

Zynyz® (retifanlimab-dlwr) (Intravenous)

Document Number: IC-0700

Last Review Date: 04/07/2025

Date of Origin: 03/31/2023

Dates Reviewed: 04/2023, 09/2023, 12/2023, 03/2024, 07/2024, 10/2024, 01/2025, 04/2025

I. Length of Authorization ^{Δ 1,13-15}

Coverage will be provided for 6 months and may be renewed. Coverage can be authorized up to a maximum of 24 months (26 total doses) of therapy.

II. Dosing Limits

Max Units (per dose and over time) [HCPCS Unit]:

- 500 billable units every 4 weeks

III. Initial Approval Criteria ¹

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**

Universal Criteria ^{1,2}

- Patient has not received previous therapy with a programmed death (PD-1/PD-L1)-directed therapy ^Δ; **AND**
- Used as single agent therapy; **AND**

Anal Carcinoma ‡ ^{2,9,10}

- Used as subsequent therapy for metastatic disease

Merkel Cell Carcinoma (MCC) † ‡ Φ ¹⁻⁴

- Patient has metastatic or recurrent locally advanced disease †; **OR**
- Patient has primary locally advanced disease ‡; **AND**
 - Both curative surgery and curative radiation therapy are not feasible; **OR**
- Patient has primary or recurrent regional disease ‡; **AND**
 - Both curative surgery and curative radiation therapy are not feasible

Small Bowel Adenocarcinoma (SBA) ‡ ^{2,13}

- Patient has deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) disease OR polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype [e.g.,

tumor mutational burden (TMB) >50 mut/Mb) as determined by an FDA-approved or CLIA-compliant test❖; **AND**

- Patient has advanced or metastatic disease; **OR**
- Patient has locally unresectable or medically inoperable disease; **AND**
 - Used as primary treatment

Colon Cancer ‡^{2,14}

- Patient has MSI-H/dMMR disease OR POLE/POLD1 mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb) as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Used for locally unresectable, medically inoperable, advanced, or metastatic disease

Appendiceal Adenocarcinoma – Colon Cancer ‡^{2,14}

- Patient has MSI-H/dMMR disease OR POLE/POLD1 mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb) as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Used for advanced or metastatic disease

Rectal Cancer ‡^{2,15}

- Patient has MSI-H/dMMR disease OR POLE/POLD1 mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb) as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Used for advanced or metastatic disease

❖ *If confirmed using an FDA approved assay – <http://www.fda.gov/CompanionDiagnostic>*

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Ⓢ Orphan Drug

IV. Renewal Criteria^{Δ 1,2}

Coverage may be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria identified in section III; **AND**
- Duration of authorization has not been exceeded (*refer to Section I*); **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe infusion-related reactions, severe immune-mediated adverse reactions (e.g., pneumonitis, hepatitis, colitis, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions/rash, etc.), complications of allogeneic hematopoietic stem cell transplantation (HSCT), solid organ transplant rejection, etc.

Δ Notes:

- Patients responding to therapy who relapse ≥ 6 months after discontinuation due to duration (i.e., receipt of 24 months of therapy) are eligible to re-initiate PD-directed therapy.
- Patients previously presenting with aggressive disease who are exhibiting stable disease on treatment as their best response (or if therapy improved performance status) may be eligible for continued therapy beyond the 24-month limit without interruption or discontinuation.

V. Dosage/Administration ^{Δ 1,9-15}

Indication	Dose
All indications	Administer 500 mg intravenously every four weeks until disease progression or unacceptable toxicity, or up to 24 months.

VI. Billing Code/Availability Information

HCPCS Code:

- J9345 – Injection, retifanlimab-dlwr, 1 mg; 1 billable unit = 1 mg

NDC:

- Zynyz 500 mg/20 mL solution in a single-dose vial: 50881-0006-xx

VII. References

1. Zynyz [package insert]. Wilmington, DE; Incyte Corporation; April 2024. Accessed March 2025.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) retifanlimab-dlwr. National Comprehensive Cancer Network, 2025. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2025.
3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Merkel Cell Carcinoma. Version 1.2025. National Comprehensive Cancer Network, 2025. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2025.
4. Grignani G, Rutkowski P, Lebbé C. A Phase 2 Study of Retifanlimab in Patients With Advanced or Metastatic Merkel Cell Carcinoma (POD1UM-201)
Presented at the Society for Immunotherapy of Cancer's 36th Annual Meeting Washington, DC • November 10–14, 2021 [Epub ahead of print]
5. Gupta S, Sonpavde G, Grivas P, et al. Defining “platinum-ineligible” patients with metastatic urothelial cancer (mUC). J Clin Oncol. 2019 Mar 1;37(7_suppl):451.

6. Fahrenbruch R, Kintzel P, Bott AM, et al. Dose Rounding of Biologic and Cytotoxic Anticancer Agents: A Position Statement of the Hematology/Oncology Pharmacy Association. J Oncol Pract. 2018 Mar;14(3):e130-e136.
7. Hematology/Oncology Pharmacy Association (2019). Intravenous Cancer Drug Waste Issue Brief. Retrieved from http://www.hoparx.org/images/hopa/advocacy/Issue-Briefs/Drug_Waste_2019.pdf
8. Bach PB, Conti RM, Muller RJ, et al. Overspending driven by oversized single dose vials of cancer drugs. BMJ. 2016 Feb 29;352:i788.
9. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Anal Carcinoma. Version 2.2025. National Comprehensive Cancer Network, 2025. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2025.
10. Rao S, Anandappa G, Capdevila J, et al. A phase II study of retifanlimab (INCMGA00012) in patients with squamous carcinoma of the anal canal who have progressed following platinum-based chemotherapy (POD1UM-202). ESMO Open. 2022 Aug;7(4):100529. doi: 10.1016/j.esmoop.2022.100529. Epub 2022 Jul 8. PMID: 35816951; PMCID: PMC9463376.
11. Berton D, Pautier P, Lorusso D, et al. Antitumor activity and safety of the PD-1 inhibitor retifanlimab in patients with recurrent microsatellite instability-high or deficient mismatch repair endometrial cancer: Final safety and efficacy results from cohort H of the POD1UM-101 phase I study. Gynecol Oncol 2024 Jul;186:191-198. doi: 10.1016/j.ygyno.2024.05.025. Epub 2024 Jun 1.
12. Lakhani N, Cosman R, Banerji U, et al. A first-in-human phase I study of the PD-1 inhibitor, retifanlimab (INCMGA00012), in patients with advanced solid tumors (POD1UM-101). ESMO Open. 2024 Apr;9(4):102254. doi: 10.1016/j.esmoop.2024.102254. Epub 2024 Feb 21.
13. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Small Bowel Adenocarcinoma. Version 2.2025. National Comprehensive Cancer Network, 2025. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2025.
14. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Colon Cancer. Version 1.2025. National Comprehensive Cancer Network, 2025. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2025.
15. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Rectal Cancer. Version 1.2025. National Comprehensive Cancer Network,

2025. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2025.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C17.0	Malignant neoplasm duodenum
C17.1	Malignant neoplasm jejunum
C17.2	Malignant neoplasm ileum
C17.3	Meckel's diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestines
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0	Malignant neoplasm of anus, unspecified
C21.1	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C4A.0	Merkel cell carcinoma of lip
C4A.10	Merkel cell carcinoma of unspecified eyelid, including canthus
C4A.111	Merkel cell carcinoma of right upper eyelid, including canthus
C4A.112	Merkel cell carcinoma of right lower eyelid, including canthus
C4A.121	Merkel cell carcinoma of left upper eyelid, including canthus
C4A.122	Merkel cell carcinoma of left lower eyelid, including canthus
C4A.20	Merkel cell carcinoma of unspecified ear and external auricular canal
C4A.21	Merkel cell carcinoma of right ear and external auricular canal
C4A.22	Merkel cell carcinoma of left ear and external auricular canal

ICD-10	ICD-10 Description
C4A.30	Merkel cell carcinoma of unspecified part of face
C4A.31	Merkel cell carcinoma of nose
C4A.39	Merkel cell carcinoma of other parts of face
C4A.4	Merkel cell carcinoma of scalp and neck
C4A.51	Merkel cell carcinoma of anal skin
C4A.52	Merkel cell carcinoma of skin of breast
C4A.59	Merkel cell carcinoma of other part of trunk
C4A.60	Merkel cell carcinoma of unspecified upper limb, including shoulder
C4A.61	Merkel cell carcinoma of right upper limb, including shoulder
C4A.62	Merkel cell carcinoma of left upper limb, including shoulder
C4A.70	Merkel cell carcinoma of unspecified lower limb, including hip
C4A.71	Merkel cell carcinoma of right lower limb, including hip
C4A.72	Merkel cell carcinoma of left lower limb, including hip
C4A.8	Merkel cell carcinoma of overlapping sites
C4A.9	Merkel cell carcinoma, unspecified
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C7B.1	Secondary Merkel cell carcinoma
Z85.068	Personal history of other malignant neoplasm of small intestine
Z85.821	Personal history of Merkel cell carcinoma

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: <https://www.cms.gov/medicare-coverage-database/search.aspx>. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	Applicable State/US Territory	Contractor
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC