# Retifanlimab (Zynyz®) as monotherapy for the first-line treatment of patients with metastatic or recurrent locally advanced Merkel cell carcinoma

## General information [1]

### Drug description

The active substance of Zynyz® is Retifanlimab (INCMGA00012), an antineoplastic agent that binds to PD 1 (programmed cell death protein 1) receptor, blocks its interaction with its ligands PD L1 and PD L2, and potentiates T-cell response in the tumour microenvironment.

### Indication

Retifanlimab (Zynyz®) is indicated as monotherapy for the first-line treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC) not amenable to curative surgery or radiation therapy.

## Incidence [2]

The incidence of MCC is approx. 0.2-0.3/100,000/year in Europe, 0.66/100,000/year in the U.S. and up to 1.6/100,000/year in Australia.
Median age at diagnosis is approx. 75 years; men are more often affected than women.

## Current treatment

For the treatment of solitary skin or soft tissue metastasis other than melanoma, incl. MCC, **Onkopedia** recommends [3]:

- ❖ Surgical resection, followed by radiotherapy, if indicated.
- ❖ For Merkel cell tumour, immune checkpoint blockade with avelumab or pembrolizumab, if curative resection/radiotherapy is not possible.

According to the **European consensus-based interdisciplinary guideline**, the following is recommended [4]:

- ❖ Immunocompetent patients with locally advanced or metastatic MCC (surgery no feasible) shall receive anti PD-(L)1 -based immunotherapy as first line treatment (Grade of recommendation A, Level of evidence 2, Strength of consensus 100%)
  - Anti-PD-1/PD-L1 agents in MCC: avelumab, pembrolizumab, nivolumab
  - The safety profile of anti PD-(L)1 immune check point inhibitors in MCC showed that these drugs were generally well-tolerated and that their side-effects were comparable to known side-effects in other indications for solid tumours.
- ❖ In locally advanced or metastatic MCC, chemotherapy can be used when patients fail to respond, are intolerant or present contraindication to anti-PD-(L)1 immunotherapy, or when immunotherapy or clinical trials are not available (Grade of recommendation C, level of evidence 3—4, Strength of consensus 100%).
  - The regimens include platinum-based drugs, etoposide, taxanes and anthracyclins, either alone or in various combinations.
- ❖ In patients with locally advanced or metastatic MCC, if available and appropriate, inclusion in clinical trial should be encouraged (Strength of consensus 100%).

## Regulatory status

| EMA [1] | FDA [5] |
|---|---|
| **Approval status for this indication**: On 22 February 2024, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Zynyz®, intended for the treatment of MCC.<br><br>The full indication is:<br><br>❖ Zynyz® is indicated as monotherapy for the first-line treatment of adult patients with metastatic or recurrent locally advanced MCC not amenable to curative surgery or radiation therapy.<br><br>**Other indications**: none<br><br>✓ **Orphan status** | **Approval status for this indication**: On 22 March 2023, the FDA granted accelerated approval to retifanlimab-dlwr (Zynyz®) for adult patients with metastatic or recurrent locally advanced MCC.<br><br>✓ Priority review<br>✓ Fast track<br>✓ Orphan drug designation<br><br>**Other indications**: none |

## Manufacturer

The manufacturer of Zynyz® is Incyte Biosciences Distribution B.V.

## Costs

Currently, there is no cost information available.

## Warnings and precautions[1]

- **Immune-mediated adverse reactions**
  - 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.
- **Infusion-related reactions**
  - Interrupt, slow the rate of infusion, or permanently discontinue Zynyz® based on severity of reaction.
- **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.
- **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus and use of effective contraception.

## Study characteristics [6-9]

| Trial name | *n* | Intervention (I) | Comparator (C) | PE | Median follow-up | Characteristics | Biomarker | Funding | Publication(s) |
|---|---|---|---|---|---|---|---|---|---|
| POD1UM-201 NCT03599713 | 65 | retifanlimab 500 mg IV every 4 weeks (Q4W) for up to 2 years | - | ORR assessed by ICR per RECIST v1.1 | NA | **ongoing**[2], open-label, single-arm, multicentre, phase 2 study | PD-1 | Incyte Corporation | POD1UM-201 (abstract only) [7] |

### Inclusion criteria

- ≥18 years with a diagnosis of MCC with distant metastatic disease or recurrent, advanced locoregional disease not amenable to surgery or radiation.
- ECOG PS of 0 to 1.
- Measurable disease according to RECIST v1.1.
- Availability of tumour tissue (fresh or archival) for central pathology review.
- Willingness to avoid pregnancy or fathering children based on protocol-defined criteria.
- Signed informed consent.

### Exclusion criteria

- Prior systemic therapy for MCC, including chemotherapy and prior PD-1 or PD-L1-directed therapy.
- Treatment with anticancer drugs or participation in another interventional clinical study within 21 days before the first administration of study drug.
- Has not recovered to ≤ Grade 1 or baseline from toxic effects of prior therapy (with the exceptions for anaemia not requiring transfusion support and any grade of alopecia) and/or complications from prior surgical intervention within 7 days before starting study treatment.
- Radiation therapy administered within 2 weeks of first dose of study treatment or radiation therapy to the thoracic region that is > 30 Gy within 6 months of the first dose of study treatment.
- Known CNS metastases and/or carcinomatous meningitis.
- History of second malignancy within 3 years (with exceptions).
- Laboratory values outside the protocol-defined range at screening.
- Clinically significant pulmonary, cardiac, gastrointestinal or autoimmune disorders.
- Active bacterial, fungal, or viral infections, including hepatitis A, B, and C.
- Receipt of a live vaccine within 28 days of planned start of study therapy.
- Current use of protocol-defined prohibited medication.
- Known hypersensitivity to another monoclonal antibody that cannot be controlled with standard measures.

### Patient characteristics at baseline (n=65)

- Median age: 71 years (range: 44-90)
- ≥ 75 years: 37%
- Male sex: 65%
- White: 78%
- Race unknown or not reported: 20%
- Asian: 2%
- ECOG PS of 0: 74%
- ECOG PS of 1: 26%
- HIV-negative: 98%.
- Prior surgery: 72%
- Prior radiotherapy: 38%
- Metastatic disease at baseline: 88%
- Tumour samples were evaluated for Merkel cell polyomavirus:
  - Positive: 71%
  - Negative: 23%
  - Equivocal: 2%
  - Missing: 5%

[1] Referring to the FDA label information (EMA EPAR is not available yet).
[2] The POD1UM-201 trial is currently ongoing; estimated study completion date is 06/2024.

| | | |
|---|---|---|
| | ❖ Inability or unlikely, in the opinion of the investigator, to comply with the Protocol requirements.<br>❖ Participant who is pregnant or breastfeeding. | |

| **Efficacy** (n=65[3], chemotherapy-naïve cohort), abstract data | **Safety (n=87[4])** |
|---|---|
| **Data cutoff: 16 April 2021**<br>**Patients on treatment at data cutoff:** 52.3%<br>**Patients who had completed treatment:** 6.2%<br>**ORR:** 46.2% (CR: 12.3%; PR: 33.8%)<br>**Disease control rate:** 53.8% | **TEAEs:** 75.9%<br>**TEAE of grade ≥3:** 28.7%<br>**TRAE of grade ≥3:** 13.8%<br>**Immune-related AE**: 26.4%<br>**Immune-related AE grade ≥3:** 9.2%<br>**Infusion reaction grade 3**: 1.1%<br>**Treatment discontinuation due to disease progression**: 27.7%<br>**Treatment discontinuation due to AE:** 10.8%<br>**Treatment discontinuation due death:** 1.5%<br>**Treatment discontinuation due to physician decision:** 1.5%<br>**Treatment discontinuation due to immune-related AE:** 4.6%[5] |

## Patient-reported outcomes

The analysis of patient-reported outcomes is not provided in the POD1UM-201 trial.

## ESMO-MCBS version 1.1 [10]

| Scale | Int. | Form | MG ST | MG | HR (95% CI) | Score calculation | PM | Toxicity | QoL | AJ | FM |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Since there is only abstract data available, the ESMO-MCBS is currently not applicable. | | | | | | | | | | | |

## Risk of bias - study level (case series) [11]

| 1. | 2. | 3. | 4. | 5. | 6. | 7. | 8. | 9. |
|---|---|---|---|---|---|---|---|---|
| Was the hypothesis/ aim/ objective of the study clearly stated? | Were the cases collected in more than one centre? | Were patients recruited consecutively? | Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated? | Did participants enter the study at similar point in the disease? | Was the intervention clearly described? | Were additional interventions (co-interventions) clearly described? | Were relevant outcome measures established a priori? | Were outcome assessors blinded to the intervention that patients received? |
| - | | | | | | | | |

| 10. | 11. | 12. | 13. | 14. | 15. | 16. | 17. | 18. |
|---|---|---|---|---|---|---|---|---|
| Were the relevant outcomes measured using appropriate objective/ subjective methods? | Were the relevant outcomes measured before and after intervention? | Were the statistical tests used to assess the relevant outcomes appropriate? | Was the length of follow-up reported? | Was the loss to follow-up reported? | Did the study provide estimates of random variability in the data analysis of relevant outcomes? | Were adverse events reported? | Were the conclusions of the study supported by results? | Were both competing interest and source of support for the study reported? |
| - | | | | | | | | |

**Overall risk of bias: Since there is only abstract data available, the risk of bias is currently not evaluable.**

## Ongoing trials [12]

| NCT number/trial name | Description | Estimated study completion date |
|---|---|---|
| NCT03599713/POD1UM-201 | Please see above. | 06/2024 |

[3] The primary efficacy analyses are based on the first 65 patients assessed.
[4] All treated patients.
[5] Peripheral sensorimotor neuropathy, pancreatitis, eosinophilic fasciitis, and polyarthritis (n=1 each).

| | | |
|---|---|---|
| NCT06056895/ TRICK-MCC | A proof-of-concept study of combination therapy with INCMGA00012 (Anti-PD-1), INCAGN02385 (Anti-LAG-3), and INCAGN02390 (Anti-TIM-3) in participants with advanced or metastatic PD-(L)1 refractory MCC; phase 2. | 12/2029 |

**Available assessments**

- In November 2021, NIHR published a Heath Technology Briefing "Retifanlimab for advanced/metastatic Merkel cell carcinoma" [13].
- No further assessments are available via G-BA, NICE and ICER.

**Other aspects and conclusions**

- In February 2024, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for Zynyz®, indicated as monotherapy for the first-line treatment of adult patients with metastatic or recurrent locally advanced MCC not amenable to curative surgery or radiation therapy. In March 2023, the **FDA granted accelerated approval** to retifanlimab-dlwr (Zynyz®) for adult patients with metastatic or recurrent locally advanced MCC.
- **POD1UM-201** (NCT03599713) is an **ongoing, open-label, single-arm**, multicentre, **phase 2** study assessing the efficacy and safety of retifanlimab in patients with chemotherapy-naïve or chemotherapy-refractory advanced/metastatic MCC. Eligible patients were ≥18 years of age, had metastatic or recurrent unresectable loco-regional MCC, an ECOG PS of 0 to 1, measurable disease per RECIST v1.1, and had not received prior systemic treatment for MCC.
- The **primary endpoint is ORR** assessed by ICR per RECIST v1.1. Efficacy results from the chemotherapy-naïve cohort (n=65) showed an **ORR of 46.2%** (CR in 12.3%, PR in 33.8%).
- The evaluation of **patient-reported outcomes is not provided** by the POD1UM-201 trial.
- Since there is **only abstract data available**, currently, the **ESMO-MCBS** is **not applicable,** and the **risk of bias** is **not evaluable**.
- Beside the POD1UM-201 trial, one phase 2 trial, assessing triple immune checkpoint inhibition for advanced or metastatic PD-(L)1 refractory MCC, was identified via ClinicalTrials.gov.
- To date, the efficacy and safety of retifanlimab in patients with advanced or metastatic MCC is **not sufficiently assessable**. Since, to date, there is only phase 2 abstract data from a small trial population available, robust phase 3 data and patient-reported data are required urgently.

**First published:** 03/2024

Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, ECOG PS=Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HIV=human immunodeficiency virus, HR=hazard ratio, HSCT=haematopoietic stem cell transplantation, I=intervention, ICER=Institute for Clinical and Economic Review, ICR=independent central review, Int.=intention, MCC=Merkel cell carcinoma, MG=median gain, n=number of patients, NA=not available, NICE=National Institute for Health Care Excellence, NIHR=National Institute for Health and Research, ORR= objective response rate, OS=overall survival, PD-L1=programmed cell death ligand-1, PD-1=programmed cell death protein 1, PD-L2=Programmed cell death ligand-2, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumours, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event, TRAE=treatment-related adverse event

## References:


1. European Medicines Agency (EMA). Medicines. Zynyz. [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/zynyz-0 ].
2. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (AWMF). S2k - Guideline - Merkel cell carcinoma (MCC, neuroendocrine carcinoma of the skin) - Update 2022. [Available from: https://register.awmf.org/assets/guidelines/032-023l_S2k_Merkelzellkarziom-MZK-MCC-neuroendokrines-Karzinom-der-Haut_2023-02_02.pdf ].
3. Onkopedia, Hübner G, et al. CUP Syndrome – Cancer of Unknown Primary. [Available from: https://www.onkopedia-guidelines.info/en/onkopedia/guidelines/cup-syndrome-2013-cancer-of-unknown-primary/@@guideline/html/index.html ].
4. Gauci M-L, Aristei C, Becker JC, et al. Diagnosis and treatment of Merkel cell carcinoma: European consensus-based interdisciplinary guideline e Update 2022. European Journal of Cancer 171 (2022) 203e231.
5. U.S. Food and Drug Administration (FDA). FDA grants accelerated approval to retifanlimab-dlwr for metastatic or recurrent locally advanced Merkel cell carcinoma. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-retifanlimab-dlwr-metastatic-or-recurrent-locally-advanced-merkel ].

6. Protocol to: A Phase 2 Study of INCMGA00012 in Participants With Metastatic Merkel Cell Carcinoma (POD1UM-201). [Available from: https://storage.googleapis.com/ctgov2-large-docs/13/NCT03599713/Prot_000.pdf ].
7. Grignani G RP, Lebbe C, et al. A phase 2 study of retifanlimab in patients with advanced or metastatic merkel cell carcinoma (MCC) (POD1UM-201). Abstract. Journal for ImmunoTherapy of Cancer 2021;9:doi: 101136/jitc-2021-SITC2021545.
8. U.S. Food and Drug Administration (FDA). Zynyz. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761334s000lbl.pdf ].
9. U.S. National Library of Medicine, ClinicalTrials.gov. A Study of INCMGA00012 in Metastatic Merkel Cell Carcinoma (POD1UM-201). [Available from: https://clinicaltrials.gov/study/NCT03599713 ].
10. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. . Annals of Oncology 28: 2340–2366, 2017.
11. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about
12. U.S. National Library of Medicine, ClinicalTrials.gov. [Available from: https://classic.clinicaltrials.gov/ct2/home ].
13. National Institute for Health and Reserach (NIHR). Retifanlimab for advanced/metastatic merkel cell carcinoma. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2021/12/26650-Retifanlimab-for-Merkel-Cell-Carcinoma-V1.0-NOV2021-NON-CONF.pdf ].