# ZYNYZ® (retifanlimab-dlwr)

## Prescribing Information and Data Review in SCAC

MSL-RET-US-0026 05/25

# 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
      - 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

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

- **FOR MEDICAL INFORMATION PURPOSES ONLY. NOT FOR PROMOTIONAL USE. DO NOT COPY, DISTRIBUTE, OR OTHERWISE REPRODUCE.**

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# Prescribing Information

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

# Indication, Dosing, and Administration

# 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 | 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 | 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

# 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

# POD1UM-303 Efficacy

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

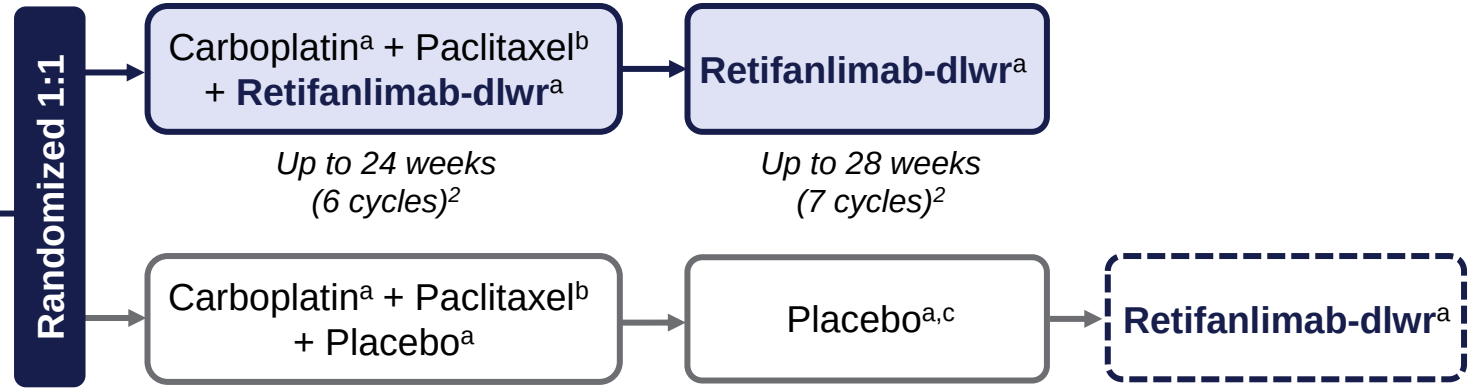
# POD1UM-303/InterAACT 2: Study Design[1-4]

**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 May 2025. https://clinicaltrials.gov/study/NCT04472429. 3. Rao S, et al. ESMO 2024. Oral presentation LBA2. 4. ZYNYZ (retifanlimab-dlwr). Prescribing Information. Incyte Corporation; May 2025.

# 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 (interim analysis)[c]** | | | |
| Deaths, n (%) | 53 (34) | | 73 (47) |
| Median (months) (95% CI) | 29.2 (24.2, NE) | | 23 (15.1, 27.9) |
| Hazard ratio[a] (95% CI) | | 0.70 (0.49, 1.01) | |
| **Objective response rate** | | | |
| Objective response rate (%) (95% CI) | 56 (48, 64) | | 44 (36, 52) |
| Complete response, n (%) | 34 (22) | | 21 (14) |
| Partial response, n (%) | 52 (34) | | 47 (31) |
| Median duration of response, in months (95% CI) | 14.0 (8.6, 22.2) | | 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; NE, not evaluable.
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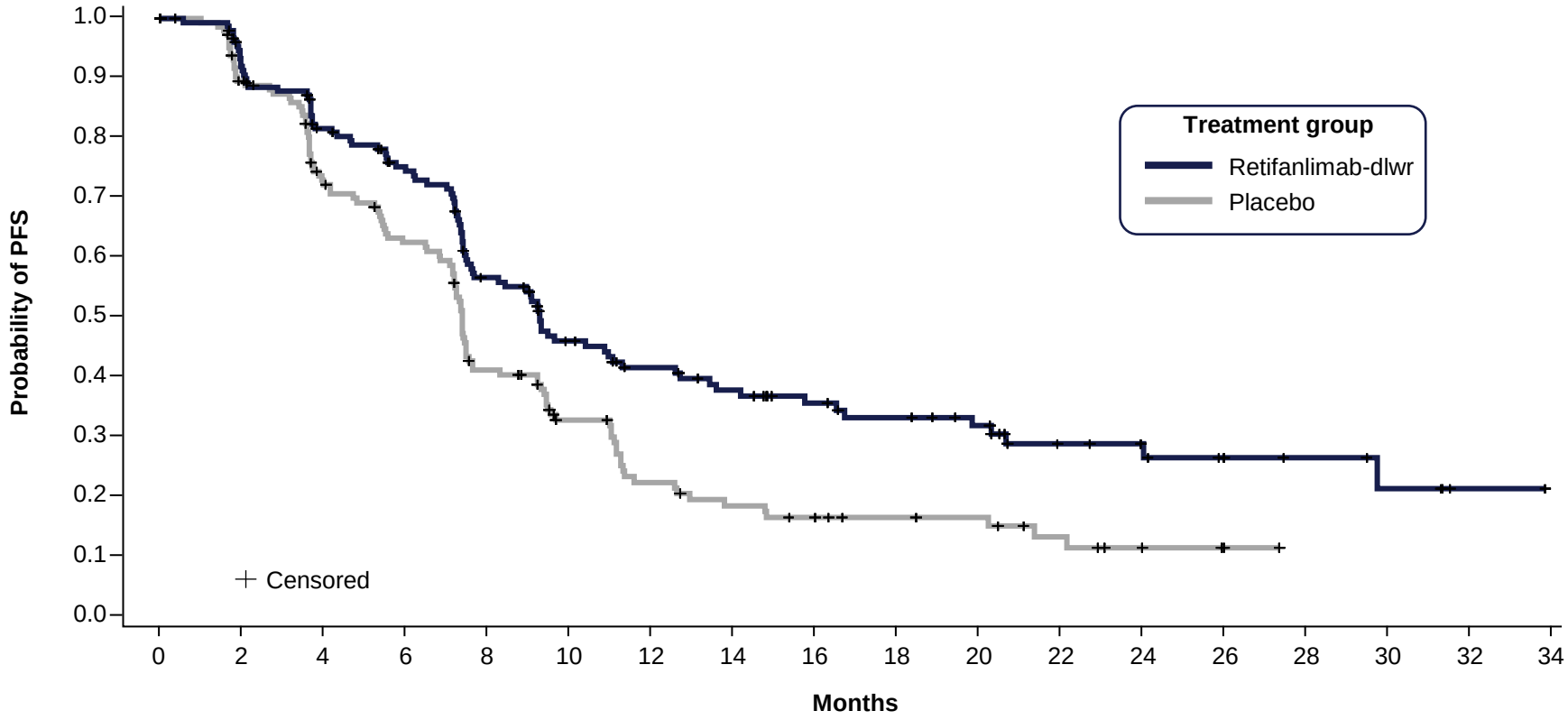
# POD1UM-303/InterAACT 2: PFS by BICR




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, 45% 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 from an interim analysis: 22.3 vs. 16.8 months; HR=0.70 (0.49–1.01)]; OS results were not statistically significant at this interim analysis

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

# 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 May 2025. https://clinicaltrials.gov/study/NCT03597295. 3. ZYNYZ (retifanlimab-dlwr). Prescribing Information. Incyte Corporation; May 2025. 4. Di Giacomo AM, et al. ESMO Open. 2024;9:102387.

# 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

# POD1UM-303 Safety

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

# 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

# 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 | Placebo in Combination with Carboplatin and Paclitaxel[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

# 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% (13/440) of patients receiving retifanlimab-dlwr, including 1 (0.2%) patient with fatal pneumonitis, Grade 3 (0.9%), and Grade 2 (1.4%). Pneumonitis led to permanent discontinuation of retifanlimab-dlwr in 1 patient and withholding of retifanlimab-dlwr in 0.9% of patients
- Systemic corticosteroids were required in 77% (10/13) of patients with pneumonitis. Pneumonitis resolved in 10 of the 13 patients. Of the 4 patients in whom retifanlimab-dlwr was withheld for pneumonitis, 3 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 1.6% (7/440) of patients receiving retifanlimab-dlwr, including Grade 4 (0.2%), Grade 3 (0.2%), and Grade 2 (0.7%). Colitis led to permanent discontinuation of retifanlimab-dlwr in 1 patient and withholding of retifanlimab-dlwr in 0.9% of patients. Systemic corticosteroids were required in 71% (5/7) of patients. Colitis resolved in 4 of the 7 patients. Of the 4 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

ZYNYZ (retifanlimab-dlwr). Prescribing Information. Incyte Corporation; May 2025.

# 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% (13/440) of patients receiving retifanlimab-dlwr, including Grade 4 (0.2%), Grade 3 (2.3%), and Grade 2 (0.5%). Hepatitis led to permanent discontinuation of retifanlimab-dlwr in 1.4% of patients and withholding of retifanlimab-dlwr in 0.9% of patients.
- Systemic corticosteroids were required in 85% (11/13) of patients. Hepatitis resolved in 6 of the 13 patients. Of the 4 patients in whom retifanlimab-dlwr was withheld for hepatitis, 2 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 0.7% (3/440) of patients receiving retifanlimab-dlwr, including Grade 3 (0.5%) and Grade 2 (0.2%). 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 3 patients

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# Warnings & Precautions

## 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 0.5% (2/440, 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 2 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% (3/440, 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% (42/440) of patients receiving retifanlimab-dlwr, including Grade 2 (4.8%). No patients discontinued retifanlimab-dlwr due to hypothyroidism. Hypothyroidism led to withholding of retifanlimab-dlwr in 0.5% of patients. Systemic corticosteroids were required for 1 patient and 79% (33/42) of patients received endocrine therapy

*Hyperthyroidism*

- Hyperthyroidism occurred in 6% (24/440) of patients receiving retifanlimab-dlwr, including Grade 2 (2.5%). No patients discontinued retifanlimab-dlwr due to hyperthyroidism. Hyperthyroidism led to withholding of retifanlimab-dlwr in 1 patient. Systemic corticosteroids were required for 13% (3/24) of patients and 46% (11/24) 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% (1/440) of patients receiving retifanlimab-dlwr, including Grade 3 (0.2%) adverse reactions. Type 1 diabetes mellitus led to withholding of retifanlimab-dlwr in 1 patient. 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 1.6% (7/440) of patients receiving retifanlimab-dlwr, including Grade 4 (0.5%), Grade 3 (0.7%), and Grade 2 (0.5%). Nephritis led to permanent discontinuation of retifanlimab-dlwr in 0.9% of patients and withholding of retifanlimab-dlwr in 1 patient
- Systemic corticosteroids were required in 57% (4/7) of patients. Nephritis resolved in 3 of the 7 patients. The 1 patient in whom retifanlimab-dlwr was withheld for immune-mediated nephritis had retifanlimab-dlwr reinitiated 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 8% (36/440) of patients receiving retifanlimab-dlwr, including Grade 3 (1.1%) and Grade 2 (7%). Immune mediated dermatologic adverse reactions led to permanent discontinuation of retifanlimab-dlwr in 1 patient and withholding of retifanlimab-dlwr in 2.3% of patients
- Systemic corticosteroids were required in 25% (9/36) of patients. Immune-mediated dermatologic adverse reactions resolved in 75% (27/36) of patients. Of the 10 patients in whom retifanlimab-dlwr was withheld for immune-mediated dermatologic adverse reactions, 7 reinitiated retifanlimab-dlwr after symptom improvement; of these, 1 had recurrence of immune-mediated dermatologic adverse reactions

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# Warnings & Precautions

## 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 440 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
  - *Other (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

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# Warnings & Precautions

## Infusion-Related Reactions

- A severe infusion-related reaction (Grade 3) occurred in 4 (0.7%) of 594 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.
ZYNYZ (retifanlimab-dlwr). Prescribing Information. Incyte Corporation; May 2025.

# 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.
ZYNYZ (retifanlimab-dlwr). Prescribing Information. Incyte Corporation; May 2025.