ZYNYZ® (retifanlimab-dlwr)

Prescribing Information and Data Review in Squamous Cell Carcinoma of the Anal Canal (SCAC)

MSL-RET-US-0026 05/26

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Notice

- Some information contained in this presentation may not be included in the approved Prescribing Information for ZYNYZ (retifanlimab-dlwr). This presentation is not intended to offer recommendations for any administration, indication, dosage, or other use for ZYNYZ in a manner inconsistent with the approved Prescribing Information

Indication and Usage

- ZYNYZ is a programmed death receptor-1 (PD-1)-blocking antibody indicated:
  - Squamous Cell Carcinoma of the Anal Canal (SCAC)
    - In combination with carboplatin and paclitaxel for the first-line treatment of adult patients with inoperable locally recurrent or metastatic SCAC
    - As a single agent for the treatment of adult patients with locally recurrent or metastatic SCAC with disease progression on or intolerance to platinum-based chemotherapy
  - Merkel Cell Carcinoma (MCC)
    - For the treatment of adult patients with metastatic or recurrent locally advanced MCC

- **Please see the Full Prescribing Information, including Warnings & Precautions, and Medication Guide for ZYNYZ**

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Prescribing Information

- Indication, Dosing, and Administration
- Dosage Modifications for Adverse Reactions
- Clinical Data Review
- Safety Overview
- Warnings & Precautions

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Indication, Dosing, and Administration

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Indication and Dosing and Administration

Indication

Retifanlimab-dlwr in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of adult patients with inoperable locally recurrent or metastatic SCAC and as a single agent for the treatment of adult patients with locally recurrent or metastatic SCAC with disease progression on or intolerance to platinum-based chemotherapy

Recommended Dosing and Administration

Administer as an intravenous infusion after dilution, over 30 minutes, as recommended

Indication	Recommended Dosage	Duration of Treatment
Combination Therapy[a]		
Adult patients with inoperable locally recurrent or metastatic SCAC in combination with carboplatin and paclitaxel	500 mg every 4 weeks or 375 mg every 3 weeks	Until disease progression, unacceptable toxicity, or up to 12 months
Monotherapy		
Adult patients with locally recurrent or metastatic SCAC with disease progression on or intolerance to platinum-based chemotherapy	500 mg every 4 weeks or 375 mg every 3 weeks	Until disease progression, unacceptable toxicity, or up to 24 months

[a] Refer to the Prescribing Information for the agents administered in combination with retifanlimab-dlwr for recommended dosing information, as appropriate.
SCAC, squamous cell carcinoma of the anal canal.
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Dosage Modifications for Adverse Reactions

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Dosage Modifications for Adverse Reactions

- No dose reduction of retifanlimab-dlwr is recommended. In general, withhold retifanlimab-dlwr for severe (Grade 3) immune-mediated adverse reactions
- Permanently discontinue retifanlimab-dlwr for life threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating steroids

Select for dosage modifications for adverse reactions that require management different from these general guidelines

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Clinical Data Review in SCAC

- POD1UM-303: Use in Combination with Carboplatin and Paclitaxel
- POD1UM-202: Use as Single Agent

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POD1UM-303 Efficacy

Retifanlimab-dlwr in Combination with Carboplatin and Paclitaxel for the Treatment of Inoperable Locally Recurrent or Metastatic SCAC

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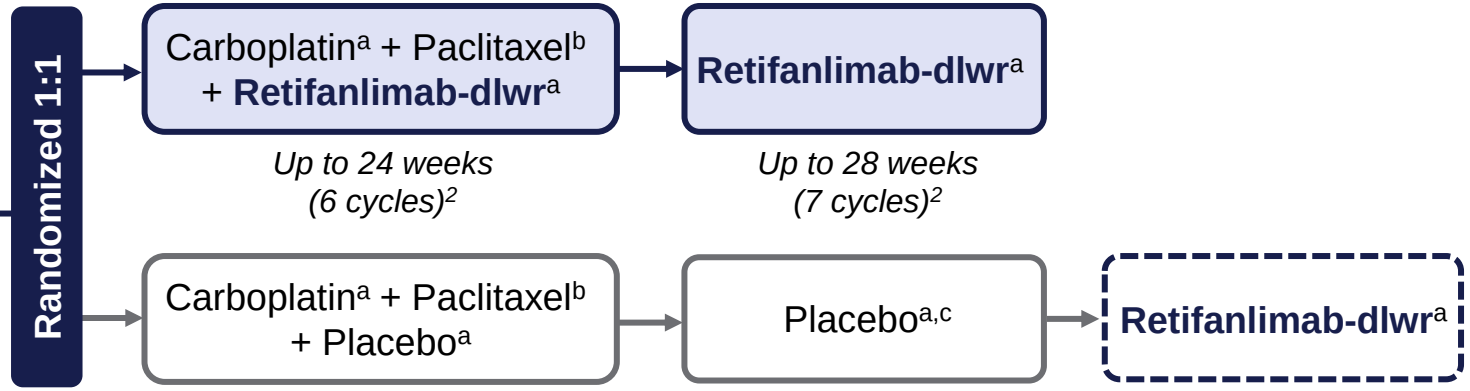
POD1UM-303/InterAACT 2: Study Design[1-4]

Study Design: Phase 3, randomized, double-blind study of carboplatin-paclitaxel with retifanlimab-dlwr or placebo in inoperable, locally recurrent, or metastatic SCAC not previously treated with systemic chemotherapy[1]

N=308

Select Eligibility Criteria:

- Inoperable, locally recurrent, or metastatic SCAC
- No prior systemic therapy other than chemoradiotherapy, or prior neoadjuvant or adjuvant therapy if completed ≥6 months before study entry
- Measurable disease per RECIST v1.1
- ECOG PS of 0 to 1
- If HIV-positive: stable with CD4+ count ≥200/µL, undetectable viral load, and under treatment with ART/HAART and no history of any HIV-related opportunistic infection for ≥4 weeks prior to study enrollment



Primary endpoint: PFS per BICR
Key secondary endpoint: OS
Other secondary objectives: ORR, DOR, DCR, safety, PK

Stratification:

- PD-L1 expression (<1% vs ≥1%)
- Region (AUS, EU, North America, UK vs ROW)
- Extent of disease (locally recurrent vs metastatic)

[a] Carboplatin and placebo/retifanlimab-dlwr given IV on day 1 of each 28-day cycle. [b] Paclitaxel given IV on days 1, 8, and 15 of each 28-day cycle. [c] Optional crossover for qualified participants after BICR verification of PD.

ART, antiretroviral therapy; AUS, Australia; BICR, blinded independent central radiographic review; DCR, disease control rate; DOR, duration of response; ECOG PS, European Cooperative Oncology Group Performance Scale; EU, European Union; HIV, human immunodeficiency virus; IV, intravenous; NA, North America; ORR, overall response rate; OS, overall survival; PK, pharmacokinetics; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world; UK, United Kingdom.

1. Rao S, et al. *Front Oncol*. 2022;12:935383. 2. ClinicalTrials.gov. Accessed Apr 2026. https://clinicaltrials.gov/study/NCT04472429. 3. Rao S, et al. ESMO 2024. Oral presentation LBA2. 4. ZYNYZ (retifanlimab-dlwr). Prescribing Information. Incyte Corporation; May 2026.

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POD1UM-303/InterAACT 2: Baseline Demographics and Characteristics

308 patients were evaluated in the POD1UM-303 clinical study

Demographics

- **Median age:** 62 (29-86) years
- **Sex:** Female: 72%
- **Race:**
  - White: 87%
  - Black: 1.6%
  - Asian: 6%
  - Unknown: 3.2%
- **Ethnicity:**
  - Hispanic or Latino: 7%
  - Not Hispanic or Latino: 85%
  - Unknown/not reported: 8%

Characteristics

- **ECOG PS:**
  - Score of 0: 55%
  - Score of 1: 45%
- **HIV status:**
  - Positive: 3.6%
- **Prior surgery:** 35%
- **Prior radiotherapy:** 71%
- **Metastatic disease at BL:** 83%
- **PD-L1 expression ≥1%:** 91%
- **HPV(+):** 75%[a] (150/199[b])

[a] Positive for HPV P16 protein expression. [b] Patients with tumor tissue available for central review.
BL, baseline; HPV, human papillomavirus.
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POD1UM-303/InterAACT 2: Efficacy Results

Endpoint	Retifanlimab-dlwr in Combination with Carboplatin and Paclitaxel (N=154)		Placebo in Combination with Carboplatin and Paclitaxel (N=154)
Progression-free survival			
Events, n (%)	92 (60)		110 (71)
Median (months) (95% CI)	9.3 (7.5, 11.3)		7.4 (7.1, 7.7)
Hazard ratio[a] (95% CI)		0.63 (0.47, 0.84)	
p-value[b]		0.0006	
Overall survival[c]			
Deaths, n (%)	78 (51)		94 (61)
Median (months) (95% CI)	32.8 (25.7, 44.5)		22.2 (15.7, 27.2)
Hazard ratio[a] (95% CI)		0.75 (0.55, 1.01)	
Objective response rate			
Objective response rate (%) (95% CI)	57 (48, 65)		45 (37, 53)
Complete response, n (%)	38 (25)		21 (14)
Partial response, n (%)	49 (32)		48 (31)
Median duration of response, in months (95% CI)	14.7 (9.2, 22.5)		7.2 (5.6, 9.3)

[a] Based on stratified Cox model. [b] One-sided p-value based on stratified log-rank test. [C] Not statistically significant.
CI, confidence interval.
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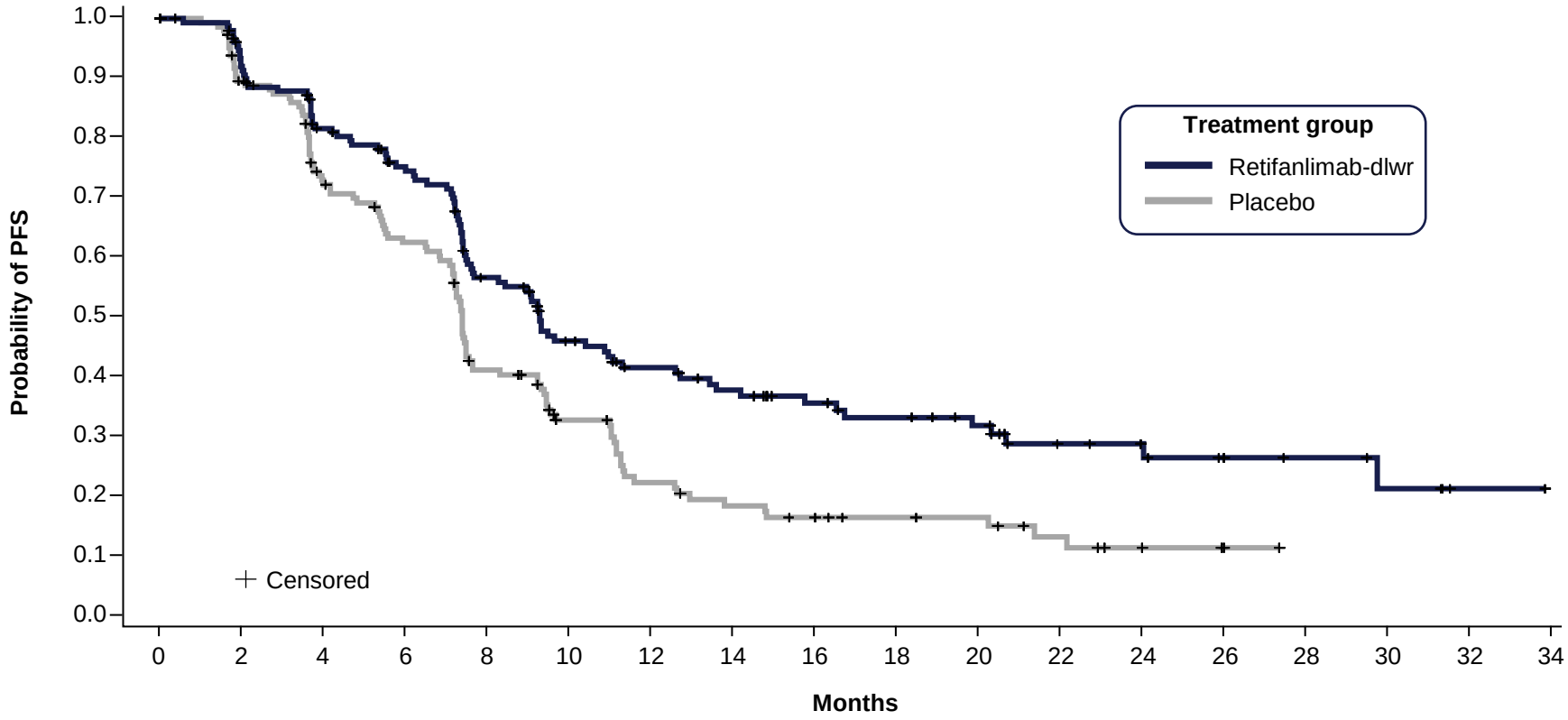
POD1UM-303/InterAACT 2: PFS by BICR



Number of participants at risk

Retifanlimab-dlwr	154	137	115	101	73	53	44	38	31	27	23	15	12	9	6	4	1	0
Placebo	154	126	98	82	52	35	23	18	15	12	11	7	2	2	0			

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POD1UM-303: Efficacy

- POD1UM-303/InterAACT 2 was a randomized, double-blind, multicenter Phase 3 trial that evaluated retifanlimab-dlwr plus carboplatin and paclitaxel versus placebo plus chemotherapy in 308 chemotherapy-naïve patients with inoperable locally recurrent or metastatic SCAC
  - Most patients had metastatic disease (83%) and PD-L1 expression ≥1% (91%). Among placebo-treated patients, 50% crossed over to receive retifanlimab-dlwr monotherapy after disease progression

- Retifanlimab-dlwr significantly improved PFS vs placebo when used in combination with carboplatin and paclitaxel [9.3 vs. 7.4 months; HR = 0.63 (0.47, 0.84); *P*= 0.0006]

- Overall survival results: 32.8 vs. 22.2 months; HR=0.75 (0.55, 1.01)]; OS results were not statistically significant

HR, hazard ratio.

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POD1UM-202 Efficacy

Retifanlimab-dlwr as Single Agent for the Treatment of Platinum-refractory or Intolerant Locally Recurrent or Metastatic SCAC

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POD1UM-202: Study Design

Study Design: Phase 2, open-label, single-arm, multicenter study in patients with locally advanced or metastatic SCAC with disease progression on or after platinum-based chemotherapy or who are ineligible for or intolerant of platinum-based therapy[1-3]

Select Eligibility Criteria:

- Age ≥18 years
- Disease progression on or after platinum-based therapy unless ineligible for or intolerant of platinum
  - ≤2 prior lines of systemic therapy for metastatic disease
  - If ineligible for platinum must have received ≥1 prior line of systemic therapy[4]
  - Receiving platinum-based radiosensitizing chemotherapy eligible if relapse occurred <6 months from completion of therapy[4]
- Measurable disease by RECIST v1.1
- ECOG PS of 0 to 1
- HIV-positive patients eligible if: CD4+ cell count ≥300/μL, undetectable viral load, and receiving HAART

N=94

Retifanlimab-dlwr
500mg q4w[a]

Treatment for up to 2 years[b] in 28-day cycles

Primary endpoint: ORR (per RECIST v1.1, determined by IRC)
Secondary objectives: DOR, DCR, PFS, OS, safety, PK
Exploratory objectives: Biomarkers, immunogenicity, efficacy by iRECIST[c], HRQoL, impact on HIV control, HIV reservoir, other HIV-related markers or mutations (translational sub-study)

[a] Whereas retifanlimab-dlwr was administered as an infusion over 60 min in this study, the recommended dosing is a 30-min infusion based on data from the POD1UM-203 study.[4] [b] In the absence of clinical disease progression, intolerable toxicity, death, withdrawal of consent, loss to follow-up, or premature discontinuation for any other reason. [c] Determined by the investigator.

HRQoL, health-related quality of life; ICR, independent central review committee; iRECIST, immune RECIST; q4w, every 4 weeks.

1. Rao S, et al. *ESMO Open.* 2022;7:100529. 2. ClinicalTrials.gov. Accessed Jan 2026. https://clinicaltrials.gov/study/NCT03597295. 3. ZYNYZ (retifanlimab-dlwr). Prescribing Information. Incyte Corporation; May 2026. 4. Di Giacomo AM, et al. ESMO Open. 2024;9:102387.

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POD1UM-202: Baseline Demographics and Characteristics

94 patients were evaluated in the POD1UM-202 clinical study

Demographics

- **Median age:** 64 (37-94) years
  - ≥65 years: 49%
- **Sex:** Female: 65%
- **Race:**
  - White: 77%
  - Black: 1.1%
  - Unknown: 22%
- **Ethnicity:**
  - Hispanic or Latino: 4.3%
  - Not Hispanic or Latino: 52%
  - Unknown/not reported: 44%

Characteristics

- **ECOG PS:**
  - Score of 0: 42%
  - Score of 1: 59%
- **HIV (+):** 10%
- **Prior surgery:** 46%
- **Prior radiotherapy:** 87%
- **Metastatic disease at BL:** 81%
- **HPV(+):** 93% (54/58[a])

[a] Patients with tumor tissue available for central review.

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POD1UM-202: Efficacy Results

Endpoint	Retifanlimab-dlwr (N=94)
Objective Response Rate (95% CI)	14% (8, 23)
Complete response, n (%)	1 (1.1)
Partial response, n (%)	12 (13)
Duration of Response	
Median, months	9.5 (4.4, NE)
Patients with DOR ≥ 6 months (95% CI)	65% (31, 85)
Patients with DOR ≥ 12 months (95% CI)	41% (11, 69)

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POD1UM-202: Efficacy

- POD1UM-202 was an open-label, single-arm trial evaluating retifanlimab-dlwr in 94 patients with locally recurrent or metastatic SCAC who progressed on or were intolerant to platinum-based chemotherapy
  - The median patient age was 64 years; 65% were female, 81% had metastatic disease at baseline, and 93% of evaluable tumors were positive for HPV
- Retifanlimab-dlwr demonstrated an ORR of 14% (95% CI, 8-23), including 1 complete response (1.1%) and 12 partial responses (13%)
- The median DOR was 9.5 months (95% CI, 4.4, NE) with 65% of responders having a DOR ≥6 months and 41% having a DOR ≥12 months

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Safety Overview

- POD1UM-303: Use in Combination with Carboplatin and Paclitaxel
- POD1UM-202: Use as Single Agent

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POD1UM-303 Safety

Retifanlimab-dlwr in Combination with Carboplatin and Paclitaxel for the Treatment of Inoperable Locally Recurrent or Metastatic SCAC

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POD1UM-303: Safety Overview

- Serious adverse reactions occurred in 47% of patients receiving retifanlimab-dlwr in combination with carboplatin and paclitaxel
- The most frequent serious adverse reactions (≥2% of patients) were:
  - Sepsis (3.2%)
  - Pulmonary embolism (3.2%)
  - Diarrhea (2.6%)
  - Vomiting (2.6%)
- Retifanlimab-dlwr, when used in combination with carboplatin and paclitaxel, was permanently discontinued in 11% of patients
- Dosage interruptions due to an adverse reaction occurred in 55% of patients who received retifanlimab-dlwr in combination with carboplatin and paclitaxel
  - Adverse reactions that resulted in dosage interruptions in ≥ 2% of patients were neutropenia, anemia, thrombocytopenia, leukopenia, fatigue, COVID-19, and urinary tract infection
- The most common (≥20%) adverse reactions were fatigue, peripheral neuropathy, nausea, alopecia, diarrhea, musculoskeletal pain, constipation, hemorrhage, rash, vomiting, decreased appetite, pruritus, and abdominal pain

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POD1UM-303: Adverse Reactions Occurring in ≥10%

Adverse Reaction	Retifanlimab-dlwr in Combination with Carboplatin and Paclitaxel (N=154)		Placebo in Combination with Carboplatin and Paclitaxel (N=152)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal disorders				
Diarrhea[a]	49	5	41	7
Stomatitis[b]	18	0	11	0
Nervous system disorders				
Peripheral neuropathy[c]	56	5	52	2.6
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[d]	40	2.6	34	0
Vascular disorders				
Hemorrhage[e]	29	3.2	21	0
Skin and subcutaneous tissue disorders				
Rash[f]	29	1.3	16	0.7
Pruritus	24	0.6	7	0
Endocrine disorders				
Hypothyroidism	14	0.6	3.3	0

Adverse reactions noted were reported based on a difference between arms of ≥5% for all grades or ≥2% for Grades 3 or 4 vs placebo in combination with carboplatin and paclitaxel.
[a] Includes diarrhea, colitis, and frequent bowel movements. [b] Includes stomatitis, aphthous ulcer, cheilitis, mouth ulceration, and mucosal inflammation. [c] Includes peripheral neuropathy, paresthesia, peripheral sensory neuropathy, neuralgia, hypoesthesia, peripheral sensorimotor neuropathy, dysesthesia, peripheral motor neuropathy, and hyperesthesia. [d] Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and spinal pain. [e] Includes hemorrhage, anal hemorrhage, anal ulcer hemorrhage, conjunctival hemorrhage, epistaxis, gastrointestinal hemorrhage, genital hemorrhage, hematuria, hemoptysis, hemorrhoidal hemorrhage, lower gastrointestinal hemorrhage, lymph node hemorrhage, rectal hemorrhage, stoma site hemorrhage, tumor hemorrhage, urinary bladder hemorrhage, uterine hemorrhage, vaginal hemorrhage, and wound hemorrhage. [f] Includes rash, eczema, dermatitis acneiform, dermatitis, rash erythematous, rash maculo-papular, rash popular, rash pustular, and rash pruritic.

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POD1UM-303: Lab Abnormalities That Worsened from Baseline to Grade 3 or 4 Occurring in ≥1% of Patients

Laboratory abnormality	Retifanlimab-dlwr in Combination with Carboplatin and Paclitaxel[a]		Placebo in Combination with Carboplatin and Paclitaxel[a]	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Decreased hemoglobin	91	20	92	24
Decreased leukocytes	88	44	90	40
Decreased neutrophils	79	52	78	39
Decreased lymphocytes	77	40	73	38
Decreased platelets	55	6	52	4
Chemistry				
Decreased albumin	37	2	38	1.3
Increased ALT	35	3.9	29	1.3
Increased AST	26	3.9	25	1.3
Increased alkaline phosphatase	26	2	33	0.7
Decreased potassium	24	5	18	3.9
Increased calcium	23	2	26	1.3
Increased lipase	18	4.9	17	0.7
Increased bilirubin	10	1.3	4.6	1.3

[a] The denominator used to calculate the rate varied from 142 to 153 based on the number of patients with a baseline value and at least one post-treatment value.

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POD1UM-202 Safety

Retifanlimab-dlwr as Single Agent for the Treatment of Platinum-refractory or Intolerant Locally Recurrent or Metastatic SCAC

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POD1UM-202: Safety Overview

- Serious adverse reactions occurred in 40% of patients receiving retifanlimab-dlwr
- The most frequent serious adverse reactions (≥2% of patients) were:
  - Non-urinary tract infection, perineal pain, abdominal pain, anemia, hemorrhage, diarrhea, pyrexia, urinary tract infection, musculoskeletal pain, and dyspnea
- Permanent discontinuation of retifanlimab-dlwr due to an adverse reaction occurred in 4.3% of patients; adverse reactions included diarrhea, non-urinary tract infection, perineal pain, and rash
- Dosage interruptions due to an adverse reaction occurred in 21% of patients
  - Adverse reactions that resulted in dose delay in ≥2% of patients included non-urinary tract infection, rash, diarrhea, abdominal pain, hemorrhage, musculoskeletal pain, pyrexia, and urinary tract infection
- The most common (≥10%) adverse reactions that occurred were fatigue, musculoskeletal pain, diarrhea, non-urinary tract infections, perineal pain, hemorrhage, urinary tract infection, rash, nausea, decreased appetite, constipation, abdominal pain, dyspnea, pyrexia, vomiting, cough, pruritus, hypothyroidism, headache, and decreased weight

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POD1UM-202: Adverse Reactions Occurring in ≥10% of Patients

Adverse Reaction	Retifanlimab-dlwr (N=94)	
	All Grades (%)	Grades 3-4 (%)
General disorders and administration site conditions		
Fatigue[a]	42	7
Pyrexia	14	2.1
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[b]	27	2.1
Gastrointestinal disorders		
Diarrhea[c]	23	2.1
Nausea	16	0
Constipation	15	0
Abdominal pain[d]	14	3.2
Vomiting	14	1.1
Infections and infestations		
Non-urinary tract infections[e]	21	12
Urinary tract infection[f]	17	2.1
Reproductive system and breast disorders		
Perineal pain[g]	19	7
Vascular disorders		
Hemorrhage[h]	19	3.2

[a] Includes fatigue and asthenia. [b] Includes arthralgia, back pain, bone pain, musculoskeletal chest pain, myalgia, non-cardiac chest pain, osteoarthritis, pain in extremity, and spinal pain. [c] Includes diarrhea, gastroenteritis, and immune-mediated enterocolitis. [d] Includes abdominal pain, abdominal discomfort, and abdominal pain upper. [e] Includes anal abscess, cellulitis, cholangitis, cholecystitis, cholecystitis acute, device related infection, herpes zoster, Lyme disease, pelvic infection, peritonitis, Pneumocystis *jirovecii pneumonia*, pneumonia, postoperative wound infection, pseudomonas infection, sepsis, skin infection, stoma site infection, and wound infection bacterial. [f] Includes urinary tract infection, cystitis, escherichia urinary tract infection, and pyelonephritis. [g] Includes anorectal discomfort, pelvic pain, proctalgia, and vulvovaginal discomfort. [h] Includes epistaxis, hematochezia, hematuria, proctitis hemorrhagic, rectal hemorrhage, stoma site hemorrhage, and vaginal hemorrhage.

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POD1UM-202: Adverse Reactions Occurring in ≥10% of Patients (cont)

Adverse Reaction	Retifanlimab-dlwr (N=94)	
	All Grades (%)	Grades 3-4 (%)
Skin and subcutaneous tissue disorders		
Rash[a]	16	2.1
Pruritus	12	0
Metabolism and nutrition disorders		
Decreased appetite[b]	15	2.1
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	14	3.2
Cough[c]	13	0
Endocrine disorders		
Hypothyroidism	10	0
Nervous system disorders		
Headache	10	0
Investigations		
Weight decreased	10	0

[a] Includes rash, dermatitis, dermatitis acneiform, eczema, erythema, palmar-plantar erythrodysesthesia syndrome, rash erythematous, and rash maculo-papular. [b] Includes decreased appetite and hypophagia. [c] Includes cough and productive cough.

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POD1UM-202: Lab Abnormalities That Worsened from Baseline to Grade 3 or 4 Occurring in ≥1% of Patients

Laboratory abnormality	Retifanlimab-dlwr[a]	
	All Grades (%)	Grades 3-4 (%)
Hematology		
Decreased hemoglobin	35	2.3
Decreased lymphocytes	33	6
Chemistry		
Decreased albumin	36	1.2
Increased AST	28	1.1
Decreased sodium	24	1.2
Increased triglycerides	19	3.4
Increased lipase	17	1.3
Increased ALT	16	1.1
Increased bilirubin	8	2.3

[a] The denominator used to calculate the rate varied from 59 to 87 based on the number of patients with a baseline value and at least one post-treatment value.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.
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Warnings & Precautions

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Warnings & Precautions

Severe and Fatal Immune-Mediated Adverse Reactions

- Retifanlimab-dlwr is a monoclonal antibody that belongs to a class of drugs that binds to either the programmed death receptor-1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response with the potential for breaking of peripheral tolerance and induction of immune-mediated adverse reactions. Important immune mediated adverse reactions listed under Warnings and Precautions may not be inclusive of all possible severe and fatal immune-mediated reactions
- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1–blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1–blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1–blocking antibodies. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously
- Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1–blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate

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Warnings & Precautions

Severe and Fatal Immune-Mediated Adverse Reactions (cont)

- Withhold or permanently discontinue retifanlimab-dlwr depending on severity. In general, if retifanlimab-dlwr requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids
- Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below

Immune-Mediated Pneumonitis

- Retifanlimab-dlwr can cause immune-mediated pneumonitis. In patients treated with other PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation
- Immune-mediated pneumonitis occurred in 3.1% (14/452) of patients receiving retifanlimab-dlwr, including 1 (0.2%) patient with fatal pneumonitis, Grade 3 (0.9%), and Grade 2 (1.3%). Pneumonitis led to permanent discontinuation of retifanlimab-dlwr in 1 patient and withholding of retifanlimab-dlwr in 1.1% of patients
- Systemic corticosteroids were required in 71% (10/14) of patients with pneumonitis. Pneumonitis resolved in 11 of the 14 patients. Of the 5 patients in whom retifanlimab-dlwr was withheld for pneumonitis, 4 reinitiated retifanlimab-dlwr after symptom improvement; of these, 1 had recurrence of pneumonitis

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Warnings & Precautions

Severe and Fatal Immune-Mediated Adverse Reactions (cont)

Immune-Mediated Colitis

- Retifanlimab-dlwr can cause immune-mediated colitis. Cytomegalovirus infection/reactivation have occurred in patients with corticosteroid-refractory immune-mediated colitis treated with PD 1/PD-L1–blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies
- *Retifanlimab-dlwr as a Single Agent*: Immune-mediated colitis occurred in 2.7% (12/4452) of patients receiving retifanlimab-dlwr, including Grade 4 (0.2%), Grade 3 (0.4%), and Grade 2 (1.1%). Colitis led to permanent discontinuation of retifanlimab-dlwr in 0.9% of patients and withholding of retifanlimab-dlwr in 1.3% of patients. Systemic corticosteroids were required in 75% (9/12) of patients. Colitis resolved in 8 of the 12 patients. Of the 6 patients in whom retifanlimab-dlwr was withheld for colitis, 1 reinitiated retifanlimab-dlwr after symptom improvement; this patient did not have recurrence of colitis
- *Retifanlimab-dlwr in Combination with Carboplatin and Paclitaxel*: Immune-mediated colitis occurred in 10% (16/154) of patients receiving retifanlimab-dlwr in combination with carboplatin and paclitaxel, including Grade 4 (0.6%), Grade 3 (2.6%), and Grade 2 (3.2%). Colitis led to permanent discontinuation of retifanlimab-dlwr in 2 patients and withholding of retifanlimab-dlwr in 2 patients. Systemic corticosteroids were required in 94% (15/16) of patients. Colitis resolved in 15 of the 16 patients. Of the 2 patients in whom retifanlimab-dlwr was withheld for colitis, both reinitiated retifanlimab-dlwr after symptom improvement; neither patient had a recurrence of colitis

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Warnings & Precautions

Severe and Fatal Immune-Mediated Adverse Reactions (cont)

Immune-Mediated Hepatitis

- Retifanlimab-dlwr can cause immune-mediated hepatitis.
- Immune-mediated hepatitis occurred in 3.5% (16/452) of patients receiving retifanlimab-dlwr, including Grade 4 (0.2%), Grade 3 (2.4%), and Grade 2 (0.9%). Hepatitis led to permanent discontinuation of retifanlimab-dlwr in 1.5% of patients and withholding of retifanlimab-dlwr in 1.1% of patients.
- Systemic corticosteroids were required in 81% (13/16) of patients. Hepatitis resolved in 9 of the 16 patients. Of the 5 patients in whom retifanlimab-dlwr was withheld for hepatitis, 3 reinitiated retifanlimab-dlwr after symptom improvement; of these, 1 had recurrence of hepatitis

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

- Retifanlimab-dlwr can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment per institutional guidelines, including hormone replacement as clinically indicated. Withhold or permanently discontinue retifanlimab-dlwr depending on severity
- *Retifanlimab-dlwr as a Single Agent*: Adrenal insufficiency occurred in 0.9% (4/452) of patients receiving retifanlimab-dlwr, including Grade 3 (0.4%) and Grade 2 (0.4%). Adrenal insufficiency did not lead to permanent discontinuation of retifanlimab-dlwr. retifanlimab-dlwr was withheld for 1 patient with adrenal insufficiency. All patients required systemic corticosteroids. Adrenal insufficiency resolved in 1 of the 4 patients

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Severe and Fatal Immune-Mediated Adverse Reactions (cont)

Immune-Mediated Endocrinopathies (cont)

Adrenal Insufficiency (cont)

- *Retifanlimab-dlwr in Combination with Carboplatin and Paclitaxel*: Adrenal insufficiency occurred in 5.8% (9/154) of patients receiving retifanlimab-dlwr in combination with carboplatin and paclitaxel, including Grade 3 and Grade 2 (1.9% each). Adrenal insufficiency led to permanent discontinuation of retifanlimab-dlwr in 1 patient and withholding of retifanlimab-dlwr in 3 patients. All patients required systemic corticosteroids. Adrenal insufficiency resolved in 4 of the 9 patients

Hypophysitis

- Retifanlimab-dlwr can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue retifanlimab-dlwr depending on severity
- Hypophysitis occurred in 0.7% (3/452, both Grade 2) of patients receiving retifanlimab-dlwr. No patients discontinued or withheld retifanlimab-dlwr due to hypophysitis. All patients required systemic steroids. Hypophysitis resolved in 1 of the 3 patients

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Warnings & Precautions

Severe and Fatal Immune-Mediated Adverse Reactions (cont)

Immune-Mediated Endocrinopathies (cont)

Thyroid Disorders

- Retifanlimab-dlwr can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue retifanlimab-dlwr depending on
- Thyroiditis occurred in 0.7% (3/452, all Grade 1) of patients receiving retifanlimab-dlwr. No patients discontinued or withheld retifanlimab-dlwr due to thyroiditis. Thyroiditis resolved in 1 of the 3 patients

Hypothyroidism

- Hypothyroidism occurred in 10% (46/452) of patients receiving retifanlimab-dlwr, including Grade 2 (4.9%). No patients discontinued retifanlimab-dlwr due to hypothyroidism. Hypothyroidism led to withholding of retifanlimab-dlwr in 0.4% of patients. Systemic corticosteroids were required for 1 patient and 78% (36/46) of patients received endocrine therapy

Hyperthyroidism

- Hyperthyroidism occurred in 6% (26/452) of patients receiving retifanlimab-dlwr, including Grade 2 (2.7%). No patients discontinued retifanlimab-dlwr due to hyperthyroidism. Hyperthyroidism led to withholding of retifanlimab-dlwr in 0.4% of patients. Systemic corticosteroids were required for 15% (4/26) of patients and 50% (13/26) of patients received endocrine therapy

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Warnings & Precautions

Severe and Fatal Immune-Mediated Adverse Reactions (cont)

Immune-Mediated Endocrinopathies (cont)

Type 1 Diabetes Mellitus, Which Can Present with Diabetic Ketoacidosis

- Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold retifanlimab-dlwr depending on severity
- Type 1 diabetes mellitus occurred in 0.2% (1/452) of patients receiving retifanlimab-dlwr, including Grade 3 (0.2%). This event led to retifanlimab-dlwr being withheld and did not lead to permanent discontinuation of retifanlimab-dlwr. The patient received insulin

Immune-Mediated Nephritis with Renal Dysfunction

- Retifanlimab-dlwr can cause immune-mediated nephritis
- Immune-mediated nephritis occurred in 2% (9/452) of patients receiving retifanlimab-dlwr, including Grade 4 (0.4%), Grade 3 (1.1%), and Grade 2 (0.4%). Nephritis led to permanent discontinuation of retifanlimab-dlwr in 1.1% of patients and withholding of retifanlimab-dlwr in 0.7% of patients
- Systemic corticosteroids were required in 67% (6/9) of patients. Nephritis resolved in 4 of the 9 patients. Of the 3 patients in whom retifanlimab-dlwr was withheld for immune-mediated nephritis, 1 reinitiated retifanlimab-dlwr after symptom improvement and did not have recurrence of immune-mediated nephritis

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Warnings & Precautions

Severe and Fatal Immune-Mediated Adverse Reactions (cont)

Immune-Mediated Dermatologic Adverse Reactions

- Retifanlimab-dlwr can cause immune-mediated rash or dermatitis. Bullous and exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1–blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue retifanlimab-dlwr depending on severity
- Immune-mediated skin reactions occurred in 10% (43/452) of patients receiving retifanlimab-dlwr, including Grade 4 (0.2%), Grade 3 (1.1%) and Grade 2 (8%). Immune mediated dermatologic adverse reactions led to permanent discontinuation of retifanlimab-dlwr in 0.7% of patients and withholding of retifanlimab-dlwr in 2.7% of patients
- Systemic corticosteroids were required in 33% (14/43) of patients. Immune-mediated dermatologic adverse reactions resolved in 72% (31/43) of patients. Of the 12 patients in whom retifanlimab-dlwr was withheld for immune-mediated dermatologic adverse reactions, 8 reinitiated retifanlimab-dlwr after symptom improvement; of these, 2 had recurrence of immune-mediated dermatologic adverse reactions

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Severe and Fatal Immune-Mediated Adverse Reactions (cont)

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 452 patients who received retifanlimab-dlwr or were reported with the use of other PD-1/PD-L1–blocking antibodies, including severe or fatal cases
  - *Cardiac/vascular:* myocarditis, pericarditis, vasculitis
  - *Gastrointestinal:* pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis
  - *Musculoskeletal:* myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis, polymyalgia rheumatica
  - *Neurological:* meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy
  - *Ocular:* uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss
  - *Endocrine:* hypoparathyroidism
  - *Hematologic/Immune:* hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection
  - *Other:* Myocarditis-Myositis-Myasthenia Gravis (or Myasthenia-Like) Overlap Syndrome, reported as the co-occurrence of either two or all three adverse reactions

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Warnings & Precautions

Infusion-Related Reactions

- A severe infusion-related reaction (Grade 3) occurred in 5 (0.8%) of 606 patients receiving retifanlimab-dlwr. Monitor patients for signs and symptoms of infusion related reactions. Interrupt or slow the rate of infusion or permanently discontinue retifanlimab-dlwr based on severity of reaction. Consider premedication with an antipyretic and/or an antihistamine for patients who have had previous systemic reactions to infusions of therapeutic proteins

Complications of Allogeneic HSCT

- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1–blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT
- Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1–blocking antibody prior to or after an allogeneic HSCT

Embryo-Fetal Toxicity

- Based on its mechanism of action, retifanlimab-dlwr can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus, resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with retifanlimab-dlwr and for 4 months after the last dose

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Recommended Dosage Modifications for Adverse Reactions (1 of 2)

BACK

Adverse Reaction	Severity[a]	Dosage Modifications
Immune-Mediated Adverse Reactions		
Pneumonitis	Grade 2	Withhold[b]
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[b]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT >3 but no more than 8 times ULN ***or*** TBIL increases to >1.5 and up to 3 times ULN	Withhold[b]
	AST or ALT increases to >8 times ULN ***or*** TBIL >3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[c]	Baseline AST or ALT is >1 and up to 3 times ULN and increases >5 and up to 10 times ULN ***or*** Baseline AST or ALT is >3 and up to 5 times ULN and increases >8 and up to 10 times ULN	Withhold[b]
	AST or ALT increases to >10 times ULN ***or*** TBIL increases to >3 times ULN	Permanently discontinue

[a] Toxicity graded per National Cancer Institute CTCAE v5. [b] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 12 weeks of initiating steroids. [c] If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue retifanlimab-dlwr based on recommendations for hepatitis with no liver involvement.
CTCAE, Common Terminology Criteria for Adverse Events; TBIL, total bilirubin; ULN, upper limit of normal.
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Recommended Dosage Modifications for Adverse Reactions (2 of 2)

BACK

Adverse Reaction	Severity[a]	Dosage Modifications
Immune-Mediated Adverse Reactions (cont'd)		
Endocrinopathies[b]	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with renal dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[b]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative dermatologic conditions	Grade 3 or suspected SJS, TEN, or DRESS	Withhold[c]
	Grade 4 or confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological toxicities	Grade 2	Withhold[c]
	Grade 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

[a] Toxicity graded per National Cancer Institute CTCAE v5. [b] Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved. [c] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 12 weeks of initiating steroids.
DRESS, drug rash with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
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