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Updated Results From POD1UM-201: A Phase 2 Study of Retifanlimab in Patients With Advanced or Metastatic Merkel Cell Carcinoma

Presented at the
European Society for Medical Oncology Congress 2023
Madrid, Spain • October 20-24, 2023

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Introduction

- Merkel cell carcinoma (MCC) is an aggressive neoplasm with rising incidence rates, especially in adults >70 years of age[1]
- Response rates following chemotherapy are high, but responses are not durable[2,3]
  - Chemotherapy is also limited by high rates of severe toxicities, especially in the elderly[1,4,5]
- MCC is a highly immunogenic tumor[6,7]
  - Cell surface expression of programmed cell death protein/ligand 1 (PD-[L]1) by tumor cells and tumor-infiltrating lymphocytes is present in approximately half of MCC tumor specimens[6]
- Avelumab is approved for treatment of metastatic MCC in the European Union[8,9]
- Pembrolizumab and nivolumab also have clinical activity[10-12]
- Retifanlimab (Zynyz®) is a humanized immunoglobulin G4 (IgG4) monoclonal antibody targeting human PD-1, approved in the United States for the treatment of adult patients with metastatic or recurrent locally advanced MCC based on primary results from the phase 2 POD1UM-201 study (NCT03599713)[13,14]
- POD1UM-201 assessed efficacy and safety of retifanlimab in chemotherapy-naive patients with recurrent locally advanced or metastatic MCC[14]
  - In the primary analysis performed with the first 65 patients, the objective response rate (ORR) was 52%, with safety as expected for the PD-(L)1 inhibitor class
- Here, we present updated efficacy and safety results from the full cohort of 101 chemotherapy-naive patients enrolled in the POD1UM-201 study

Study Objectives

Primary

- To evaluate the ORR of retifanlimab in chemotherapy-naive patients with recurrent locally advanced or metastatic MCC

Secondary

- To evaluate duration of response (DOR), disease control rate, progression-free survival (PFS), and overall survival (OS)
- To evaluate the safety of retifanlimab in MCC
- To determine the pharmacokinetics of retifanlimab

Methods

Study Design and Treatment

- Phase 2, open-label, single-arm, multicenter study
- Per protocol amendment 5 (April 9, 2020), enrollment was limited to chemotherapy-naive patients **(Table 1)**
  - 6 chemotherapy-refractory patients were enrolled under a previous version of the protocol and are not included in this analysis
- Retifanlimab was administered at a flat dose of 500 mg intravenously over 60 minutes every 4 weeks (q4w; on day 1 of each 28-day cycle)
  - Premedication was not required
- Treatment could continue up to 2 years in the absence of disease progression, intolerable toxicity, death, withdrawal of consent, loss to follow-up, or premature discontinuation for any other reason
- Efficacy analysis is based on patients treated with retifanlimab who had >12 months follow-up for response as of the data cutoff date
- Safety analysis is based on all enrolled patients who received ≥1 dose of retifanlimab

Table 1. Key Eligibility Criteria

Inclusion	• Male and female patients ≥18 years of age with distant metastatic disease or recurrent, advanced locoregional disease not amenable to surgery or radiation, measurable per RECIST v1.1 • Eastern Cooperative Oncology Group performance status of 0 or 1 • Available tumor tissue (fresh or archival) for central pathology review • HIV-positive patients are eligible if CD4 cell count is ≥300 cells/µL, have undetectable viral load, and are receiving highly active antiretroviral therapy
Exclusion	• Previous systemic treatment for MCC, including chemotherapy and any anti–PD-1 or anti–PD-(L)1 therapy • Treatment with anticancer drugs or participation in another interventional clinical trial ≤21 days before first study dose • Radiation therapy ≤2 weeks before first dose or radiation therapy to the thoracic region >30 Gy ≤6 months before first dose • Known central nervous system metastases and/or carcinomatous meningitis • Interstitial lung disease or active, noninfectious pneumonitis • Active autoimmune disease requiring systemic immunosuppression beyond maintenance treatment with corticosteroids, or chronic or current active infections requiring systemic antibiotics, antifungal, or antiviral treatment

CD, cluster of differentiation; Gy, gray; MCC, Merkel cell carcinoma; PD-L1, programmed death receptor-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors.

Assessments

- Objective responses were assessed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 every 8 weeks for the first 12 months, and then every 12 weeks thereafter by independent central review
  - Modified version of RECIST v1.1 for immune-based therapeutics (iRECIST) was also used to evaluate patient responses and guide treatment decisions
- Adverse events were graded (CTCAE v5.0) and monitored until ≥90 days after the last dose of study drug or until the start of new anticancer therapy, whichever occurred first
  - Comprehensive prespecified algorithms were used to identify immune-related adverse events (irAEs) and infusion-related reactions (IRRs)
- Tumor tissue was collected during screening to measure PD-(L)1 expression levels and Merkel cell polyomavirus large T-antigen (MCPyV), as well as for biomarker and translational analyses
  - PD-L1 expression was determined using a validated PD-L1 immunohistochemistry assay (22C3)
- Exploratory assessments included HIV control and health-related quality of life

Results

Patients

- Patients were enrolled from February 2019 to June 2021; as of the March 10, 2023, data cutoff, 101 chemotherapy-naive patients had received ≥1 dose of retifanlimab
  - Median (range) duration of follow-up for DOR was 17.6 (1.1-38.7) months
- Patient demographics and disease characteristics are presented in **Table 2**
- At data cutoff, 7 patients (6.9%) were still undergoing treatment

Drug Exposure

- Median (range) number of retifanlimab infusions was 12.0 (1-28) months
- Median (range) duration of treatment was 10.3 months (1 day-24.8 months)

Table 2. Baseline Demographics and Disease Characteristics

Variable	Chemotherapy Naive (N=101)
Age, median (range), years	71.0 (38-90)
≥75 years, n (%)	39 (38.6)
Sex, n (%)	
Male	68 (67.3)
ECOG PS, n (%)	
0	74 (73.3)
1	27 (26.7)
Time since initial diagnosis, median (range), months	4.7 (0.2-64.0)
Stage at current diagnosis, n (%)	
3*	10 (9.9)
4	91 (90.1)
Visceral metastasis, n (%)	34 (33.7)
PD-L1 TPS, n (%)	
<1%	76 (75.2)
≥1%	19 (18.8)
Not evaluable†	6 (5.9)
MCPyV status, n (%)	
Positive	73 (72.3)
Negative	20 (19.8)
Not evaluable‡	8 (7.9)
Prior radiotherapy, n (%)	37 (36.6)
Prior surgery, n (%)	69 (68.3)
HIV infection, n (%)	1 (1.0)

*Not amenable to curative surgery or radiation. †Patients for whom tissue was not submitted or sample could not be analyzed. ‡Includes missing and equivocal results. ECOG PS, Eastern Cooperative Oncology Group performance status; MCPyV, Merkel cell polyomavirus; PD-L1 TPS, programmed death receptor-ligand 1 tumor proportion score.

Antitumor Activity

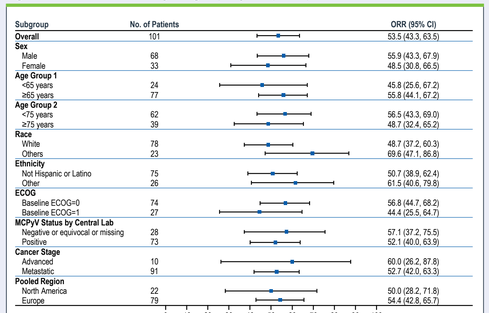
- Overall response results are summarized in **Table 3**
- ORR by patients' baseline characteristics is shown in **Figure 1**
- ORR among patients with both PD-L1 expression level and MCPyV status available at baseline is shown in **Table 4**
- The best percentage change from baseline in target lesion size among patients assessable for response is shown in **Figure 2**
- Kaplan-Meier estimates of PFS and OS are shown in **Figure 3**

Table 3. Summary of Overall Response by ICR per RECIST v1.1

Variable	Chemotherapy Naive (N=101)
Objective response rate (95% CI), %	53.5 (43.3, 63.5)
Best overall response, n (%)	
Complete response	17 (16.8)
Partial response	37 (36.6)
Stable disease	16 (15.8)
Progressive disease	21 (20.8)
Not evaluable*	10 (9.9)
Disease control rate,† n (%)	60 (59.4)
Median progression-free survival (95% CI), months	12.7 (7.3, 24.9)
Median overall survival (95% CI), months	NR (NE, NE)
Median duration of response (95% CI), months	25.3 (14.2, NE)
Event-free probability at month 6, % (95% CI)‡	82 (68, 90)
Event-free probability at month 12, % (95% CI)‡	71 (57, 82)
Event-free probability at month 24, % (95% CI)‡	56 (39, 69)

*Patients discontinued treatment prior to the first postbaseline assessment or the scan was not evaluable; per protocol, all enrolled patients were included in the response analysis. †Proportion of patients with a confirmed response or stable disease lasting ≥6 months. ‡Event-free probability by Kaplan-Meier method; the 95% CI was calculated using Greenwood's formula to estimate the standard error. CI, confidence interval; ICR, independent central review; NE, not estimable; NR, not reached; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 1. Forest Plot of ORR by Subgroups by ICR (N=101)



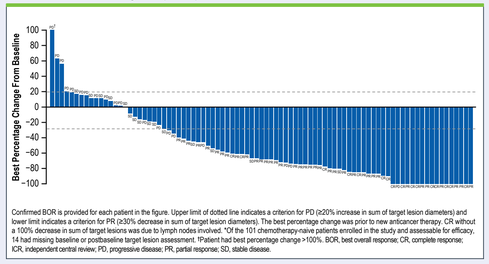
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ICR, independent central review; MCPyV, Merkel cell polyomavirus; ORR, objective response rate.

Table 4. ORR Among Patients With Both Baseline Tumor PD-L1 Expression and MCPyV Status (n=92*)

ORR, % (95% CI; n)	PD-L1 TPS <1%	PD-L1 TPS ≥1%
MCPyV positive	43.9 (30.7, 57.6; n=25/57)	86.7 (59.5, 98.3; n=13/15)
MCPyV negative	43.8 (19.8, 70.1; n=7/16)	75.0 (19.4, 99.4; n=3/4)

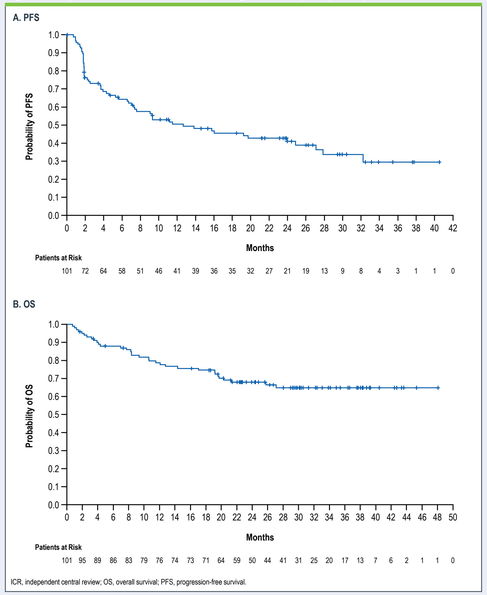
*Of the 101 chemotherapy-naive patients enrolled, 92 had both baseline tumor PD-L1 TPS and centrally confirmed MCPyV status data available and are included in the ad hoc analysis. CI, confidence interval; MCPyV, Merkel cell polyomavirus; ORR, objective response rate; PD-L1 TPS, programmed death receptor-ligand 1 tumor proportion score.

Figure 2. Best Percentage Change From Baseline in Target Lesion Size (Sum of Diameters) for Individual Patients by ICR (n=87*)



Confirmed BOR is provided for each patient in the figure. Upper limit of dotted line indicates a criterion for PD (≥20% increase in sum of target lesion diameters) and lower limit indicates a criterion for PR (≥30% decrease in sum of target lesion diameters). The best percentage change was prior to new anticancer therapy. CR without a 100% decrease in sum of target lesions was due to lymph nodes involved. *Of the 101 chemotherapy-naive patients enrolled in the study and assessable for efficacy, 14 had missing baseline or postbaseline target lesion assessment. †Patient had best percentage change >100%. BOR, best overall response; CR, complete response; ICR, independent central review; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 3. Kaplan-Meier Estimates of A) PFS by ICR and B) OS (N=101)



ICR, independent central review; OS, overall survival; PFS, progression-free survival.

Safety and Tolerability

- Grade ≥3 treatment-related treatment-emergent AEs were reported in 17 patients (16.8%) **(Table 5)**
- irAEs occurred in 35 patients (34.7%); the most common were skin reactions (9.9%) and hypothyroidism (7.9%) **(Table 6)**
  - Grade ≥3 irAEs were reported in 11 patients (10.9%)
  - 9 patients (8.9%) had an irAE that led to treatment discontinuation
- Clinically significant IRRs occurred in only 2 patients (2.0%)

Table 5. Summary of Adverse Events

Adverse Event, n (%)	Chemotherapy Naive (N=101)
TEAEs (all-grade, treatment-related, and -unrelated)	92 (91.1)
Treatment-related TEAEs	67 (66.3)
Grade ≥3 TEAEs (treatment-related and -unrelated)	32 (31.7)
Grade ≥3 treatment-related TEAEs	17 (16.8)
Serious TEAEs (all-grade, treatment-related, and -unrelated)	26 (25.7)
Serious treatment-related TEAEs	12 (11.9)
TEAEs leading to discontinuation	21 (20.8)*
TEAEs leading to death	4 (4.0)†
Immune-related TEAEs‡	35 (34.7)
Grade ≥3 immune-related TEAEs	11 (10.9)
Infusion-related reaction TEAEs‡	5 (5.0)
Grade ≥3 infusion-related reaction TEAEs	2 (2.0)

*Asthenia, atrial fibrillation, colitis, concomitant disease progression, COVID-19, demyelinating polyneuropathy, diarrhea, drug hypersensitivity, ductal adenocarcinoma of pancreas, eosinophilic fasciitis, hepatitis, hypophysitis, infusion-related reaction, lung disorder, lymphadenopathy, pancreatitis, pneumonia, polyarthritis, toxic epidermal necrolysis, transaminases increased, tubulointerstitial nephritis, each occurring in 1 patient. †Acute respiratory failure, asthenia, concomitant disease progression (CLL), COVID-19. ‡Immune-related TEAEs and infusion reaction TEAEs were identified programmatically. CLL, chronic lymphocytic leukemia; TEAE, treatment-emergent adverse event.

Table 6. Potential irAEs Occurring in ≥2 Chemotherapy-Naive Patients*

Adverse Event, n (%)	Chemotherapy Naive (N=101) Any Grade	Grade ≥3
Skin reaction	10 (9.9)†	2 (2.0)
Hypothyroidism	8 (7.9)	0
Hyperthyroidism	6 (5.9)	0
Pneumonitis	5 (5.0)‡	2 (2.0)
Adrenal insufficiency	3 (3.0)	1 (1.0)
Colitis	3 (3.0)	0

Patients were counted once under the highest grade. *irAEs occurring in 1 patient each: autoimmune thyroiditis, demyelinating polyneuropathy (grade ≥3), diabetic ketoacidosis (grade ≥3), eosinophilic fasciitis (grade ≥3), hepatitis (grade ≥3), hypophysitis (grade ≥3), pancreatitis (grade ≥3), polyarthritis, tubulointerstitial nephritis. †Skin reactions includes the following MedDRA terms (patients may have had >1 term reported): bullous dermatitis (n=1; grade ≥3), pruritus (n=4), psoriasis (n=1), rash (n=3), maculo-papular rash (n=2), and toxic epidermal necrolysis (n=1; grade ≥3). ‡Pneumonitis includes the following MedDRA terms: interstitial lung disease (n=1), organizing pneumonia (n=1; grade ≥3), and pneumonitis (n=3 [including n=1, grade ≥3]). irAE, immune-related adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

Conclusions

- **Retifanlimab demonstrated clinically meaningful activity in the full cohort of chemotherapy-naive patients with advanced or metastatic MCC enrolled in POD1UM-201, further supporting results of the primary analysis[14]**
  - **ORR was 53.5% among the full cohort of 101 patients, including 16.8% complete responses and 36.6% partial responses**
  - **Median DOR was 25.3 months, with 71% exceeding 12 months**
  - **Median OS was not reached**
- **Treatment with retifanlimab had an acceptable and manageable safety profile in all patient subgroups, including the elderly, consistent with previously reported results for the PD-(L)1 inhibitor class[9-12]**
  - **IRRs were uncommon and pretreatment prophylaxis was not required**
- **Based on these results, retifanlimab administered q4w represents a new treatment option for adult patients with recurrent locally advanced or metastatic MCC**

Disclosures

Grignani: Honoraria — *Bayer, Eisai, Eli Lilly and Company, Merck, Novartis, Pfizer, PharmaMar;* Consulting or advisory role — *Bayer, Eisai, Eli Lilly and Company, Novartis, Pfizer, PharmaMar;* Research funding — *Bayer, Novartis, PharmaMar.*

Acknowledgments

The authors wish to thank the patients and their families, the investigators, and the site personnel who participated in this study, and Sadhna Shankar (Incyte Corporation) for their contribution to the study. This study was sponsored by Incyte Corporation (Wilmington, DE). Medical writing assistance was provided by Michelle Lister of Envision Pharma Group (Wilmslow, UK), and funded by Incyte Corporation.

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