HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYNYZ safely and effectively. See full prescribing information for ZYNYZ.

ZYNYZ® (retifanlimab-dlwr) injection, for intravenous use
Initial U.S. Approval: 2023

RECENT MAJOR CHANGES

Warnings and Precautions (5.1) 4/2024

INDICATIONS AND USAGE

ZYNYZ is a programmed death receptor-1 (PD-1)–blocking antibody indicated for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma. (1)

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. (1, 14)

DOSAGE AND ADMINISTRATION

The recommended dosage of ZYNYZ is 500 mg as an intravenous infusion over 30 minutes every 4 weeks. (2.1)

See full prescribing information for dosage modifications for adverse reactions (2.2) and preparation and administration instructions. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 500 mg/20 mL (25 mg/mL) solution in a single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Immune-Mediated Adverse Reactions (5.1)
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, and immune-mediated dermatologic adverse reactions, and solid organ transplant rejection.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue ZYNYZ and administer corticosteroids based on the severity of reaction. (2.2)
- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue ZYNYZ based on severity of reaction. (2.2, 5.2)
- Complications of Allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1–blocking antibody. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)

ADVERSE REACTIONS

The most common (≥ 10%) adverse reactions are fatigue, musculoskeletal pain, pruritus, diarrhea, rash, pyrexia, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Incyte Corporation at 1-855-463-3463 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYNYZ is indicated for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (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 *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of ZYNYZ is 500 mg administered as an intravenous infusion over 30 minutes every 4 weeks until disease progression, unacceptable toxicity, or up to 24 months.

Administer ZYNYZ as an intravenous infusion after dilution *[see Dosage and Administration (2.3)]*.

2.2 Dosage Modifications for Adverse Reactions

No dose reduction of ZYNYZ is recommended. In general, withhold ZYNYZ for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue ZYNYZ 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.

Dosage modifications for ZYNYZ for adverse reactions that require management different from these general guidelines are summarized in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity**[a]	**ZYNYZ Dosage Modifications**
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
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 greater than 3 but no more than 8 times ULN OR Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold[b]

Adverse Reaction	Severity[a]	ZYNYZ Dosage Modifications
	AST or ALT increases to more than 8 times ULN OR Total bilirubin greater than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[c]	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases more than 5 and up to 10 times ULN OR Baseline AST or ALT is more than 3 and up to 5 times ULN and increases more than 8 and up to 10 times ULN	Withhold[b]
	AST or ALT increases to more than 10 times ULN OR Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies[d]	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[b]
	Grade 4 or confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological toxicities	Grade 2	Withhold[b]
	Grade 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

AST = aspartate aminotransferase; ALT = alanine aminotransferase; DRESS = drug rash with eosinophilia and systemic symptoms; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; ULN = upper limit of normal.

[a] Toxicity graded per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (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 ZYNYZ based on recommendations for hepatitis with no liver involvement.
[d] Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved.

2.3 Preparation and Administration

Do not administer ZYNYZ using a polyurethane infusion set.

Visually inspect the vial for particulate matter and discoloration prior to administration. ZYNYZ is a clear to slightly opalescent, colorless to pale yellow solution and is free of particles. Discard the vial if the solution is cloudy, discolored, or contains particulate matter.

Do not shake the vial.

Preparation

1. Withdraw 20 mL (500 mg) of ZYNYZ from one vial and discard vial with any unused portion.
2. Dilute ZYNYZ with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 1.4 mg/mL to 10 mg/mL. Use polyvinylchloride (PVC) and di-2-ethylhexyl phthalate (DEHP), polyolefin copolymer, polyolefin with polyamide, or ethylene vinyl acetate infusion bags.
3. Mix diluted solution by gentle inversion. Do not shake.
4. Visually inspect the infusion bag for particulate matter and discoloration prior to administration. Discard if the solution is discolored or contains particulate matter.

Storage of diluted ZYNYZ solution

Protect the diluted ZYNYZ solution from light during storage.

Store diluted ZYNYZ solution:

- At room temperature [up to 25°C (77°F)] for no more than 8 hours from the time of preparation to the end of the infusion.

  OR

- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of preparation to the end of the infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration. The diluted solution must be administered within 4 hours (including infusion time) once it is removed from the refrigerator.

Do not freeze or shake diluted solution.

Administration

- Administer diluted ZYNYZ solution by intravenous infusion over 30 minutes through a polyethylene or PVC with DEHP intravenous line containing a sterile, non-pyrogenic, low-

protein binding polyethersulfone, polyvinylidene fluoride, or cellulose acetate 0.2 micron to 5 micron in-line or add-on filter or 15 micron mesh in-line or add-on filter. DO NOT administer ZYNYZ as an intravenous push or bolus injection.

- Do not co-administer other drugs through the same infusion line.

3 DOSAGE FORMS AND STRENGTHS

Injection: 500 mg/20 mL (25 mg/mL), clear to slightly opalescent, colorless to pale yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

ZYNYZ 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.

Withhold or permanently discontinue ZYNYZ depending on severity *[see Dosage and Administration (2.2)]*. In general, if ZYNYZ 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

ZYNYZ 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 ZYNYZ, including 1 (0.2%) patient with fatal pneumonitis, Grade 3 (0.9%), and Grade 2 (1.4%). Pneumonitis led to permanent discontinuation of ZYNYZ in 1 patient and withholding of ZYNYZ 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 ZYNYZ was withheld for pneumonitis, 3 reinitiated ZYNYZ after symptom improvement; of these, 1 had recurrence of pneumonitis.

Immune-Mediated Colitis

ZYNYZ 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.

Immune-mediated colitis occurred in 1.6% (7/440) of patients receiving ZYNYZ, including Grade 4 (0.2%), Grade 3 (0.2%), and Grade 2 (0.7%). Colitis led to permanent discontinuation of ZYNYZ in 1 patient and withholding of ZYNYZ 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 ZYNYZ was withheld for colitis, 1 reinitiated ZYNYZ after symptom improvement; this patient did not have recurrence of colitis.

Immune-Mediated Hepatitis

ZYNYZ can cause immune-mediated hepatitis.

Immune-mediated hepatitis occurred in 3% (13/440) of patients receiving ZYNYZ, including Grade 4 (0.2%), Grade 3 (2.3%), and Grade 2 (0.5%). Hepatitis led to permanent discontinuation of ZYNYZ in 1.4% of patients and withholding of ZYNYZ 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 ZYNYZ was withheld for hepatitis, 2 reinitiated ZYNYZ after symptom improvement; of these, 1 had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

ZYNYZ 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 ZYNYZ depending on severity *[see Dosage and Administration (2.2)]*.

Adrenal insufficiency occurred in 0.7% (3/440) of patients receiving ZYNYZ, including Grade 3 (0.5%) and Grade 2 (0.2%). Adrenal insufficiency did not lead to permanent discontinuation of ZYNYZ. ZYNYZ was withheld for 1 patient with adrenal insufficiency. All patients required systemic corticosteroids. Adrenal insufficiency resolved in 1 of the 3 patients.

Hypophysitis

ZYNYZ 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 ZYNYZ depending on severity *[see Dosage and Administration (2.2)]*.

Hypophysitis occurred in 0.5% (2/440, both Grade 2) of patients receiving ZYNYZ. No patients discontinued or withheld ZYNYZ due to hypophysitis. All patients required systemic steroids. Hypophysitis resolved in 1 of the 2 patients.

Thyroid Disorders

ZYNYZ 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 ZYNYZ depending on severity *[see Dosage and Administration (2.2)]*.

Thyroiditis occurred in 0.7% (3/440, all Grade 1) of patients receiving ZYNYZ. No patients discontinued or withheld ZYNYZ due to thyroiditis. Thyroiditis resolved in 1 of the 3 patients.

Hypothyroidism

Hypothyroidism occurred in 10% (42/440) of patients receiving ZYNYZ, including Grade 2 (4.8%). No patients discontinued ZYNYZ due to hypothyroidism. Hypothyroidism led to withholding of ZYNYZ 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 ZYNYZ, including Grade 2 (2.5%). No patients discontinued ZYNYZ due to hyperthyroidism. Hyperthyroidism led to withholding of ZYNYZ in 1 patient. Systemic corticosteroids were required for 13% (3/24) of patients and 46% (11/24) of patients received endocrine therapy.

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 ZYNYZ depending on severity *[see Dosage and Administration (2.2)]*.

Type 1 diabetes mellitus occurred in 0.2% (1/440) of patients receiving ZYNYZ, including Grade 3 (0.2%) adverse reactions. Type 1 diabetes mellitus led to withholding of ZYNYZ in 1 patient. This event led to ZYNYZ being withheld and did not lead to permanent discontinuation of ZYNYZ. The patient received insulin.

Immune-Mediated Nephritis with Renal Dysfunction

ZYNYZ can cause immune-mediated nephritis.

Immune-mediated nephritis occurred in 1.6% (7/440) of patients receiving ZYNYZ, including Grade 4 (0.5%), Grade 3 (0.7%), and Grade 2 (0.5%). Nephritis led to permanent discontinuation of ZYNYZ in 0.9% of patients and withholding of ZYNYZ 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 ZYNYZ was withheld for immune-mediated nephritis had ZYNYZ reinitiated after symptom improvement and did not have recurrence of immune-mediated nephritis.

Immune-Mediated Dermatologic Adverse Reactions

ZYNYZ 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 ZYNYZ depending on severity *[see Dosage and Administration (2.2)]*.

Immune-mediated skin reactions occurred in 8% (36/440) of patients receiving ZYNYZ, including Grade 3 (1.1%) and Grade 2 (7%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation of ZYNYZ in 1 patient and withholding of ZYNYZ 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 ZYNYZ was withheld for immune-mediated dermatologic adverse reactions, 7 reinitiated ZYNYZ after symptom improvement; of these, 1 had recurrence of immune-mediated dermatologic adverse reactions.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% in 440 patients who received ZYNYZ *[see Adverse Reactions (6.1)]* 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.

5.2 Infusion-Related Reactions

A severe infusion-related reaction (Grade 3) occurred in 1 (0.2%) of 440 patients receiving ZYNYZ *[see Adverse Reactions (6.1)]*. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue ZYNYZ based on severity of reaction *[see Dosage and Administration (2.2)]*. Consider premedication with an antipyretic and/or an antihistamine for patients who have had previous systemic reactions to infusions of therapeutic proteins.

5.3 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.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, ZYNYZ 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 ZYNYZ and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling.

- Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*
- Complications of Allogeneic HSCT *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in Warnings and Precautions reflect exposure to ZYNYZ 500 mg as an intravenous infusion every 4 weeks as a single agent in 105 patients with MCC enrolled in the POD1UM-201 trial and in 335 patients with other solid tumors. All patients received ZYNYZ until disease progression or unacceptable toxicity; those in the POD1UM-201 trial received ZYNYZ for up to 24 months. The median duration of exposure of the pooled population was 4.6 months (range: 1 day to 27 months).

The safety of ZYNYZ was evaluated in 105 patients enrolled in the POD1UM-201 trial with metastatic or recurrent locally advanced MCC *[see Clinical Studies (14)]*. Patients received ZYNYZ 500 mg intravenously every 4 weeks until disease progression, unacceptable toxicity, or up to 24 months. The median duration of exposure was 5.6 months (range: 1 day to 23 months). The median age of patients who received ZYNYZ was 71 years (range: 38-90); 74% ≥ 65 years; 68% male; 79% White, 20% were race unknown or not reported, and 1% were Asian.

Serious adverse reactions occurred in 22% of patients receiving ZYNYZ. The most frequent serious adverse reactions (≥ 2% of patients) were fatigue, arrhythmia, and pneumonitis.

Permanent discontinuation of ZYNYZ due to an adverse reaction occurred in 11% of patients. These included asthenia, atrial fibrillation, concomitant disease progression of chronic lymphocytic leukemia, demyelinating polyneuropathy, eosinophilic fasciitis, increased transaminases, infusion-related reaction, lung disorder, pancreatitis, polyarthritis, and radiculopathy (1 patient each).

Dosage interruptions due to an adverse reaction occurred in 25% of patients who received ZYNYZ. Adverse reactions or laboratory abnormalities that required dosage interruption in ≥ 2% of patients who received ZYNYZ were increased transaminases, increased lipase, increased amylase, pneumonitis, and pyrexia.

The most common (≥ 10%) adverse reactions that occurred in patients receiving ZYNYZ were fatigue, musculoskeletal pain, pruritus, diarrhea, rash, pyrexia, and nausea.

Table 2 and Table 3 summarize adverse reactions and laboratory abnormalities, respectively, that occurred in POD1UM-201.

Table 2: Adverse Reactions in ≥ 10% of Patients with Metastatic or Recurrent Locally Advanced MCC Receiving ZYNYZ in POD1UM-201

Adverse Reaction	ZYNYZ (N = 105)	
	All Grades (%)	Grades 3-4 (%)
General disorders and administration site conditions		
Fatigue[a]	28	1
Pyrexia	10	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[b]	22	2.9
Skin and subcutaneous tissue disorders		
Pruritus	18	0
Rash[c]	11	1
Gastrointestinal disorders		
Diarrhea	15	0
Nausea	10	0

Graded according to NCI CTCAE v5.0.
[a] Includes fatigue and asthenia.
[b] Includes arthralgia, back pain, bone pain, pain in extremity, neck pain, and myalgia.
[c] Includes rash, dermatitis, dermatitis bullous, rash erythematous, rash maculo-papular, rash papular, and rash pruritic.

Table 3: Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 Occurring in ≥ 1% of Patients with Metastatic or Recurrent Locally Advanced MCC Receiving ZYNYZ in POD1UM-201

Laboratory Test	ZYNYZ (N = 105)	
	All Grades (%)[a]	Grades 3-4 (%)[a]
Hematology		
Decreased hemoglobin	38	1.1
Decreased lymphocytes	29	10
Decreased neutrophils	13	3.3
Decreased leukocytes	12	1.1
Chemistry		
Increased lipase	30	3.4

Laboratory Test	ZYNYZ (N = 105)	
	All Grades (%)[a]	Grades 3-4 (%)[a]
Decreased sodium	23	3.3
Increased aspartate aminotransferase	23	2.2
Increased alanine aminotransferase	21	3.3
Increased alkaline phosphatase	20	1.1
Increased amylase	19	1.2
Decreased potassium	9	1.1
Increased calcium	8	1.1

Graded according to NCI CTCAE v5.0.

[a] The denominator used to calculate the rate varied from 86 to 92 based on the number of patients with a baseline value and at least one post-treatment value.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ZYNYZ can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of ZYNYZ in pregnant women. 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 (see *Data*). Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, retifanlimab-dlwr has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with ZYNYZ to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering ZYNYZ during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to retifanlimab-dlwr may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of retifanlimab-dlwr in human milk, or its effects on the breastfed child or on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to ZYNYZ are unknown. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 4 months after the last dose of ZYNYZ.

8.3 Females and Males of Reproductive Potential

ZYNYZ can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating ZYNYZ *[see Use in Specific Populations (8.1)]*.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with ZYNYZ and for 4 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of ZYNYZ have not been established in pediatric patients.

8.5 Geriatric Use

Of the 65 patients with metastatic or recurrent locally advanced MCC treated with ZYNYZ, 79% were 65 years or older, and 37% were 75 years or older. Clinical studies of ZYNYZ did not include sufficient numbers of younger adult patients to determine if patients 65 years of age and older respond differently than younger adult patients.

11 DESCRIPTION

Retifanlimab-dlwr is a programmed death receptor-1 (PD-1)–blocking antibody. Retifanlimab-dlwr is a humanized IgG4 kappa monoclonal antibody produced in Chinese hamster ovary cells. Retifanlimab-dlwr has an approximate molecular weight of 148 kDa.

ZYNYZ (retifanlimab-dlwr) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for intravenous use. The solution is free from visible particles.

Each single-dose vial contains 500 mg of retifanlimab-dlwr in 20 mL of solution. Each mL contains 25 mg of retifanlimab-dlwr, glacial acetic acid (0.18 mg), polysorbate 80 (0.1 mg), sodium acetate (0.57 mg), sucrose (90 mg), and Water for Injection, USP. The pH is 5.1.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors, and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors.

Retifanlimab-dlwr binds to the PD-1 receptor, blocks interaction with its ligands PD-L1 and PD-L2, and potentiates T-cell activity.

12.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for safety and effectiveness of retifanlimab-dlwr have not been fully characterized.

12.3 Pharmacokinetics

The pharmacokinetics of retifanlimab-dlwr were evaluated in patients with various solid tumors, including patients with MCC. Retifanlimab-dlwr exposures (maximum concentration [C_{max}] and area under the curve [AUC]) increased proportionally over a dosage range from 375 mg to 750 mg (0.75- to 1.5-fold of the approved recommended dose).

Following administration of retifanlimab-dlwr at 500 mg every 4 weeks, steady-state concentrations were achieved at Cycle 6 (approximately 6 months) and systemic accumulation was 1.3-fold.

Distribution

The geometric mean volume of distribution at steady state for retifanlimab-dlwr is 6.0 L (coefficient of variation [CV]: 20%).

Elimination

The elimination half-life of retifanlimab-dlwr at steady state is 19 days (CV: 29%). Clearance of retifanlimab-dlwr after the first dose was 0.31 L/day (CV: 36%) and decreased over time by approximately 23%, resulting in a steady-state clearance of 0.24 L/day.

Specific Populations

The following factors have no clinically meaningful effect on the pharmacokinetics of retifanlimab-dlwr: age (18 to 94 years), sex, body weight (35 to 133 kg), race (White, Black, Asian), albumin level (21 to 54 g/L), Eastern Cooperative Oncology Group (ECOG) score (0 to 2), tumor burden (sum of the target lesion diameters: 10 to 360 mm), HIV status, renal function (estimated glomerular filtration rate $\geq$ 26 mL/min/1.73 m^2), or mild hepatic impairment (total bilirubin less than or equal to the ULN and AST greater than ULN or total bilirubin greater than ULN and less than or equal to 1.5 times ULN and any AST). The pharmacokinetics of retifanlimab-dlwr have not been studied in patients with moderate or severe hepatic impairment.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADAs in the studies described below with the incidence of ADAs in other studies, including those of ZYNYZ or of other retifanlimab products.

ADAs were tested in 104 patients with MCC who received ZYNYZ. The incidence of retifanlimab treatment-emergent ADAs was 2.9% (3/104) using a bridging enzyme-linked immunosorbent assay following a median exposure time of 169 days. Neutralizing antibodies were detected in 2 of 3 patients with treatment-emergent ADAs. The effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of retifanlimab products is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of retifanlimab-dlwr for carcinogenicity or genotoxicity.

In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. *Mycobacterium tuberculosis*–infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 blockade using a primate anti–PD-1 antibody was also shown to exacerbate *M. tuberculosis* infection in rhesus macaques. PD-L1 and PD-1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

The efficacy of ZYNYZ was evaluated in study POD1UM-201 (NCT03599713), an open-label, multiregional, single-arm study in 65 patients with metastatic or recurrent locally advanced MCC who had not received prior systemic therapy for their advanced disease. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients who were HIV-positive, with an undetectable viral load, a CD4+ count $\geq$ 300 cells/microliter and receiving antiretroviral therapy were eligible.

Patients received ZYNYZ 500 mg intravenously every 4 weeks until disease progression, unacceptable toxicity, or up to 24 months. Tumor response assessments were performed every 8 weeks for the first year of therapy and 12 weeks thereafter.

The major efficacy outcomes were objective response rate (ORR) and duration of response (DOR) as assessed by an independent central review committee (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The median age of enrolled patients was 71 years (range: 44-90); 37% were ≥ 75 years; 65% of patients were male; 78% of patients were White, 20% were race unknown or not reported, 2% were Asian; 74% had an ECOG performance status of 0 and 26% had an ECOG performance status of 1; 98% were HIV-negative. Seventy-two percent of patients had prior surgery and 38% of patients had prior radiotherapy. Eighty-eight percent of patients had metastatic disease at baseline. Tumor samples were evaluated for Merkel cell polyomavirus (MCPyV): 71% were positive, 23% negative, 2% equivocal, and 5% missing.

Efficacy results are summarized in Table 4.

Table 4: Efficacy Results from Study POD1UM-201

Endpoint	**ZYNYZ (N = 65)**
Objective Response Rate (95% CI)	52% (40, 65)
Complete responses, n (%)	12 (18)
Partial responses, n (%)	22 (34)
Duration of Response	**N = 34**
Range, months	1.1 to 24.9+
Patients with DOR ≥ 6 months, n (%)	26 (76)
Patients with DOR ≥ 12 months, n (%)	21 (62)

CI = confidence interval; DOR = duration of response; + denotes ongoing response.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZYNYZ (retifanlimab-dlwr) injection is a clear to slightly opalescent, colorless to pale yellow solution. It is supplied in a carton containing one single-dose vial of:

- 500 mg/20 mL (25 mg/mL) (NDC 50881-006-03)

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Advise patients that ZYNYZ can cause immune-mediated adverse reactions including the following *[see Warnings and Precautions (5.1)]*:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of pneumonitis, including new or worsening symptoms of cough, chest pain, or shortness of breath.

- Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of colitis, including diarrhea, blood or mucus in stools, or severe abdominal pain.
- Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, or type 1 diabetes mellitus.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.
- Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.
- Other immune-mediated adverse reactions:
  - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new or worsening signs or symptoms *[see Warnings and Precautions (5.1)]*.

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT or Solid Organ Transplant Rejection

Advise patients to contact their healthcare provider immediately if they develop signs or symptoms of post-allogeneic HSCT complications or of solid organ transplant rejection *[see Warnings and Precautions (5.1, 5.3)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential that ZYNYZ can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment and for 4 months after the last dose of ZYNYZ *[see Use in Specific Populations (8.3)]*.

Lactation

Advise female patients not to breastfeed while taking ZYNYZ and for 4 months after the last dose *[see Use in Specific Populations (8.2)]*.

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