Pr ZYNYZ®
retifanlimab for injection
500 mg / 20 mL (25 mg / mL)

A TREATMENT OPTION IN MERKEL CELL CARCINOMA (MCC)

PrZYNYZ® (retifanlimab for injection), as monotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent locally advanced MCC not amenable to curative surgery or radiation therapy.[1]

The **first anti-PD-1 monoclonal antibody** indicated in MCC.[1-3]*

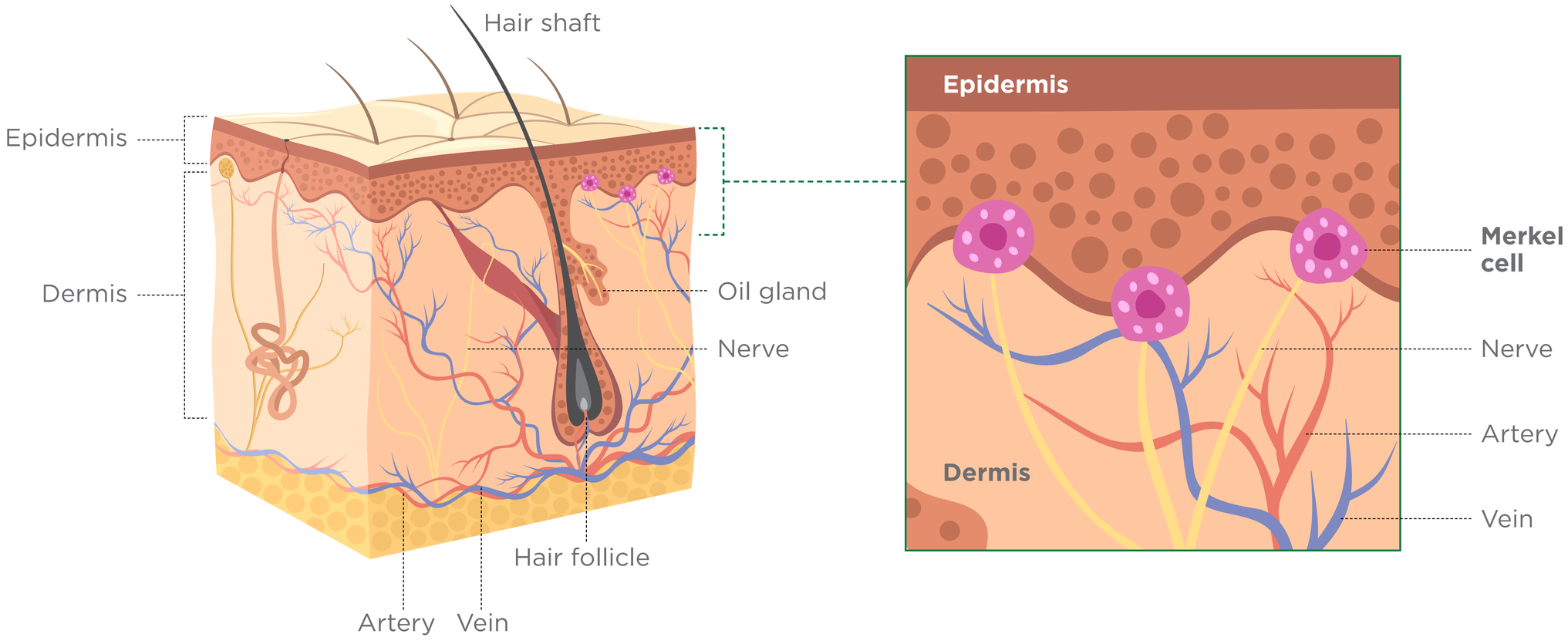
* Comparative clinical significance is unknown.
PD-1: programmed death receptor 1.

Incyte

MCC IS A RARE AND AGGRESSIVE TYPE OF NON-MELANOMA SKIN CANCER[4]

The primary growth typically presents as an asymptomatic, rapidly enlarging skin lesion on sun-exposed skin, with the head and neck region most commonly involved.[4,5]

A rapidly growing neuroendocrine cancer arising in the dermoepidermal junction[4]



Adapted from the National Cancer Institute (2024).[4]

MCC IS A NEUROENDOCRINE CARCINOMA WITH INCREASING INCIDENCE[4]

Between 2000–2013, cases of MCC increased by 95% in the United States.

Owing to the aging population, the case incidence is expected to rise from 2,500 per year to 3,250 per year by 2025.[5]

MCC can **grow rapidly** and **metastasize early**, with **63%** of primary lesions having grown rapidly in the first 3 months prior to diagnosis.[3]

Given how quickly MCC advances, it's not unusual for several distant metastases to be detected simultaneously.[3]

MCC is the **second most common cause of skin cancer death** after melanoma.[4]

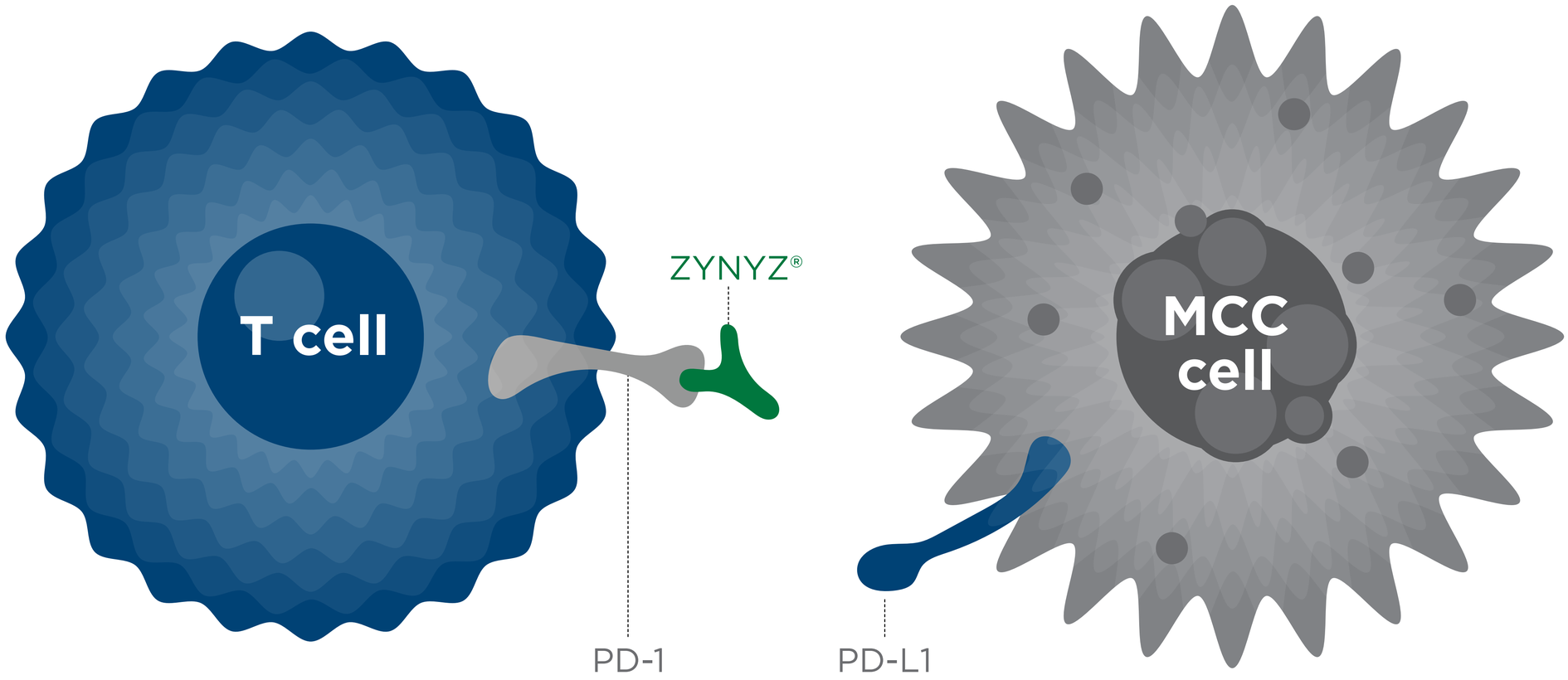
ZYNYZ® IS THE FIRST ANTI-PD-1 MONOCLONAL ANTIBODY INDICATED IN MCC[1-3*]

AN IgG4 MONOCLONAL ANTIBODY THAT BINDS TO PD-1 AND BLOCKS ITS INTERACTION WITH ITS LIGANDS PD-L1 AND PD-L2[1]

- PD-L1 and PD-L2 are expressed by antigen presenting cells and may be expressed by tumor cells and/or other cells in the tumor microenvironment
- Engagement of PD-1 with these ligands results in inhibition of T-cell function, such as:
  - Proliferation
  - Cytokine secretion
  - Cytotoxic activity

* Clinical significance is unknown.
MOA: mechanism of action; IgG4: immunoglobulin G4; PD-1: programmed death receptor 1; PD-L1: programmed death ligand 1; PD-L2: programmed death ligand 2.

ZYNYZ® binds to the PD-1 receptor, blocks interaction with its ligands PD-L1 and PD-L2, and potentiates T-cell activity.[1,3,6]



Adapted from the ZYNYZ® Product Monograph, NCCN Guidelines®, and the National Cancer Institute (2022).[1,3,6]

PD-L1: programmed death ligand 1; PD-L2: programmed death ligand 2; PD-1: programmed death receptor 1.

EFFICACY OF ZYNYZ® WAS EVALUATED IN THE POD1UM-201 STUDY

POD1UM-201 STUDY DESIGN[1]

An open-label, single-arm, multiregional study that enrolled 101 patients with metastatic or recurrent locally advanced MCC who had not received prior systemic therapy for their advanced disease.

Eligibility criteria

- Metastatic or recurrent locally advanced MCC who had not received prior systemic therapy for their advanced disease
  - Eligible: HIV-positive, with an undetectable viral load, a CD4+ count ≥300 cells/microliter and receiving antiretroviral therapy
  - Ineligible: active autoimmune disease or a medical condition that required immunosuppression, severe hepatic or renal impairment, evidence of interstitial lung disease, clinically significant cardiac disease, history of organ transplant, known central nervous system metastases or ECOG performance score ≥2

Select baseline characteristics

- Median age 71.0 years (range: 38–90 years)
  - 38.6% age 75 or older
- 67.3% of patients were male
- 77.2% of patients were Caucasian
- 1.0% of patients were Asian
- 21.8% of patients were race unknown or not reported
- ECOG performance status was 0 (73.3%) or 1 (26.7%)
- 36.6% were reported to have had prior radiotherapy
- 68.3% had prior surgery
- 90.1% had metastatic disease
- 1 patient was HIV positive

N=101

Major efficacy endpoints

- Primary: Objective response rate (ORR)
- Key secondary: Duration of response (DOR)

HIV: human immunodeficiency virus; ECOG: Eastern Cooperative Oncology Group.

PATIENTS RECEIVED ZYNYZ® IV 500 mg EVERY 4 WEEKS[1]

Until disease progression or unacceptable toxicity for a maximum of 2 years.

Tumor response assessment was performed every 8 weeks for the first year of therapy and 12 weeks thereafter.

IV: intravenous.

ZYNYZ®: DEMONSTRATED ORR AND DOR IN THE POD1UM-201 STUDY*

Objective response rate (ORR)[1]

ORR 53.5%
(n=54/101)
(95% CI: 43.3–63.5)

16.8% CR (n=17/101)

36.6% PR (n=37/101)

Duration of response (DOR) (secondary endpoint)[1]

MEDIAN DOR
among the 54 patients who responded:

25.3 months
(95% CI: 14.2–NE)

* The median duration of follow-up was 17.6 months (range: 1.1–38.7 months).
CR: complete response; PR: partial response; CI: confidence interval; NE: not estimable.

ZYNYZ® DEMONSTRATED A WELL-TOLERATED SAFETY PROFILE

The safety of ZYNYZ® was evaluated in 101 patients enrolled in the POD1UM-201 trial with metastatic or recurrent locally advanced MCC who had not received prior systemic therapy for MCC.[1]

Adverse reactions ≥10% of patients with metastatic or recurrent locally advanced MCC who received ZYNYZ®[1]

Adverse reaction	ZYNYZ® (N=101)	
	All Grades n (%)	Grade 3–4 n (%)
Gastrointestinal disorders		
Diarrhea	19 (18.8)	0
Constipation	12 (11.9)	0
General disorders and administration site conditions		
Fatigue*	31 (30.7)	1 (1)
Pyrexia	11 (10.9)	0
Infections and infestations		
COVID-19	14 (13.9)	2 (2)
Musculoskeletal and connective tissue disorders		
Arthralgia	17 (16.8)	1 (1)
Musculoskeletal pain†	17 (16.8)	2 (2)
Respiratory, thoracic and mediastinal disorders		
Cough‡	11 (10.9)	0
Skin and subcutaneous skin disorders		
Pruritus	22 (21.8)	0
Rash§	18 (17.8)	2 (2)

Adapted from the ZYNYZ® Product Monograph.[1]

INFUSION-RELATED REACTIONS (INCLUDES INFUSION-RELATED REACTION AND DRUG HYPERSENSITIVITY)[1]

- All Grades: Occurred in 4% of patients (4/101)
- Grade 3–4: Occurred in 2% of patients (2/101)

Infusion-related reactions led to discontinuation in 2.0% of patients.

* Includes fatigue and asthenia.
† Includes back pain, bone pain, musculoskeletal chest pain, neck pain, and pain in extremity.
‡ Includes cough and productive cough.
§ Includes rash, rash maculo-papular, rash erythematous, rash pruritic, dermatitis, psoriasis, rash papular, dermatitis bullous, and toxic epidermal necrolysis.

ZYNYZ® OFFERS THE CONVENIENCE OF A ONCE-EVERY-4-WEEK DOSING SCHEDULE

ADMINISTRATION OF ZYNYZ® IV EVERY 4 WEEKS MAY ALIGN WITH ROUTINE OFFICE VISITS[1]

Quick infusion delivers ZYNYZ® 500 mg over 30 minutes[1]

- The recommended dose of ZYNYZ® is 500 mg every 4 weeks administered as an IV infusion after dilution over 30 minutes.
- Treatment should continue until disease progression, unacceptable toxicity, or up to 24 months.
- Routine prophylaxis for infusion reactions is not required.
  - For patients who have had previous clinically significant reactions to infusions of therapeutic proteins, premedication with an antipyretic and/or an antihistamine should be considered.
- No dose reductions are recommended.
- Dosing delay or discontinuation may be required based on individual safety and tolerability.

ZYNYZ® is supplied in a carton containing one single-dose vial of 500 mg/20 mL (25 mg/mL).

IV: intravenous.

ZYNYZ® PREPARATION, RECONSTITUTION, AND ADMINISTRATION[1]

1 Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.

Discard the vial if the solution is cloudy, discolored, or visible particles are observed.

2 Withdraw 20 mL (500 mg) of ZYNYZ® concentrate from the vial and discard vial with any unused portion.

3 Dilute ZYNYZ® with either sodium chloride 9 mg/mL (0.9%) solution for injection, USP or glucose 50 mg/mL (5%) solution for injection, USP to prepare a diluted solution with a final concentration between 1.4 mg/mL to 10 mg/mL.

4 Mix the diluted solution by gentle inversion. Do not shake the infusion bag.

Do not freeze or shake diluted solution. Once prepared, administer the diluted solution immediately:[1]

Administer as an IV infusion over 30 minutes. After each dose, flush the infusion line.

Use a polyethylene, polyurethane, or PVC with DEHP IV 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 co-administer other drugs through the same infusion line.

If not administered immediately, it may be stored temporarily.*

Please refer to the Product Monograph for complete dosing and administration information.

* It may be stored temporarily either: (1) at room temperature up to 25°C for no more than 8 hours from the time of preparation to the end of the infusion or (2) under refrigeration at 2°C to 8°C 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.

IV: intravenous; PVC: polyvinylchloride; DEHP: di-2-ethylhexyl phthalate.

NO DOSE REDUCTIONS OF ZYNYZ® ARE RECOMMENDED

Recommended dosage modifications for adverse reactions[1]

Adverse reaction	Severity*	Dosage modification
Pneumonitis	Grade 2	Withhold until ≤Grade 1.†
	Grade 3 or 4	Permanently discontinue.
Colitis	Grade 2 or 3	Withhold until ≤Grade 1.†
	Grade 4	Permanently discontinue.
Hepatitis with no tumor involvement of the liver OR Increased total bilirubin	ALT or AST greater than 3 but no more than 8 times the ULN OR Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold until ≤Grade 1.†
	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 OR Increased total bilirubin	AST or ALT more than 5 and up to 10 times ULN OR Total bilirubin greater than 1.5 but no more than 3 times ULN	Withhold until ≤Grade 1.†
	ALT or AST increase to more than 10 times ULN OR Total bilirubin greater than 3 times ULN	Permanently discontinue.

Adapted from the ZYNYZ® Product Monograph.[1]

* Toxicity graded per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.
† Permanently discontinue once diagnosis is confirmed, or if symptoms have 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.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

Recommended dosage modifications for adverse reactions (cont'd)[1]

Adverse reaction	Severity*	Dosage modification
Endocrinopathies Adrenal insufficiency Hypothyroidism Hyperthyroidism Type 1 diabetes mellitus Hyperglycemia Hypophysitis	Grade 2 adrenal insufficiency	Withhold until ≤Grade 1 or otherwise clinically stable.
	Grade 3 or 4 adrenal insufficiency	Withhold until ≤Grade 1.† Permanently discontinue for worsening while on adequate hormonal therapy.
	Grade 3 or 4 hypothyroidism	Withhold until ≤Grade 1 or is otherwise clinically stable.
	Grade 3 or 4 hyperthyroidism	Withhold until ≤Grade 1 or is otherwise clinically stable.
	Grade 3 or 4 type 1 diabetes mellitus (or hyperglycemia)	Withhold until ≤Grade 1 or is otherwise clinically stable.
	Grade 2 hypophysitis (asymptomatic)	Withhold until ≤Grade 1. May restart after controlled by hormone replacement therapy.
	Grade 2 hypophysitis (symptomatic; e.g., headaches, visual disturbances)	Withhold until ≤Grade 1. May restart study drug after controlled with hormone replacement therapy, if indicated and steroid taper is complete.
	Grade 3 or 4 hypophysitis (symptomatic)	Withhold until ≤Grade 1.† Permanently discontinue for worsening while on adequate hormonal therapy.

Adapted from the ZYNYZ® Product Monograph.[1]

* Toxicity graded per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.
† Permanently discontinue once diagnosis is confirmed, or if symptoms have 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.

Recommended dosage modifications for adverse reactions (cont'd)[1]

Adverse reaction	Severity*	Dosage modification
Nephritis with renal dysfunction	Grade 2 increased blood creatinine	Withhold until ≤Grade 1.†
	Grade 3 or 4 increased blood creatinine	Permanently discontinue.‡
Skin reactions	Grade 3 or suspected SJS or suspected TEN	Withhold until ≤Grade 1.
	Grade 4 or confirmed SJS or confirmed TEN	Permanently discontinue.
Myocarditis	Confirmed Grades 2, 3 or 4	Permanently discontinue.
Other immune-mediated adverse reactions (including myositis, encephalitis, demyelinating neuropathy, Guillain-Barré syndrome, sarcoidosis, autoimmune hemolytic anemia, pancreatitis, uveitis, diabetic ketoacidosis, arthralgia)	Grade 3 (symptomatic)	Withhold until ≤Grade 1.†
	Confirmed Grade 3 and Grade 4	Permanently discontinue.

Adapted from the ZYNYZ® Product Monograph.[1]

* Toxicity graded per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.
† Permanently discontinue once diagnosis is confirmed, or if symptoms have 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.
‡ Permanently discontinue only if retifanlimab is directly implicated in renal toxicity.
SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

Recommended dosage modifications for adverse reactions (cont'd)[1]

Adverse reaction	Severity*	Dosage modification
Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies)	Grade 2 or 3 adverse reactions ≥12 weeks after last dose	Permanently discontinue.
Recurrent immune-mediated adverse reactions	Recurrent Grade 3 or 4	Permanently discontinue.
	Recurrent Grade 2 pneumonitis	
Infusion-related reactions	Grades 1 and 2	Interrupt or slow the rate of infusion.
	Grade 3† or 4 or persistent Grade 2	Permanently discontinue.

Adapted from the ZYNYZ® Product Monograph.[1]

* Toxicity graded per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.
† Grade 3 infusion-related reactions: if rapidly responsive to symptomatic medication and/or to brief interruption of infusion, retifanlimab does not need to be permanently discontinued.

NCCN GUIDELINES® RECOMMENDATIONS FOR RETIFANLIMAB-DLWR

Recommended as a **"preferred regimen"** in:[3]

- Recurrent locally advanced MCC (if curative surgery and curative radiation therapy is not feasible)
- Disseminated disease for distant metastatic MCC

NCCN: National Comprehensive Cancer Network.

PATIENT RESOURCES

Additional support is available to patients – they can be referred to the following online resources, where they may find support and community:

saveyourskin.ca

save your skin FOUNDATION

melanomacanada.ca

MELANOMA CANADA

Incyte Biosciences Canada Corporation does not operate, and is not responsible for, the content on these third-party sites. If you have any questions or concerns about the services or content on these third-party sites, please contact the third-party directly.

ZYNYZ® SAFETY INFORMATION[1]

Clinical use:

Marketing authorization was based on tumor response and durability of response. An improvement in survival or disease-related symptoms has not yet been established.

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Contraindications:

- ZYNYZ® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.

Relevant warnings and precautions:

- Exercise caution when driving or operating a vehicle or potentially dangerous machinery
- Immune-mediated adverse reactions, which may be severe or fatal, can occur in patients treated with antibodies blocking the programmed death receptor 1/programmed death ligand 1 (PD-1/PD-L1) pathway, including ZYNYZ®; these reactions usually occur during treatment with PD-1/PD-L1 blocking antibodies, but symptoms can also manifest after treatment discontinuation
- Immune-mediated adverse reactions: pneumonitis, immune-mediated colitis, immune-mediated nephritis, immune-mediated hepatitis, immune-mediated skin reactions (including toxic epidermal necrolysis), immune-mediated endocrinopathies, immune-mediated hypothyroidism and hyperthyroidism (including thyroiditis), immune-mediated hypophysitis, immune-mediated adrenal insufficiency, immune-mediated type 1 diabetes mellitus, have been reported in patients receiving ZYNYZ®
- Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors; treatment with ZYNYZ® may increase the risk of rejection in solid organ transplant recipients
- 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)
- As with any therapeutic protein, ZYNYZ® can cause infusion-related reactions, some of which may be severe
- Based on its mechanism of action, ZYNYZ® can cause fetal harm when administered to a pregnant woman; there are no available data on the use of ZYNYZ® in pregnant women
- ZYNYZ® has the potential to be transmitted from the mother to the developing fetus
- ZYNYZ® is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk
- Women of childbearing potential should use effective contraception during treatment with ZYNYZ® and for at least 4 months after the last dose
- Women should be advised not to breastfeed during treatment and for at least 4 months after the last dose of ZYNYZ®; a risk to the breastfeeding newborns/infants cannot be excluded

For more information:

Please consult the Product Monograph at pdf.hres.ca/dpd_pm/00078531.PDF for important information relating to monitoring and laboratory tests, adverse reactions, drug interactions, and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling 1-833-309-2759 or contacting medinfocanada@incyte.com.

REFERENCES

1. ZYNYZ® Product Monograph. Incyte Corporation. February 6, 2025. **2.** Incyte biosciences Canada Corporation. Letter of attestation for ZYNYZ®. March 31, 2025. **3.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Merkel Cell Carcinoma. Version 1.2024. November 22, 2023. **4.** National Cancer Institute (NCI). Merkel Cell Carcinoma Treatment (PDQ®) – Health Professional Version. Available at: https://www.cancer.gov/types/skin/hp/merkel-cell-treatment-pdq. Accessed December 6, 2024. **5.** Leonidas *et al*. Advances in Oncology, E-Book 2023. Netherlands, Elsevier, 2023. **6.** National Cancer Institute (NCI). Immune checkpoint inhibitors. Available at: https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors. Accessed December 6, 2024.

A TREATMENT OPTION IN MCC

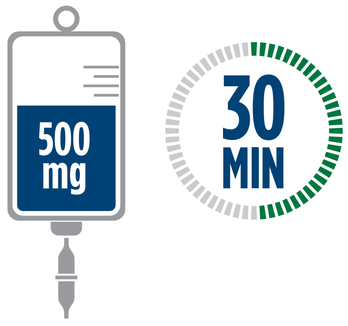
The **first anti-PD-1 monoclonal antibody** indicated in MCC.[1-3*]

ZYNYZ® (retifanlimab for injection), as monotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent locally advanced MCC not amenable to curative surgery or radiation therapy.[1]

- Demonstrated 53.5% ORR (n=54/101; 95% CI: 43.3–63.5)
- Durable DOR
  - Median DOR among the 54 patients who responded: 25.3 months (95% CI: 14.2–NE)
- The most common adverse reactions (≥15%; all Grades) were diarrhea (18.8%; 19/101), fatigue (30.7%; 31/101), arthralgia (16.8%; 17/101), musculoskeletal pain (16.8%; 17/101), pruritus (21.8%; 22/101), and rash (17.8%; 18/101)
  - Infusion-related reactions (all Grades) occurred in 4% of patients (4/101)

The convenience of a once-every-4-week dosing schedule

Recommended dose after dilution:[†]



Visit our resource hub for additional resources: **www.IncyteOnco.ca**.

* Clinical significance is unknown.
† Treatment should continue until disease progression, unacceptable toxicity, or up to 24 months.
PD-1: programmed death receptor 1; ORR: objective response rate; CR: complete response; PR: partial response; DOR: duration of response; CI: confidence interval; NE: not estimable.

Incyte

REVIEWED BY PAAB

MEMBER OF INNOVATIVE MEDICINES CANADA

Pr ZYNYZ® retifanlimab for injection 500 mg / 20 mL (25 mg / mL)