is detected in up to 70-90% of anal cancers.[3,4] Another risk factor is infection with the human immunodeficiency virus (HIV), where HIV infection is associated with a 15-35-fold increase in the risk of anal cancer.[5,6] Approximately 8.1% of patients with anal cancer have HIV.[7] The incidence of anal cancer is higher among patients with HIV compared to the general population (standardized incidence ratio [SIR], 19.1; 95% CI: 18-20), and even higher in men who have sex with men (SIR range: 33-39).[8] Other risk factors for anal cancer include sexual practices; sexually transmitted disease; history of cervical, vulvar, or vaginal cancer; immunosuppression after solid organ transplantation; hematological malignancies; some autoimmune disorders; and smoking.[5,6]

Per SEER data, median age of diagnosis is 63 years with approximately 44% of patients age 65 or older at diagnosis.[1] Anal cancer is slightly more common in women than men (2.3 versus [vs.] 1.6 cases per 100,000, respectively), Black men than White men (2.2 vs. 1.6 cases per 100,000, respectively), and White women than Black women (2.5 vs. 1.8 cases per 100,000, respectively).[1]

### 3.2 Available Therapies for Locally Advanced or Metastatic SCAC

The first-line treatment for locally advanced or metastatic SCAC includes platinum-based chemotherapy regimens. There are no approved treatments in the second-line metastatic setting for SCAC.

Carboplatin in combination with paclitaxel is the preferred regimen for the first-line

treatment of locally advanced or metastatic SCAC based on the results of the InterAACT trial, a prospective trial that randomized (1:1) 91 patients to receive carboplatin in combination with paclitaxel vs. cisplatin in combination with 5-fluorouracil (5-FU).[9] The primary endpoint was objective response rate (ORR) and secondary outcomes included progression-free survival (PFS) and overall survival (OS). The ORR was 59% (95% CI: 42.1, 74.4%) in the carboplatin/paclitaxel arm vs. 57% (95% CI: 39.4% to 73.7%) in the cisplatin/5-FU arm. Median OS was 20 months (95% CI: 12.7, not reached) and 12.3 months (95% CI: 9.2, 17.7) in the carboplatin/paclitaxel and cisplatin/5-FU arms, respectively (hazard ratio [HR] 2; 95% CI: 1.2 to 3.5). Other treatments in the first-line setting include cisplatin in combination with 5-FU and leucovorin (LV) (FOLFCIS), oxaliplatin in combination with 5-FU and LV (FOLFOX), and cisplatin in combination with docetaxel and 5-FU (DCF).[6]

Evidence is limited regarding treatment effects of therapies following progression on carboplatin/paclitaxel (or other regimens). Reported ORRs with different chemotherapy agents, combinations, or anti-PD-1 therapies range from 17-33% in small, single-institution studies (**Table 1**).[10-13] Of note, the reported ORR results across these trials were not independently reviewed.

**Table 1 - Summary of Published Results of Drugs used for Second-line Treatment**

| Drug (Trial) | Disease setting (n) | Dosage | ORR (%) Response Type | Median DoR (months) | Grade ≥3 AEs (%) |
|---|---|---|---|---|---|
| **Nivolumab** (NCI9673[10]) | Unresectable or metastatic (n=37) | 3 mg/kg Q2W | 24 (95% CI: 15, 33) 2 CR, 7 PR | 5.8 (interquartile range 3.9 to 8.1) | 13 |
| **Pembrolizumab** (KEYNOTE-028[11]) | Locally advanced or metastatic, PD-L1 ≥1% (n=24) | 10 mg/kg Q2W | 17 (95% CI: 5, 37) 4 PR | Not reached (range <0.1+ to 9.2+) | 17 |
| **5-FU + MMC**[a] (Retrospective, single-institution, patients seen 2000-2017[12]) | Metastatic after platinum-based regimen (n=19) | MMC 10 mg/m$^2$ + 5-FU 1000 mg/m$^2$/d for 96 hours Q28D | 26 (95% CI: 7, 46) 1 CR, 4 PR | 4 (95% CI: 1.8 to 6.1) | Not reported |
| **Chemotherapy**[b] (Retrospective, single-institution, patients seen 1997-2014[13]) | Inoperable and locally recurrent, or metastatic (n=21) | Variable | 33 (95% CI not reported) | Not reported | Not reported |

Abbreviations: SCAC = squamous cell carcinoma of the anal canal, ORR = objective response rate, DoR = duration of response, AE = adverse event, PD-L1 = programmed death-ligand 1, 5-FU = 5-fluorouracil, Q2W = every 2 weeks, Q28D = every 28 days, CI = confidence interval, CR = complete response, PR = partial response,
a= Mitomycin, b=most chemotherapy regimens were platinum +/- fluoropyrimidine

### 3.3 Regulatory History of Retifanlimab

Retifanlimab is not approved for any indication in the U.S. **Table 2** summarizes key

meetings and submissions relevant for this BLA.

**Table 2 - Key Meetings and Submissions Relevant for this BLA**

| Date | Summary of meeting or submission |
|---|---|
| Jan 8 2020 | FDA issued preliminary comments for a Type B, End-of-Phase 2 meeting request (Incyte subsequently requested cancellation of the meeting). FDA stated there was insufficient information for FDA to make a determination of the adequacy of POD1UM-202 to support an accelerated approval for retifanlimab in SCAC and asked Incyte to request a pre-BLA meeting when the top-line results of POD1UM-202 were available. FDA provided feedback on the design of the proposed confirmatory trial, Protocol INCMGA 0012-303 (POD1UM-303). |
| Mar 24 2020 | Retifanlimab received Orphan Drug designation for the treatment of patients with locally advanced or metastatic SCAC who progressed on or are intolerant of platinum-based chemotherapy. |
| Mar 24 2020 | Incyte submitted the protocol for clinical trial POD1UM-303 to IND 139333. |
| Sep 10 2020 | FDA conveyed the following comments during the Type B, pre-BLA meeting:<br>• ORR magnitude was modest in POD1UM-202 and less than the target ORR of 25% that was proposed by Incyte in POD1UM-202; thus, it was unclear if the ORR was reasonably likely to predict clinical benefit,<br>• DoR data was limited – only 7 of the 13 responders had DoR >6 months,<br>• the BLA would be a stronger application if it were supported by positive results from the POD1UM-303/InterAACT 2 clinical trial, and<br>• if the BLA is submitted with results only from the POD1UM-202 clinical trial, FDA might elect to discuss the application in an ODAC. |
| Nov 25 2020 | Incyte submitted original BLA requesting accelerated approval. |

Abbreviations: BLA = biologics license application, ORR = objective response rate, DoR = duration of response, ODAC = Oncologic Drugs Advisory Committee

### 3.4 ORR as an Early Endpoint to Predict Clinical Benefit

According to accelerated approval provisions of FDASIA in section 506(c) of the FD&C Act, FDA may grant accelerated approval to:

> . . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

To support accelerated approval based on an intermediate endpoint, the magnitude of the effect on the endpoint should be reasonably likely to predict clinical benefit. The clinical benefit of low ORRs with anti-PD-1/PD-L1 antibodies is not clear in the context of an inconsistent relationship between low response rates in single arm trials and outcomes observed in randomized trials.[14]

As discussed in the ODAC meetings held on April 27-29, 2021, of the first 76 approvals granted to immune checkpoint inhibitors, 35 employed the accelerated approval pathway. The required confirmatory trials did not confirm benefit for 10 of the indications approved under the accelerated approval pathway; 9 of these trials were single-arm trials with ORR as the primary endpoint. Seven of these showed response rates of 10 to 20% (with CIs that do not exclude single digit response rates), but the approvals were granted because of the prolonged duration of the responses - in some cases years - and the lack of other available therapies. The multiple negative trials raise questions about marginal response rates observed in single-arm trials for accelerated approvals for this drug class.[14]Therefore, given the inconsistent relationship between low ORRs and PFS or OS, there is uncertainty regarding whether results in randomized trials of checkpoint inhibitors in squamous cell histology can be extrapolated to anal cancer or whether the results of a randomized trial is needed to characterize the benefit of retifanlimab.

Finally, an interpretation of the benefits of the treatment should consider the population enrolled in the trial and whether the trial adequately represents the known population of patients with the disease who will receive the drug. The limited number of patients who responded in POD1UM-202 reflects uncertainties with respect to whether these results would be replicated in a larger group of patients in the community.

## 4. CLINICAL TRIAL SUPPORTING THE APPLICATION: POD1UM-202

### 4.1 Trial Design, Trial Population, and Statistical Analysis Plan

POD1UM-202 is an ongoing, open-label, multicenter, single-arm clinical trial in adult patients with locally advanced or metastatic SCAC who progressed on or were ineligible for (or intolerant to) platinum-based chemotherapy. Eligible patients could not have received more than 2 prior lines of systemic therapy for metastatic SCAC, must have received at least 1 prior line of systemic therapy if ineligible for platinum-based therapy, and must have relapsed <6 months from therapy completion if received platinum-based chemoradiation. Patients with HIV-positive status were eligible if they had CD4+ count ≥300 cells/µL, an undetectable viral load, and were receiving anti-retroviral therapy. Patients who had received prior treatment with anti-PD-1 or anti-PD-L1 therapy were not eligible.

The primary endpoint was ORR according to RECIST 1.1 guidelines as determined by ICR. Secondary endpoints were duration of response (DoR), disease control rate

(DCR), PFS, OS, safety parameters, and pharmacokinetic parameters.

Patients received retifanlimab 500 mg by IV infusion over 30 minutes every 4 weeks. Treatment continued for up to 2 years in the absence of clinical disease progression, intolerable toxicity, or other discontinuation criteria. Treatment beyond RECIST 1.1 or immune-RECIST progression was permitted.

Tumor imaging was conducted at screening and every 8 weeks +/- 7 days thereafter until disease progression. Complete responses or partial responses were confirmed by imaging at least 4 weeks after initial documentation of response, consistent with RECIST 1.1.

Statistical Analysis Plan

There were no formal hypothesis tests for the primary or secondary endpoints of the trial. The targeted point estimate along with the exact two-sided 95% CIs were provided for ORR. Assuming a targeted ORR of 25% and a sample size of 81 patients, the trial had 80% power at a two-sided Type I error rate of 5% to exclude a response rate of 13% from the lower bound of the 95% CI. DoR was summarized with Kaplan-Meier estimates of median and corresponding 95% CIs.

### 4.2 Results

#### 4.2.1 Trial Population

Based on a June 8, 2020, data cutoff date, a total of 94 patients were enrolled and received at least one dose of retifanlimab. At the time of data cutoff, 76 patients (81%) had discontinued treatment, and 18 patients (19%) remained on treatment. Fifty-eight patients (62%) and 6 patients (6%) discontinued treatment due to disease progression, and adverse events, respectively. **Table 3** and **Table 4** summarize the baseline demographic and disease characteristics of patients enrolled in POD1UM-202, respectively.

Members of racial minority groups relevant to who would receive the drug in the U.S. were under-represented in POD1UM-202, with only 1 Black patient and 4 Hispanic or Latino patients among the patients for whom race or ethnicity were reported.

**Table 3 - Baseline Demographics in POD1UM-202**

| Demographic Group | All Patients N = 94 n (%) |
|---|---|
| **Sex** | |
| Male | 33 (35) |
| Female | 61 (65) |
| **Age** | |
| Mean years (SD) | 62 (11.4) |

| Demographic Group | All Patients N = 94 n (%) |
|---|---|
| Median (years) | 64 |
| Min, max (years) | 37, 94 |
| **Age Group** | |
| <65 years | 48 (51) |
| ≥65 years | 46 (49) |
| **Race** | |
| White | 72 (77) |
| Black | 1 (1.1) |
| Other | 15 (16) |
| Unknown | 6 (6) |
| **Ethnicity** | |
| Hispanic or Latino | 4 (4.3) |
| Not Hispanic or Latino | 49 (52) |
| Not Reported | 33 (35) |
| Unknown | 4 (4.3) |
| Missing | 4 (4.3) |

Abbreviations: SD = standard deviation, min = minimum, max = maximum

**Table 4** summarizes the disease characteristics and treatments prior to trial entry. Most patients had metastatic disease and received prior platinum-based chemotherapy and radiotherapy.

Although FDA acknowledges that the Applicant included patients with HIV-positive status in the trial, only 9 patients with HIV-positive status were enrolled and the trial required (relatively) preserved immunological function with a CD4 count above 300 cells/µL.

HPV status was not reported in 38% of the trial population and microsatellite instability status was not reported in 27% of the population.

**Table 4 - Disease Characteristics and Prior Treatment at Baseline in POD1UM-202**

| Baseline Disease Characteristics and Prior Treatment | All Patients N = 94 n (%) |
|---|---|
| **ECOG performance status** | |
| 0 | 39 (41) |
| 1 | 55 (59) |
| **Distant Metastasis** | |
| Yes | 77 (82) |

| Baseline Disease Characteristics and Prior Treatment | All Patients N = 94 n (%) |
|---|---|
| **Sites of Disease** | |
| Lymph nodes | 61 (65) |
| Liver | 39 (41) |
| Lungs | 31 (33) |
| Bone | 14 (15) |
| Anus/Anal Canal | 13 (14) |
| Rectum | 10 (11) |
| Other | 27 (29) |
| **Prior Anticancer Therapy Type** | |
| Platinum-based therapy in chemoradiation or as systemic therapy | 91 (97) |
| Radiation | 83 (88) |
| Surgery | 44 (47) |
| **Settings of Prior Therapy** | |
| Neoadjuvant | 29 (31) |
| Adjuvant | 58 (62) |
| Advanced/Metastatic or Palliative | 89 (95) |
| **Number of Prior Therapy (includes neoadjuvant, adjuvant, advanced/metastatic, and palliative)** | |
| 1 | 29 (31) |
| 2 | 56 (60) |
| ≥ 3 | 9 (10) |
| **PD-L1 Status** | |
| ≥1% | 44 (47) |
| <1% | 23 (24) |
| Unknown | 27 (29) |
| **MMR** | |
| Proficient | 67 (71) |
| Deficient | 2 (2.1) |
| Unknown | 25 (27) |
| **HPV** | |
| Negative | 4 (4.3) |
| Positive | 54 (57) |
| Unknown | 36 (38) |
| **HIV** | |
| Negative | 85 (90) |
| Positive | 9 (10) |

Abbreviations: ECOG = Eastern Cooperative Oncology Group, M = metastasis stage based on TNM staging system, M0 = no metastasis, M1 = metastasis present, PD-L1 = programmed death-ligand 1, MMR = mismatch repair deficient, HPV = human papillomavirus virus, HIV = human immunodeficiency virus

### 4.2.2 Efficacy Results

ORR and DoR

Responses according to RECIST 1.1. and per the IRC were observed in 13 patients with an observed ORR in POD1UM-202 of 14% (95% CI: 8, 22), with a median estimated DoR of 9.5 months (95% CI: 4.4, not estimable). There were 8 responses among 67 patients (12% [95% CI: 5, 22]) with *known* proficient mismatch repair status.

The DoR was based on the updated efficacy dataset provided by the Applicant (data cut-off date October 1, 2020). The results are summarized in **Table 5**. Two and four of the 13 patients with ongoing responses had <6 months and <12 months of response follow-up, respectively.

**Table 5 - POD1UM-202 Efficacy Results**

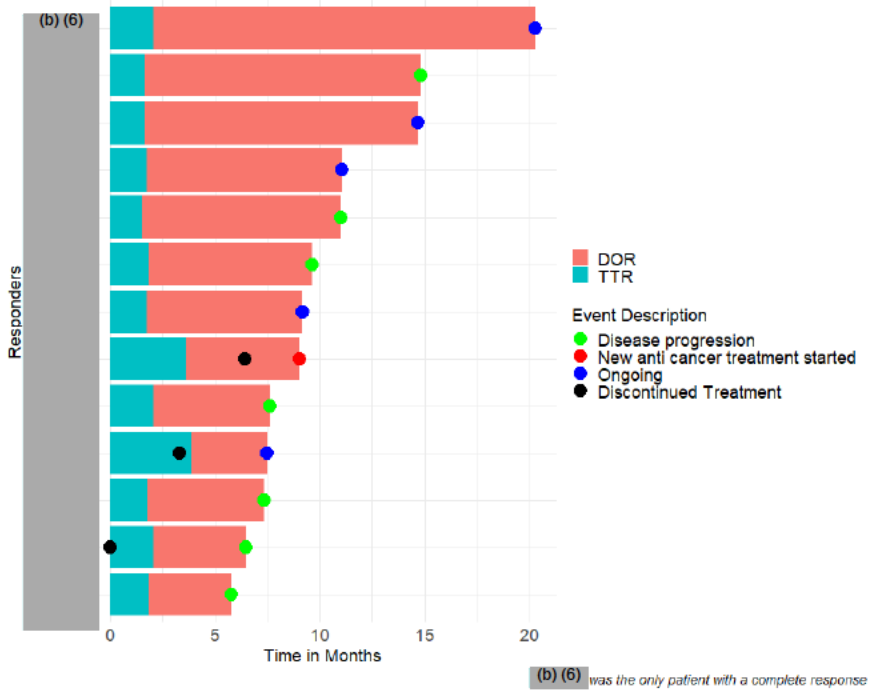
| **ORR** | **All Patients N = 94** |
|---|---|
| N (%) | 13 (14) |
| 95% CI | (8, 22) |
| **DoR** | **Responders N = 13** |
| Median (months, 95% CI) | 9.5 (4.4, NE) |
| Responders with DoR ≥6 months (%) [a] | 7 (54) |
| Responders with DoR ≥12 months (%) [a] | 3 (23) |

Abbreviations: ORR = objective response rate, CI = confidence interval, DoR = duration of response, NE = not estimable

[a] Observed landmark rates, 2 patients with ongoing response had <6 months of response follow-up, and 4 patients with ongoing response had <12 months of response follow-up

The swimmer plot for responding patients is shown in **Figure 1** and is based on the updated data cutoff date of October 1, 2020, at which time 5 patients (38%) had ongoing response, and 8 patients (61%) had progressed or started a subsequent anti-cancer treatment. One out of the 5 patients with ongoing response had clinical progression but not radiographic progression as of the last valid imaging assessment prior to the October 1, 2020 data cutoff date.

**Figure 1 - Swimmer Plot for Responders in POD1UM-202**

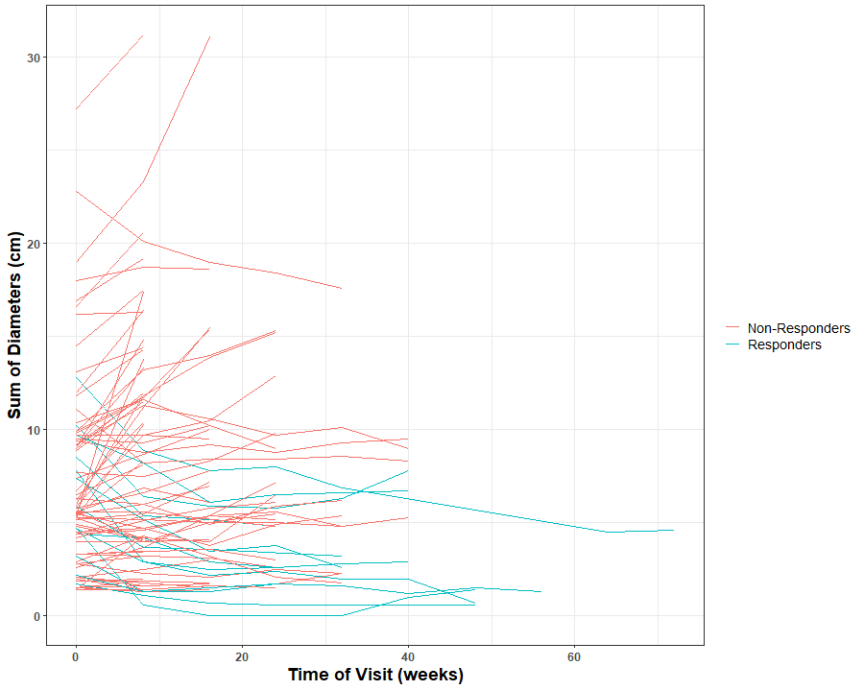



Abbreviations: DoR = duration of response, TTR = time to response
Data cutoff date: October 1, 2020

Tumor burden

The spider plot for the sum of diameters (SOD) of target lesions in scheduled CT scans is shown in **Figure 2** for 93 patients as assessed by IRC based on RECIST 1.1 (one of the 94 patients who received retifanlimab did not have any scans assessed by IRC, including baseline scans; this patient received one dose of retifanlimab and discontinued therapy due to disease progression).

**Figure 2 - Spider Plot of the Sum of Diameters of Target Lesions in POD1UM-202**




Data cutoff date: June 8, 2020

While the single-arm design of POD1UM-202 limits the assessment of retifanlimab's effect on ORR relative to patient tumor burden, FDA notes that that the average size of the target lesions in the overall trial population was relatively small. The mean and median dimensions of the target lesions were 3.0-3.2 cm and 2.5 cm, respectively, in both responders and non-responders. Furthermore, the ORR of 14% was based on tumor size reductions observed in a total of 25 target lesions. Among these 25 target lesions in the responding patients, 8 (32%) were non-bulky lymph nodes (1.6 - 3.1 cm). Four (31%) of the 13 responding patients had only non-bulky LNs as target lesions, and 2 had only lymph nodes for both target and non-target lesions. Only 3 (23%) of the responding patients had a rectal mass as a target lesion.

### 4.2.3 Safety Overview

The POD1UM-202 clinical trial provides the primary safety information for retifanlimab in adult patients with locally advanced or metastatic SCAC who progressed on or were ineligible for (or intolerant to) platinum-based chemotherapy. The safety population included all 94 patients in POD1UM-202; all patients received at least one dose of retifanlimab using the original data cutoff date of June 8, 2020.

FDA acknowledges differences between FDA's analysis and the Applicant's analysis of safety. In general, these differences are due to FDA's use of composite terms to describe an adverse event (e.g., under hemorrhage, events of hematuria, proctitis

hemorrhagic, and rectal hemorrhage have been grouped) or due to differences in the analysis (e.g., an analysis of nonfatal SAEs versus all SAEs).

**Table 6** reports the summary safety analysis results for all patients.

**Table 6 - Summary Safety Analysis for POD1UM-202**

| | **All Patients N=94 n (%)** |
|---|---|
| Median duration of treatment (range) | 2.8 months (1 day to 19.4 months) |
| Patient with ≥1 TEAE | 90 (96) |
| Any TEAE leading to or prolonging hospitalization | 49 (52) |
| Nonfatal serious TEAEs | 46 (49) |
| Grade 3-4 TEAEs[a] | 44 (47) |
| Deaths due to TEAEs | 10 (11) |
| TEAEs leading to retifanlimab dosage interruption | 26 (28) |
| TEAEs leading to retifanlimab discontinuation | 7 (7) |

Abbreviations: HIV = human immunodeficiency virus, TEAE = treatment-emergent adverse event
[a] Where maximum TEAE grade experienced by patient was Grade 3 or Grade 4

Overall, in the 94 patients exposed to retifanlimab in POD1UM-202, the safety profile is consistent with the toxicity profile of approved immune checkpoint inhibitors as no new safety signals were identified. However, given the relatively small size of the safety database with respect to the SCAC population and the single-arm nature of the trial, residual uncertainty remains regarding the risks in the indicated population.

A total of 37 patients (39%) died in POD1UM-202. Most deaths were attributed to disease progression (n=26, 28%). There were 10 (11%) fatal treatment-emergent adverse events (TEAEs). The TEAEs leading to death were interstitial lung disease, pneumocystis jirovecii pneumonia, pelvic infection, peritonitis, femur fracture, hypercalcemia, pleural effusion, pulmonary embolism, lymphangiosis carcinomatosa, and pancreatic carcinoma.

One fatal event was attributed to pancreatic carcinoma in a patient hospitalized for treatment for complications of hepatitis. The patient's liver biopsy reported "toxic/medical affection" without evidence for liver metastasis, and retifanlimab was discontinued due to "hepatic coma" or "hepatitis." The patient's was treated with high doses of corticosteroids and the hepatitis was reported to have resolved 26 days after retifanlimab was discontinued; however, the patient subsequently developed gastrointestinal bleed from a Grade 4 gastric ulcer, seizure, somnolence, and unconsciousness with "hepatic coma/encephalopathy." Autoimmune encephalitis was also on the differential diagnosis. The patient ultimately died 46 days after retifanlimab

was discontinued.

One patient's death was attributed to lymphangiosis carcinomatosa; however, this patient had previously received antibiotics and corticosteroids after developing pulmonary infiltrates 10 days after the first dose of retifanlimab and a pathological diagnosis was not obtained.

Forty-six patients (49%) had nonfatal serious adverse events (SAEs). **Table 7** summarizes the nonfatal SAEs with ≥2% incidence.

**Table 7 - Nonfatal SAEs in ≥2% of the Safety Population of POD1UM-202**

| | **All Grades (n=94) n (%)** |
|---|---|
| Non-urinary tract infections* | 12 (13) |
| Abdominal pain | 5 (5) |
| Anemia | 4 (4.3) |
| Hemorrhage* | 4 (4.3) |
| Urinary tract infection | 4 (4.3) |
| Diarrhea* | 3 (3.2) |
| Dyspnea | 3 (3.2) |
| Intestinal obstruction* | 3 (3.2) |
| Pelvic pain | 3 (3.2) |
| Pyrexia | 3 (3.2) |
| General physical health deterioration | 2 (2.1) |
| Hypercalcemia | 2 (2.1) |
| Mental status changes* | 2 (2.1) |
| Musculoskeletal pain* | 2 (2.1) |
| Proctalgia | 2 (2.1) |
| Thrombosis* | 2 (2.1) |

* Composite terms of similar preferred terms with the same pathophysiology

Seven patients (7%) discontinued retifanlimab due to TEAEs. Most of these patients (n=5) had Grade 3-4 TEAEs leading to retifanlimab discontinuation (coma hepatic, diffuse large B-cell lymphoma, immune-mediate enterocolitis, pneumonitis, and pseudomonas infection). One patient had a fatal event of pleural effusion.

Immune-mediated adverse events (IMAEs)

Based on the Applicant's datasets that flagged events as IMAEs, infusion-related reactions, or use of corticosteroids (of any formulation, including topical), other immunosuppressants, or hormone replacement therapy, 41 patients (44%) had potential IMAEs (**Table 8**). In the Applicant's analysis of events designated as an IMAE, 24

patients (26%) experienced an IMAE.

Fourteen patients (15%) had potential Grade ≥3 IMAEs, and 2 deaths (2.1%) were potentially attributable to an IMAE: interstitial lung disease, and lymphangiosis carcinomatosa (see above for a summary of the patient's clinical history and potential reclassification of the event). In the Applicant's analysis, 6 patients (6%) experienced a Grade 3 or greater immune-related AE with one fatality.

**Table 8 - Potential IMAEs[a] in ≥2% of the Safety Population of POD1UM-202**

| | All Grades (n=94) n (%) | Grade 3-4 (n=94) n (%) |
|---|---|---|
| Rash* | 9 (10) | 2 (2.1) |
| Hypothyroidism | 8 (9) | 0 |
| Dyspnea | 4 (4.3) | 0 |
| Hyperthyroidism | 4 (4.3) | 0 |
| Pneumonitis* | 4 (4.3) | 1 (1.1) |
| Pruritis | 4 (4.3) | 0 |
| Diarrhea* | 2 (2.1) | 1 (1.1) |
| Pyrexia | 2 (2.1) | 0 |

[a] Based on the Applicant's analysis datasets that flagged events as IMAEs, infusion-related reactions, or use of corticosteroids (of any formulation, including topical) or other immunosuppressants or hormone replacement therapy
* Composite terms of similar preferred terms with the same pathophysiology

In the Applicant's analysis of designated IMAEs (Grade 3 or 4 in parenthesis), 9% (2.1%) of patients had skin reactions; 4.3% (2.1%) pneumonitis; 2.1% (1.1%) colitis, 1.1% (1.1%) nephritis; 1.1% (1.1%) hepatitis; and 1.1% (0) experienced myositis.

Four patients experienced infusion-related reactions, all Grade 1-2.

TEAEs

**Table 9** summarizes the TEAEs in POD1UM-202 occurring in >10% of patients. TEAEs that occurred in ≥20% of patients were fatigue, non-urinary tract infections, musculoskeletal pain, anemia, and diarrhea. No new safety signals that would be considered unexpected for an anti-PD-1 antibody were found in the analysis of the TEAEs; some TEAEs were likely due to SCAC and sequelae of previous treatment, such as hemorrhage and perineal pain. However, without a randomized comparison and because this is a rare cancer with limited published data, the safety data in POD1UM-202 are more difficult to interpret.

**Table 9 - TEAEs in >10% of the Safety Population of POD1UM-202**

| TEAE | All Grades (n=94) n (%) | Grade 3-4 (n=94) n (%) |
|---|---|---|
| **General Disorders and Administration Site Conditions** | | |
| Fatigue* | 36 (38) | 6 (6) |
| Pyrexia | 12 (13) | 2 (2.1) |
| **Infections and Infestations** | | |
| Non-urinary tract infections* | 33 (35) | 10 (11) |
| Urinary tract infection* | 14 (15) | 3 (3.2) |
| **Musculoskeletal and Connective Tissue Disorders** | | |
| Musculoskeletal pain* | 22 (23) | 2 (2.1) |
| **Blood and Lymphatic System Disorders** | | |
| Anemia | 19 (20) | 6 (6) |
| **Gastrointestinal Disorders** | | |
| Diarrhea* | 19 (20) | 3 (3.2) |
| Abdominal pain | 13 (14) | 4 (4.3) |
| Constipation | 13 (14) | 0 |
| Nausea | 13 (14) | 0 |
| Perineal pain* | 11 (12) | 3 (3.2) |
| Vomiting | 11 (12) | 1 (1.1) |
| **Vascular disorders** | | |
| Hemorrhage* | 18 (19) | 3 (3.2) |
| **Skin and Subcutaneous Tissue Disorders** | | |
| Rash* | 15 (16) | 2 (2.1) |
| Pruritus | 11 (12) | 0 |
| **Metabolism and Nutrition Disorders** | | |
| Decreased appetite* | 14 (15) | 2 (2.1) |
| **Respiratory, Thoracic and Mediastinal Disorders** | | |
| Dyspnea | 13 (14) | 4 (4.3) |
| Cough* | 12 (13) | 0 |

* Composite terms

Laboratory abnormalities

Potential important treatment-emergent laboratory abnormalities occurring in at least 20% of patients where it is difficult to exclude an immune-related etiology include aspartate aminotransferase increased, alkaline phosphatase increased, triiodothyronine or free triiodothyronine decreased, and thyrotropin increased. One patient (1.1%) likely had retifanlimab-related drug-induced liver injury based on the laboratory abnormalities.

## 5. PROPOSED CONFIRMATORY TRIAL

POD1UM-303 is an ongoing randomized (1:1), double-blind, placebo-controlled clinical trial investigating retifanlimab in combination with chemotherapy vs. placebo in combination with chemotherapy; the chemotherapy backbone is carboplatin with paclitaxel based on the InterAACT trial (Rao et al., 2020).[9] Up to 300 patients with inoperable, locally recurrent or metastatic SCAC not previously treated for advanced disease are randomized to one of the two treatment arms. The primary endpoint is PFS based on RECIST 1.1 per blinded ICR (BICR). OS is a key secondary endpoint. The trial is designed to demonstrate a 33% reduction in the hazard rate for PFS, (corresponding to an increase in median PFS from 8 to 12 months under an exponential model assumption). Treatment crossover is permitted for patients who experience BICR-confirmed radiographic progression.

Regarding the trial design, in preliminary minutes issued to the applicant on January 8, 2020, FDA stated that a decision regarding whether the results from POD1UM-303 are adequate to support regular approval of retifanlimab for the proposed indication will depend on the totality of the evidence provided, including the observed magnitude of improvement in PFS, consistency of the effect across relevant subsets, and the overall benefit:risk assessment. At a minimum, the application would also need to provide data to show that treatment with retifanlimab does not adversely impact overall survival.

Top-line results of POD1UM-303 are projected to be available during the fourth quarter of 2024 with submission of a trial report in the second half of 2025.

## 6. SUMMARY OF FDA REVIEW ISSUES

It is unclear whether an ORR of 14% (95% CI: 8, 22) (12% among 67 patients with known microsatellite stable disease) as observed in the POD1UM-202 trial is reasonably likely to predict retifanlimab's clinical benefit in adult patients with locally advanced or metastatic SCAC who progressed on or were ineligible for (or intolerant to) platinum-based chemotherapy, particularly in the context of an inconsistent relationship between low response rate and outcomes in randomized trials of other anti-PD-1/PD-L1 antibodies.

Adding to the uncertainty of whether this low ORR is reasonably likely to predict clinical benefit, is that the efficacy data is based on tumor shrinkage of 25 target lesions in 13 patients. Among the 13 responders, 4 (31%) had only non-bulky LNs as target lesions and 2 had only LNs for both target and non-target lesions. Only 3 of the responders had a rectal mass as a target lesion.

The median DoR was 9.5 months (95% CI: 4.4, not estimable), 7 patients had a response lasting ≥6 months, and 3 patients had a response lasting ≥12 months. At the time of the October 1, 2020, data cutoff, only 5 patients had an ongoing response.

Given the inconsistent relationship between low ORRs (with CIs that do not exclude single digit response rates) and PFS or OS in clinical trials, it is unclear whether it is appropriate to extrapolate results of other trials of tumors with squamous histology to the effects of retifanlimab for SCAC and a randomized trial will better assess the risks and benefits of retifanlimab.

The safety profile of retifanlimab in patients with advanced or metastatic recurrent SCAC appears similar to the known safety profile of checkpoint inhibitors in other disease settings. Most (96%) patients experienced a TEAE, 52% of patients were either hospitalized for a TEAE or had hospitalization prolonged due to a TEAE, and 47% experienced a Grade 3-4 TEAE. At the time of data cutoff, 39% patients have died, and in 10 of these 37 patients the death was attributed to a TEAE (cause other than disease progression). Attribution of specific events to treatment (vs. underlying disease) is challenging in the setting of the single arm trial.

Seven patients discontinued retifanlimab treatment due to a TEAE, including hepatitis, immune-mediated enterocolitis, and pneumonitis. Potential IMAEs (including all TEAEs for which treatment with corticosteroid, immune suppression, or hormonal replacement therapy was necessary) were reported in 44% patients: 14 patients (15%) had potential Grade ≥3 IMAEs. Patients ≥65-year-old and patients with HIV-positive status did not appear to experience a disproportionately higher incidence of safety events, including infections, compared to the overall trial population. However, POD1UM-202 did not include a sufficient number of patients aged ≥65 years nor patients with HIV-positive status to allow FDA to draw conclusions. In addition, the trial enrolled patients with well-controlled HIV infection and thus, the trial results are not applicable to patients with CD4 counts less than 300 cells/µL or a detectable viral load.

Given the uncertainties with respect to risk/benefit based on these results and the potential for serious toxicities in a subgroup of patients who receive retifanlimab, confirmation of clinical benefit with a randomized controlled trial is needed. In addition, given the limited trial size of POD1UM-202, few patients with HIV-positive status were enrolled, and members of racial minority groups relevant to the U.S. population are underrepresented, bringing additional uncertainty regarding whether the trial results are applicable to the population for which retifanlimab would be prescribed (or whether even the observed low response rate would be replicated in a more general patient population with anal cancer).

## 7. ISSUES FOR THE COMMITTEE

- Discuss whether the demonstrated magnitude of effect in overall response rate (and duration of response) constitutes a clinically meaningful treatment effect in patients with recurrent advanced or metastatic squamous cell carcinoma of the anal canal, particularly in the setting of an inconsistent relationship between low response rate and clinical benefit observed in other trials with immune checkpoint inhibitors and the limitations of the small trial size, which may preclude a conclusion that the results are applicable to the general patient population. Considering these uncertainties, is the observed ORR reasonably likely to predict clinical benefit?

- Should a regulatory decision on retifanlimab for the treatment of advanced or metastatic SCAC be deferred until further data are available from clinical trial POD1UM-303?

## 8. REFERENCES

1. Cancer Stat Facts: Anal Cancer. *NCI Surveillance, Epidemiology, and End Results (SEER) Program*. Accessed April 24, 2021. https://seer.cancer.gov/statfacts/html/anus.html
2. Simpson JA, and Scholefield JH. Diagnosis and management of anal intraepithelial neoplasia and anal cancer. *BMJ*. 2011;343:d6818. doi: 10.1136/bmj.d6818
3. Frisch M, Glimelius B, van den Brule AJ, et al. Sexually transmitted infection as a cause of anal cancer. *N Engl J Med*. 1997;337(19):1350-8.
4. Daling JR, Madeleine MM, Johnson LG, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer*. 2004;101(2):270-80.
5. Valvo F, Ciurlia E, Avuzzi B, et al. Cancer of the anal region. *Critical Reviews in Oncology/ Hematology*. 2019;135:115-27.
6. Anal Carcinoma, version 1.2021 – February 16, 2021. *NCCN Guidelines*. Accessed April 24, 2021. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf
7. Shiels MS, Pfeiffer RM, Chaturvedi AK, et al. Impact of the HIV Epidemic on the Incidence Rates of Anal Cancer in the United States. *J Natl Cancer Inst*. 2012;104(20):1591-8. doi: 10.1093/jnci/djs371
8. Colon-Lopez V, Shiels MS, Machin M, et al. Anal Cancer Risk Among People with HIV Infection in the United States. *J Clin Onc*. 2018;36(1):68-75.
9. Rao S, Sclafani F, Eng C, et al. International Rare Cancers Initiative Multicenter Randomized Phase II Trial of Cisplatin and Fluorouracil Versus Carboplatin and Paclitaxel in Advanced Anal Cancer: InterAAct. *J Clin Onc*. 2020;38(22):2510-8.
10. Morris VK, Salem ME, Nimeiri H, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2017;18(4):446-53.

11. Ott PA, Piha-Paul SA, Munster P, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal. *Ann Oncol*. 2017;28(5):1036-41.
12. Saint A, Evesque L, Falk AT, et al. Mitomycin and 5-fluorouracil for second-line treatment of metastatic squamous cell carcinomas of the anal canal. *Cancer Medicine*. 2019;8(16):6853-9.
13. Sclafani F, Morano F, Cunningham D, et al. Platinum-Fluoropyrimidine and Paclitaxel-Based Chemotherapy in the Treatment of Advanced Anal Cancer Patients. *Oncologist*. 2017;22(4):402-8.
14. Beaver JA and Pazdur R. “Dangling” Accelerated Approvals in Oncology. *N Engl J Med*. 2021; 384:e68.