# BLA 761209 - Retifanlimab

## Oncologic Drugs Advisory Committee Meeting

## Introductory Comments

## June 24, 2021

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Division of Oncology 3
Office of Oncologic Diseases

# Applicant's Proposed Indication

*Treatment of adult patients with locally advanced or metastatic squamous carcinoma of the anal canal (SCAC) who have progressed on or are intolerant of platinum-based chemotherapy.*

*This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.*

# POD1UM-202: Trial Design

- Ongoing, open-label, multicenter, single-arm trial
- Patients with no more than 2 prior lines of therapy for metastatic SCAC
- Primary endpoint: overall response rate (ORR) by Independent Central Review (ICR) by RECIST 1.1
- Treatment: retifanlimab 500 mg IV every 4 weeks up to 2 years
- Imaging assessments every 8 weeks

# Uncertainty Regarding Risk-Benefit of Retifanlimab in SCAC

- Unclear if current results of POD1UM-202 are reasonably likely to predict benefit
  - Low ORR of 14% (95% CI 8, 22)
  - Small number of patients (and target lesions); only 13 with a response
  - Only 7 patients with responses lasting ≥ 6 months

- Inconsistent relationship between low ORRs observed in other single-arm studies with immune checkpoint inhibitors and clinical benefit in confirmatory studies

# Accelerated Approval

The accelerated approval provisions of FDASIA in section 506(c) of the FD&C Act provide that 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 an intermediate endpoint that is reasonably likely to predict clinical benefit
- taking into account the availability or lack of alternative treatments.

For drugs granted accelerated approval, postmarketing confirmatory trials conducted to verify and describe the anticipated effect.

# Accelerated Approvals in Oncology Trials Using Immune Checkpoint Inhibitors

- Seven antibodies approved against PD-(L)1 for more than 75 indications
- 35 accelerated approvals for PD-(L)1 antibodies, 31 based on ORR
- 9/31 confirmatory studies successfully confirmed benefit
- 9/31 confirmatory studies did not support the original findings
  - 7/9 ORR between 10-20%

4/9 resulted in voluntary withdrawal of the indications before ODAC discussions

Indications withdrawn before ODAC discussions

| | |
|---|---|
| **Previously treated locally advanced or metastatic urothelial carcinoma** | |
| Atezolizumab | ORR: 14.8% (95% CI: 11.1% to 19.3%), DoR: NR (range: 2.1+ to 13.8+ m) |
| Durvalumab | ORR: 17% (95% CI: 11.9% to 23.3%), DoR: NR (range: 0.9+ to 19.9+ m) |
| **Previously treated metastatic small cell lung cancer** | |
| Nivolumab | ORR: 12% (95% CI: 6.5% to 19.5%), DoR: 3.0 to 42.1 m |
| Pembrolizumab | ORR: 19% (95% CI: 11% to 29%), DoR: 4.1 to 35.8+ m |

DoR: duration of response; NR: not reached

# Indications Discussed at 4/27 – 4/29 ODAC Meetings

(Accelerated Approvals Based on ORR)

Indications discussed at ODAC - April 2021

| | |
|---|---|
| **Locally advanced or metastatic urothelial carcinoma in patients who are not eligible for cisplatin** | |
| Atezolizumab | ORR: 23.5% (95% CI: 16.2% to 32.2%)<br>DoR: NR (range: 3.7 to 16.6+ m) |
| Pembrolizumab | ORR: 29% (95% CI: 24% to 34%)†<br>DoR: NR (range: 1.4+ to 17.8+ m) |
| **Previously treated locally advanced or metastatic PD1+ gastric or GEJ carcinoma** | |
| Pembrolizumab | ORR: 13.3% (95% CI: 8.2% to 20%)<br>DoR range: 2.8+ to 19.4+ m |
| **Previously treated unresectable or metastatic hepatocellular carcinoma** | |
| Nivolumab | ORR: 14.3% (95% CI: 9.2% to 20.8%)<br>DoR: 3.2 to 38.2+ m |
| Pembrolizumab | ORR: 17% (95% CI: 11% to 26%)<br>DoR: 89% ≥6 m and 56% at ≥12 m |

- Recommended removal of two indications
- Reasons to maintain indications
  - Additional data support original determination of an effect reasonably likely to predict benefit
  - Another study will read out

# POD1UM-202: 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 (%) | 7 (54) |
| Responders with DoR ≥12 months (%) | 3 (23) |

- 94 patients
  - 9 patients were HIV+
  - 1 Black patient; 4 Hispanic patients
  - 37% unknown PD-L1 status
  - 27% unknown MMR status
  - 38% unknown HPV status
- Responders: total of 25 target lesions, 8 of these non-bulky (≤ 3.1 cm longest perpendicular axis)

# POD1UM-202: Summary of Safety

- Safety profile consistent with the pharmacological class
- Although infrequent, immune-related adverse events can be serious or even fatal (at least one death attributed to pneumonitis and immune-related reactions may have contributed to two additional fatal events)
- **Limitation:** Small number of patients, few patients with HIV+ status, and single-arm study

# Uncertainty Regarding Risk-Benefit of Retifanlimab in SCAC

- Not clear if results of POD1UM-202 reasonably likely to predict benefit
  - Low ORR: 14% (95% CI 8, 22); only 13 responders; small number of target lesions
  - Small number of patients with
    - positive HIV status, and
    - racial/ethnic minorities
  - Only 7 patients with responses lasting ≥ 6 months
  - Immune-mediated toxicity

- Inconsistent relationship between low ORRs and clinical benefit in other anti-PD-(L)1 studies

# Single Arm Trials in Oncology

- **Benefits**
  - Expedite development (esp. for drugs with unprecedented effects)
  - Obtain preliminary information about drug

- **Risks**
  - Increased uncertainty regarding a drug's risk/benefit
  - May delay availability of important data regarding drug's effects

# Issues for the Committee

- Discuss whether the demonstrated magnitude of effect in overall response rate (and duration of response) is clinically meaningful and reasonably likely to predict clinical benefit in patients with recurrent advanced or metastatic squamous cell carcinoma of the anal canal.

- 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?


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# BLA 761209: Retifanlimab

## FDA Presentation, Oncologic Drugs Advisory Committee (ODAC) Meeting

May Tun Saung, MD
Clinical Reviewer
Division of Oncology 3 (DO3)
Office of Oncologic Diseases
June 24, 2021

# FDA Review Team

| | |
|---|---|
| Division Director (DO3) | Steven Lemery |
| Deputy Director (DO3) | Lola Fashoyin-Aje |
| Cross-Discipline Team Leader and Clinical Team Leader (DO3) | Sandra Casak |
| Clinical Reviewer (DO3) | May Tun Saung |
| Division Director (OB) | Yuan Li Shen |
| Statistical Team Leader | Pallavi Mishra-Kalyani |
| Statistical Reviewer | Pourab Roy |
| Division Director (OCP) | Atiqur Rahman |
| Office of Clinical Pharmacology Team Leader | Hong Zhao |
| Office of Clinical Pharmacology Reviewer | Vicky Hsu |
| Division Director (DHOT) | John Leighton |
| Nonclinical Team Leader | Matthew Thompson |
| Nonclinical Reviewer | Emily Place |

| | |
|---|---|
| OBP (Acting) | Bazaraa Damdinsuren |
| OPDP (Reviewer) | Lynn Panholzer |
| Patient Labeling Reviewer | Ruth Mayrosh |
| Patient Labeling Team Leader | Barbara Fuller |
| OSI Reviewer | Michele Fedowitz |
| OSI Team Leader | Karen Bleich |
| OSE/DEPI Team Leader | Steven Bird |
| OSE/DPV Reviewer | Peter Waldron |
| OSE/DPV Team Leader | Afrouz Nayernama |
| OSE/DMEPA Reviewer | Janine Stewart |
| OSE/DMEPA Team Leader | Ashleigh Lowery |
| OSE/DRM Reviewer | Mei-Yean Chen |
| OSE/DRM Team Leader | Naomi Boston |
| Regulatory Project Manager | Autumn Zack-Taylor |
| Supervisory Associate Director(OOD) (designated signatory authority) | Paul Kluetz |
| Director (OOD) | Richard Pazdur |

# Outline

- Introduction
- Overview of POD1UM-202
- Review Issues
- Summary
- Discussion and Voting Questions for ODAC

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# Uncertainty Regarding Risk-Benefit of Retifanlimab in Squamous Cell Carcinoma of the Anal Canal (SCAC)

- Not clear that current results of POD1UM-202 are reasonably likely to predict benefit
  - Low overall response rate (ORR) of 14% (95% confidence interval [CI]: 8%, 22%)
  - Only 13 responding patients, who had a small number of target lesions
  - Only 7 patients with responses lasting ≥6 months
  - Small number of patients with human immunodeficiency virus (HIV) and patients from racial/ethnic minorities
  - Added immune-mediated toxicity

- Inconsistent relationship between low ORRs observed in other single-arm trials with anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death protein ligand 1 (PD-L1) antibodies and clinical benefit

# Available Therapy

- Based on FDA Guidance for Industry - Expedited Programs for Serious Conditions, FDA generally considers available therapy as a therapy that:
  - Is approved or licensed in the United States for the same indication being considered for the new drug, and
  - Is relevant to current U.S. standard of care (SOC) for the indication

  In evaluating the current SOC, FDA may consider recommendations by authoritative scientific bodies based on clinical evidence and other reliable information that reflects current clinical practice.

# Published Results of Anti-PD-1 Antibodies in Previously Treated Anal Squamous Cell Carcinoma

| Drug (Trial) | Disease setting (n) | ORR (%)<br>-Response Type | Median DoR (months) | Grade ≥3 AEs (%) |
|---|---|---|---|---|
| **Nivolumab (NCI9673[1])** | Unresectable or metastatic SCAC (n=37) | 24<br>95% CI: 15, 33<br>-2 CR, 7 PR | 5.8<br>interquartile range 3.9 to 8.1 | 13 |
| **Pembrolizumab (KEYNOTE-028[2])** | Locally advanced or metastatic SCAC, PD-L1 ≥1% (n=24) | 17<br>95% CI: 5, 37<br>-4 PR | Not reached<br>range <0.1+ to 9.2+ | 17[4] |
| **Pembrolizumab (KEYNOTE-158[3])** | Unresectable or metastatic anal squamous cell carcinoma (n=112) | 12<br>95% CI: 6, 19<br>-5 CR, 8 PR | Not reached<br>range 6.0+ to 29.1+ | 19[4] |

Abbreviations: DoR – duration of response, AE – adverse event, 5-FU – 5-fluorouracil, Q2W – every 2 weeks, Q28D – every 28 days, CR – complete response, PR – partial response

[1] Morris et al., **2017**; [2] Ott et al., **2017**; [3] Marabelle et al., 2020; [4] treatment-related adverse events

# Dangling Accelerated Approvals: 4/27-29 ODAC meetings

- 9 accelerated approvals – single-arm trials, primary endpoint of ORR
  - 4 anti-PD-1 or anti-PD-L1 antibodies
  - Indications:
    - urothelial cancer
    - small cell lung cancer
    - hepatocellular carcinoma
    - gastric cancer or gastroesophageal junction cancer
  - ORR: 12% to 29%

# Dangling Accelerated Approvals – Voluntary Withdrawal

| Drug | Indication | Approval End Points |
|---|---|---|
| Atezolizumab | LA/met UC – previously treated | ORR: 14.8% (95% CI: 11.1% to 19.3%)<br>DoR: median not reached (range: 2.1+ to 13.8+ m) |
| Durvalumab | LA/met UC – previously treated with platinum | ORR: 17% (95% CI: 11.9% to 23.3%)<br>DoR: median not reached (range: 0.9+ to 19.9+ m) |
| Nivolumab | Met SCLC – previously treated | ORR: 12% (95% CI: 6.5% to 19.5%)<br>DoR: 3.0 to 42.1 m |
| Pembrolizumab | Met SCLC – previously treated | ORR: 19% (95% CI: 11% to 29%)<br>DoR: 4.1 to 35.8+ m |

Abbreviations: LA/met – locally advanced or metastatic, UC – urothelial carcinoma, HCC – hepatocellular carcinoma, SCLC – small cell lung cancer, ORR – overall response rate, DoR – duration of response, CI – confidence interval, m – month

Adapted from: JA Beaver, R Pazdur. N Engl J Med 2021;384:e68.

# Dangling Accelerated Approvals – ODAC

| Drug | Indication | Approval End Points |
|---|---|---|
| Atezolizumab | LA/met UC – previously treated* | ORR: 23.5% (95% CI: 16.2% to 32.2%)†<br>DoR: median not reached (range: 3.7 to 16.6+ m) |
| Nivolumab | HCC – previously treated with sorafenib | ORR: 14.3% (95% CI: 9.2% to 20.8%)<br>DoR: 3.2 to 38.2+ m |
| Pembrolizumab | LA/met UC – previously treated* | ORR: 29% (95% CI: 24% to 34%)†<br>DoR: median not reached (range: 1.4+ to 17.8+ m) |
| Pembrolizumab | LA/met GC/GEJ – previously treated, PD-L1+ | ORR: 13.3% (95% CI: 8.2% to 20%)<br>DoR range: 2.8+ to 19.4+ m |
| Pembrolizumab | HCC – previously treated with sorafenib | ORR: 17% (95% CI: 11% to 26%)<br>DoR: 89% had ongoing responses at ≥6 m and 56% at ≥12 m |

Abbreviations: LA/met – locally advanced or metastatic, UC – urothelial carcinoma, HCC – hepatocellular carcinoma, GC/GEJ – gastric cancer/gastroesophageal junction, ORR – overall response rate, DoR – duration of response, CI – confidence interval, m – month

* cisplatin-ineligible and PD-L1+, or platinum-ineligible regardless of PD-L1 status

† ORR and DoR shown for original approval in PD-L1 unselected patients

Adapted from: JA Beaver, R Pazdur. N Engl J Med 2021;384:e68.

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# POD1UM-202: Trial Design

- **Design**: ongoing, open-label, multicenter, single-arm
- **Key eligibility criteria**:
  - locally advanced or metastatic SCAC with disease progression on or after platinum-based therapy unless ineligible for or intolerant of platinum
    - received at least 1 prior line of systemic therapy if ineligible for platinum
    - relapsed <6 months from therapy completion if received platinum-based radiosensitizing chemotherapy
  - no more than 2 prior lines of systemic therapy for metastatic SCAC
  - measurable disease by RECIST 1.1
  - ECOG performance status 0-1
  - if HIV+: CD4+ count ≥300/µL, undetectable viral load, and receiving anti-retroviral therapy

Abbreviations: RECIST – Response Evaluation Criteria in Solid Tumors, ECOG – Eastern Cooperative Oncology Group, CD – cluster of differentiation

# POD1UM-202: Baseline Demographics

| Demographic group | All patients N = 94 |
|---|---|
| **Sex (%)** | |
| Male | 33 (35%) |
| Female | 61 (65%) |
| **Age** | |
| Median in years (range) | 64 (37, 94) |
| **Race (%)** | |
| White | 72 (77%) |
| Black or African American | 1 (1%) |
| Other | 15 (16%) |
| Unknown | 6 (6%) |
| **Ethnicity (%)** | |
| Hispanic or Latino | 4 (4%) |
| Not Hispanic or Latino | 49 (52%) |
| Not Reported | 33 (35%) |
| Unknown | 4 (4%) |

| Demographic group | All patients N = 94 |
|---|---|
| **MMR (%)** | |
| Proficient | 67 (71%) |
| Deficient | 2 (2%) |
| Unknown | 25 (27%) |
| **HPV (%)** | |
| Negative | 4 (4%) |
| Positive | 54 (57%) |
| Unknown | 36 (38%) |
| **HIV (%)** | |
| Negative | 85 (90%) |
| Positive | 9 (10%) |

Abbreviations: MMR – mismatch repair, HPV – human papilloma virus

# Primary Efficacy Results

| Overall response rate (ORR) | All patients N = 94 |
|---|---|
| Number of patients with CR or PR (%) | 13 (14%) |
| 95% confidence interval (CI) | 8%, 22% |
| **Duration of response (DoR)** | **Responding patients N = 13** |
| Median (months, 95% CI) | 9.5 (4.4, NE) |
| Responding patients with DoR ≥6 months (n) | 7 |
| Responding patients with DoR ≥12 months (n) | 3 |

Abbreviations: CR – complete response, PR – partial response, NE – not estimable, n – number of patients
Data cutoff date: October 1, 2020

# Primary Efficacy Results

- Among the 13 responding patients, 5 patient's mismatch repair status were unknown

- 67 patients with known proficient mismatch repair status in POD1UM-202

| ORR in patients with known proficient MMR status | All patients N = 67 |
|---|---|
| Number of patients with CR or PR (%) | 8 (12%) |
| 95% CI | 5%, 22% |

Abbreviations: MMR – mismatch repair, CR – complete response, PR – partial response, N – number of patients, CI – confidence interval
Data cutoff date: October 1, 2020

# Safety

- No unexpected safety signals, but Grade ≥3 immune-mediated adverse events (IMAEs) in 15%
- 3% died from an adverse event where an immunologic cause could not be excluded
  - hepatitis (n=1)
  - pneumonitis/interstitial lung disease (n=2)
- Tolerance in patients with HIV appears similar to the overall trial population, but limited by sample size (n=9)
- Safety findings are limited
  - small population
  - single arm trial - no treatment control arm
- Summary - safety profile consistent with the drug class including rare but potentially fatal IMAEs

# Confirmatory Clinical Trial: POD1UM-303

- **Trial design:** randomized, double-blind, placebo-controlled, add-on trial

N ~ 300
- inoperable, locally recurrent or metastatic SCAC
- no prior systemic therapy other than radiosensitizing chemotherapy
- eligible if well-controlled HIV

<u>Group A (n~150)</u>
Placebo + Carboplatin/Paclitaxel x 6 cycles followed by Placebo 7 cycles

<u>Group B (n~150)</u>
Retifanlimab + Carboplatin/Paclitaxel x 6 cycles followed by Retifanlimab 7 cycles

- **Primary endpoint:** progression-free survival (RECIST 1.1 per blinded independent committee review [BICR])
- **Key secondary endpoint:** overall survival
- **Trial status:** ongoing, 28 patients enrolled (May 25, 2021)

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  - Only 7 patients with responses lasting ≥6 months
  - Small number of patients with HIV and patients from racial/ethnic minorities
  - Added immune-mediated toxicity

- Inconsistent relationship between low ORRs observed in other single-arm trials with anti-PD-1 or anti-PD-L1 antibodies and the clinical benefit in confirmatory trials

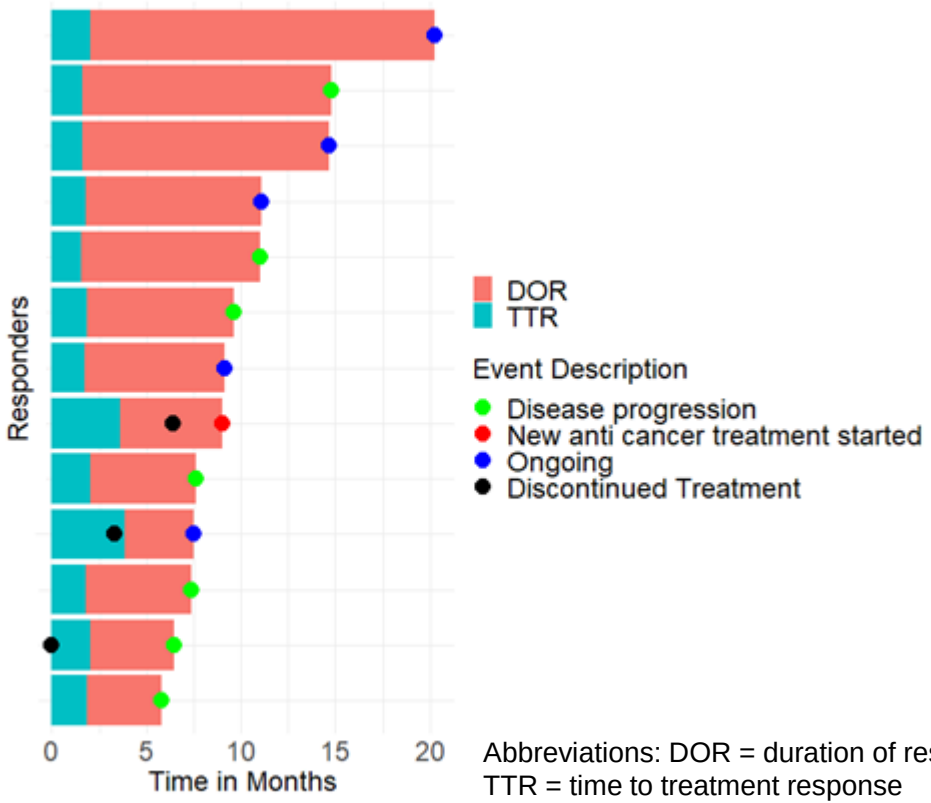
# Issue – ORR in POD1UM-202

- ORR: 14% (95% CI: 8%, 22%)

- Durable ORR in a small proportion of the trial population:
  - 7 patients (7%) had response lasting ≥6 months
  - 3 patients (3%) had response lasting ≥12 months

Data cutoff date: October 1, 2020

# Issue – ORR in POD1UM-202




Abbreviations: DOR = duration of response, TTR = time to treatment response

Only 5 patients had ongoing response at data cutoff date (October 1, 2020)

# Issue – ORR in Squamous Cell Histology

- The Applicant stated that the ORR in POD1UM-202 is comparable to what is demonstrated in other trials investigating anti-PD-1 or anti-PD-L1 antibodies for treatment of other squamous cell carcinomas where:
  - ORR ranged from 10-20%, and
  - Clinical benefit was demonstrated

# Issue – ORR in Squamous Cell Histology

- FDA disagrees for the following reasons:
  - Randomized-controlled trials designed to evaluate survival, not ORR
  - Different cancers and different risk factors:
    - Cervical cancer
    - Head and neck squamous cell carcinoma
    - Esophageal cancer
    - Non-small cell lung cancer
  - Trial submitted to support a marketing approval should stand on its own

# Issue – Limited Sample Size to Characterize DoR

| Duration of response (DoR) | Responding patients N = 13 |
|---|---|
| Median (months, 95% CI) | 9.5 (4.4, NE) |
| Responding patients with DoR ≥6 months (n) | 7 |
| Responding patients with DoR ≥12 months (n) | 3 |

Abbreviations: CI – confidence interval, NE – not estimable, n – number of patients
Data cutoff date: October 1, 2020

# Issue – Burden of Disease

- On average, each responding patient had only 2 target lesions.
- ORR of 14% (95% CI: 8, 22) is based on measurements of 25 target lesions
  - 8 target lesions (32%) were non-bulky lymph nodes (1.6-3.1 cm)
- 4 responding patients had only lymph nodes as target lesions
- 33 patients with target liver lesions in POD1UM-202
  - 5 patients had reduction of these lesions based on RECIST 1.1 as assessed by IRC

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  - Only 7 patients with responses lasting ≥6 months
  - Small number of patients with human immunodeficiency virus (HIV) and patients from racial/ethnic minorities
  - Low ORR must be considered in the context of rare but potentially fatal IMAEs
- Uncertainty requires a post-marketing requirement to verify clinical benefit, but only 10% of the planned trial population enrolled in POD1UM-303
- Inconsistent relationship between low ORRs observed in other single-arm trials with anti-PD-1 or anti-PD-L1 antibodies and clinical benefit

# Single Arm Trials in Oncology

- Benefits
  - Expedite development (especially for drugs with unprecedented effects)
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- Risks
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# Discussion and Voting Questions for ODAC

**DISCUSSION**: Discuss whether the demonstrated magnitude of effect on overall response rate (and duration of response) is clinically meaningful and reasonably likely to predict clinical benefit in patients with recurrent advanced or metastatic squamous cell carcinoma of the anal canal.

**VOTE**: 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?


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