UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Oncology (Injectable – Programmed Death Receptor-1) – Zynyz Utilization Management Medical Policy
- Zynyz™ (retifanlimab-dlwr intravenous infusion – Incyte)

REVIEW DATE: 03/19/2025

OVERVIEW

Zynyz, a programmed death receptor-1 blocking antibody, is indicated for the treatment of metastatic or recurrent locally advanced **Merkel cell carcinoma** in adults.[1]

Guidelines

Zynyz is addressed in the National Comprehensive Cancer Network (NCCN) clinical practice guidelines:

- **Anal Carcinoma** (version 2.2025 – January 17, 2025) treatment guidelines recommend Zynyz as a "Preferred Regimen" for the second-line and subsequent treatment of metastatic disease if no prior immunotherapy received (category 2A).[2,4] In addition, NCCN states that Zynyz should be considered prior to abdominoperineal resection for locally recurrent, progressive disease and for the first-line treatment of metastatic disease in combination with carboplatin and paclitaxel (category 2B).
- **Colon Cancer** (version 1.2025 – February 7, 2025) and **Rectal Cancer** (version 1.2025 – February 7, 2025) treatment guidelines recommend Zynyz as a single agent for locally unresectable or medically inoperable, or advanced or metastatic disease or neoadjuvant therapy with a deficient mismatch repair/microsatellite instability-high or polymerase epsilon/delta mutation with ultra-hypermutated phenotype. (category 2A).[2,6,7]
- **Merkel Cell Carcinoma** (version 1.2025 – January 13, 2025) treatment guidelines recommend Zynyz as a "Preferred Regimen" for recurrent locally advanced and primary or recurrent regional disease if curative surgery and radiation therapy are not feasible, and for disseminated disease.[2,3] In addition, Zynyz is recommended as an "Other Recommended Regimen" for primary locally advanced disease if curative surgery and radiation therapy are not feasible (all category 2A).
- **Small Bowel Adenocarcinoma** (version 2.2025 – January 17, 2025) treatment guidelines recommend Zynyz as a single agent as primary treatment for locally unresectable or medically inoperable, or advanced or metastatic disease with a deficient mismatch repair/microsatellite instability-high or polymerase epsilon/delta mutation with ultra-hypermutated phenotype (category 2A).[2,5]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Zynyz. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zynyz as well as the monitoring required for adverse events and long-term efficacy, approval requires Zynyz to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zynyz is recommended in those who meet one of the following criteria:

FDA-Approved Indication

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1. **Merkel Cell Carcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** Patient has primary or recurrent locally advanced disease, if according to the prescriber curative surgery and curative radiation therapy are not feasible; OR
     - **ii.** Patient has primary or recurrent regional disease, if according to the prescriber curative surgery and curative radiation therapy are not feasible; OR
     - **iii.** Patient has metastatic disease; AND
   - **C)** The medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve 500 mg administered by intravenous infusion no more frequently than once every 4 weeks.

Other Uses with Supportive Evidence

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2. **Anal Carcinoma**. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has locally recurrent, progressive disease; AND
       - **b)** Medication is administered before proceeding to abdominoperineal resection; OR
     - **ii.** Patient has metastatic disease; AND
   - **C)** The medication is prescribed by or in consultation with an oncologist.

   Dosing. Approve 500 mg administered by intravenous infusion no more frequently than once every 4 weeks.

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3. **Colon, Rectal, or Appendiceal Cancer**. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** Patient has locally unresectable or medically inoperable disease; OR
     - **ii.** Patient has advanced or metastatic disease; OR
     - **iii.** Medication is used as neoadjuvant therapy; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has a deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H); OR
     - **ii.** Patient has polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype; AND
       Note: Ultra-hypermutated phenotype is defined as tumor mutational burden > 50 mutations/megabase.

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 500 mg administered by intravenous infusion no more frequently than once every 4 weeks.

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4. Small Bowel Adenocarcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):

i. Patient has locally unresectable or medically inoperable disease; OR

ii. Patient has advanced or metastatic disease; AND

C) Patient meets ONE of the following (i or ii):

i. Patient has a deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H); OR

ii. Patient has polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype; AND

Note: Ultra-hypermutated phenotype is defined as tumor mutational burden > 50 mutations/megabase.

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 500 mg administered by intravenous infusion no more frequently than once every 4 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zynyz is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Zynyz™ intravenous infusion [prescribing information]. Wilmington, DE: Incyte; March 2023.
2. The NCCN Drugs & Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2025. Search term: retifanlimab.
3. The NCCN Merkel Cell Carcinoma Clinical Practice Guidelines in Oncology (version 1.2025 – January 13,, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2025.
4. The NCCN Anal Carcinoma Clinical Practice Guidelines in Oncology (version 2.2025 – January 17, , 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2025.
5. The NCCN Small Bowel Adenocarcinoma Clinical Practice Guidelines in Oncology (version 2.2025 – January 17, 2025 © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2025.
6. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 1.2025 – February 7, 2025 © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2025.
7. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 1.2025 – February 7, 2025 © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 7, 2025.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/29/2023
Selected Revision	**Merkel Cell Carcinoma.** Patient has recurrent regional disease added as new option of approval.	04/19/2023
Annual Revision	**Merkel Cell Carcinoma.** Removed "recurrent" from criterion "Patient has locally advanced disease". **Anal Carcinoma.** Added condition of approval.	03/27/2024
Annual Revision	**Merkel Cell Carcinoma.** Removed "patient has not received prior systemic therapy" as a requirement. Added "primary or recurrent" and "if according to the prescriber curative surgery and curative radiation therapy are not feasible" to patient has locally advanced disease. Added "primary" and "if according to the prescriber curative surgery and curative radiation therapy are not feasible" to patient has recurrent regional disease. **Anal Carcinoma**. Removed "persistent" and added "progressive" to patient has locally recurrent, progressive disease. Removed "medication is used as subsequent therapy". Added "medication is administered before proceeding to abdominoperineal resection" as new option of approval. **Small Bowel Adenocarcinoma**. Added new condition of approval. **Colon, Rectal or Appendiceal Cancer**. Added new condition of approval.	03/19/2025