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POD1UM-201: A Phase 2 Study of Retifanlimab (INCMGA00012) in Locally Advanced or Metastatic Merkel Cell Carcinoma

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Introduction

- Merkel cell carcinoma (MCC) is a rare but aggressive neuroendocrine skin cancer, with rapidly rising incidence rate especially in adults ≥65 years of age[1]
  - 5-year overall survival (OS) rate is 16% in patients with distant metastatic disease[2]
- Programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors for the treatment of patients with advanced/metastatic MCC have shown promising results in phase 2 clinical trials
  - In chemotherapy-naive patients, overall response rates (ORRs) ranged from 40% with avelumab[3] to 56% with pembrolizumab[4]; median progression-free survival (PFS) ranged from 4.1 to 16.8 months, respectively[3,4]
    - The median OS for avelumab was 20.3 months,[3] whereas the median OS for pembrolizumab has not been reported[4]
  - In previously treated patients, ORRs of 33% with avelumab[5] and 50% with nivolumab[6] have been reported, with a median PFS of 2.7 months and median OS of 12.9 months with avelumab[5]
  - Currently, avelumab and pembrolizumab are the only US Food and Drug Administration–approved immunotherapies for MCC[7,8]
- Response rates following chemotherapy are up to 70% for first-line treatment and 9–20% following 1 or more prior regimens[9]; however, duration of response is short, with high rates of fatal toxicities especially in elderly patients
  - PD-1–directed therapies have become treatment of choice in the first-line setting
- Retifanlimab (INCMGA00012) is a humanized IgG4 monoclonal antibody targeting human PD-1 that is being evaluated in phase 2 studies in patients with solid tumors
- POD1UM-201 (NCT03599713) is a phase 2 trial assessing the efficacy and safety of retifanlimab in patients with locally advanced/metastatic MCC
  - Here we report preliminary safety and efficacy results of this trial

Objectives

Primary

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

Secondary

- To evaluate the duration of response, disease control rate, PFS, and OS in chemotherapy-naive patients with locally advanced/metastatic MCC
- To evaluate the safety of retifanlimab in all enrolled patients with locally advanced/metastatic MCC

Exploratory

- Biomarkers, immunogenicity, efficacy per immune-related response criteria, and health-related quality of life

Methods

Study Design and Treatment

- Phase 2, open-label, single-arm, multicenter study
- Enrollment of approximately 60 chemotherapy-naive patients (**Table 1**)
  - Protocol amendment 5 (April 2020) limited the study population to chemotherapy-naive patients owing to changes in the standard of care for first-line treatment of MCC

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 Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Eastern Cooperative Oncology Group performance status 0 or 1
- Available tumor tissue (fresh or archival) for central pathology review
- HIV-positive patients are eligible if CD4 cell count is ≥300 µL, have undetectable viral load, and are receiving highly active antiretroviral therapy

Exclusion

- Previous treatment with any anti–PD-1 or anti–PD-L1 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
- Receiving live vaccine within ≤28 days of study entry
- History of organ transplant, including allogeneic stem cell transplantation

- Retifanlimab administered at a flat dose of 500 mg intravenously over 60 minutes every 4 weeks (Q4W; on day 1 of each 28-day cycle)
- Treatment can 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

Assessments

- Objective responses were assessed per RECIST v1.1 every 8 weeks for the first 12 months, and then every 12 weeks thereafter
  - Modified version of RECIST v1.1 for immune-based therapeutics (iRECIST) was also used to evaluate patient responses and guide treatment decisions
- Adverse events, graded by Common Terminology Criteria for Adverse Events version 5.0, will be monitored until ≥90 days after the last dose of study drug or until the start of new anticancer therapy, whichever occurs first
- Tumor tissue will be collected during screening to measure PD-L1 expression levels and Merkel cell polyomavirus large T-antigen, as well as for biomarker and translational analyses

Results

Patients

- As of the April 7, 2020 data cutoff, 40 patients (chemotherapy naive, n = 35; chemotherapy refractory, n = 5) were enrolled and received ≥1 dose of retifanlimab (full analysis set)
  - Of these patients, 25 (chemotherapy naive, n = 21; chemotherapy refractory, n = 4) were assessable for response by independent central review in this analysis because they had ≥2 postbaseline response assessments or discontinued the study early
  - Median (range) duration of follow-up for the 21 chemotherapy-naive patients was 5.6 (0.7–13.4) months
- Patient demographics and disease characteristics are presented in **Table 2**
- 26 patients (65.0%) (chemotherapy naive, n = 24 [68.6%]; chemotherapy refractory, n = 2 [40.0%]) were still ongoing treatment at the data cutoff

Table 2. Baseline Demographics and Disease Characteristics (Safety Evaluable Population)

Variable	Chemotherapy Naive (n = 35)	Chemotherapy Refractory (n = 5)	Total (N = 40)
Age, median (range), y	71.0 (44–90)	67.0 (49–78)	70.5 (44–90)
Sex, n (%)			
Female / Male	11 (31.4) / 24 (68.6)	1 (20.0) / 4 (80.0)	12 (30.0) / 28 (70.0)
Race, n (%)			
White / Other	29 (82.9) / 6 (17.1)	5 (100.0) / 0	34 (85.0) / 6 (15.0)
ECOG PS, n (%)			
0 / 1	23 (65.7) / 12 (34.3)	2 (40.0) / 3 (60.0)	25 (62.5) / 15 (37.5)
Time since initial diagnosis, median (range), months	7.0 (0.2–64.0)	10.4 (2.3–21.5)	7.4 (0.2–64.0)
Stage at current diagnosis, n (%)			
3 / 3A / 3B	1 (2.9) / 1 (2.9) / 1 (2.9)	0 / 0 / 0	1 (2.5) / 1 (2.5) / 1 (2.5)
4	32 (91.4)	5 (100.0)	37 (92.5)
Liver metastasis, n (%)	3 (8.6)	2 (40.0)	5 (12.5)
Prior systemic therapy, n (%)	0	5 (100)	5 (12.5)
Prior radiotherapy, n (%)	11 (31.4)	2 (40.0)	13 (32.5)
Prior surgery, n (%)	25 (71.4)	4 (80.0)	29 (72.5)

ECOG PS, Eastern Cooperative Oncology Group performance status.

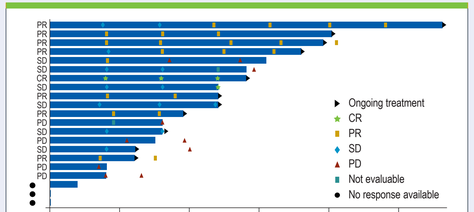
Drug Exposure

- Median (range) number of retifanlimab 500 mg Q4W infusions was 3 (1–13)
- Median (range) duration of treatment was 60.0 (1–394) days

Antitumor Activity

- The best percentage change from baseline in chemotherapy-naive patients assessable for response target lesion size is shown in **Figure 1**
- The duration of treatment and best response of individual chemotherapy-naive patients assessable for response are shown in **Figure 2**
- The median duration of response has not been reached

Figure 2. Duration of Treatment and Best Objective Responses by ICR (Chemotherapy-Naive Patients; N = 21)



CR, complete response; ICR, independent central review; PD, progressive disease; PR, partial response; SD, stable disease.

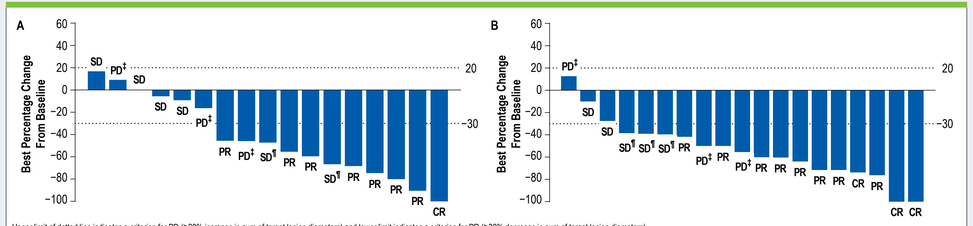
Safety and Tolerability

Table 3. Summary of Adverse Events (Safety Evaluable Population)

Adverse Event, n (%)	Chemotherapy Naive (n = 35)	Chemotherapy Refractory (n = 5)	Total (N = 40)
TEAEs (all grade, treatment-related and -unrelated)	29 (82.9)	4 (80.0)	33 (82.5)
Treatment-related TEAEs	17 (48.6)	4 (80.0)	21 (52.5)
Grade ≥3 TEAEs (treatment-related and -unrelated)	9 (25.7)	2 (40.0)	11 (27.5)
Grade ≥3 treatment-related TEAEs	3 (8.6)	1 (20.0)	4 (10.0)
Serious TEAEs (all grade, treatment-related and -unrelated)	8 (22.9)	2 (40.0)	10 (25.0)
Serious treatment-related TEAEs	2 (5.7)	1 (20.0)	3 (7.5)
Nonfatal TEAEs leading to discontinuation	4 (11.4)*	1 (20.0)†	5 (12.5)
TEAEs leading to death	2 (5.7)‡	0	2 (5.0)
Potential immune-related TEAEs	7 (20.0)	1 (20.0)	8 (20.0)

* Related to retifanlimab: polyarthritis and infusion-related reaction (n = 1 each); unrelated to retifanlimab: asthenia and arrhythmia (n = 1 each).
† Radiculopathy (n = 1; related to retifanlimab). ‡ Asthenia and acute respiratory failure (n = 1 each; unrelated to retifanlimab).
TEAE, treatment-emergent adverse event.

Figure 1. Best Percentage Change From Baseline in Target Lesion Size (Sum of Diameters) for Individual Patients by (A) ICR* and (B) Investigator Assessment† (Chemotherapy-Naive Patients)



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).
* Of the 21 chemotherapy-naive patients assessable for the efficacy evaluable analysis by ICR, 4 had missing baseline or postbaseline target lesion assessments. † Of the 22 chemotherapy-naive patients assessable for the efficacy evaluable analysis by investigator, 3 had missing baseline or postbaseline target lesion assessments. ‡ Patients had PD by nontarget lesions and new lesions by ICR (A) or investigator (B) assessment. ¶ Patients with >30% decrease in sum of target lesion diameters did not have a confirmed objective response or are pending confirmation of response.
CR, complete response; ICR, independent central review; PD, progressive disease; PR, partial response; SD, stable disease.

Table 4. Potential Immune-Related Adverse Events (Safety Evaluable Population)

Adverse Event, n (%)	Chemotherapy Naive (n = 35) Any Grade	Chemotherapy Naive (n = 35) Grade ≥3	Chemotherapy Refractory (n = 5) Any Grade	Chemotherapy Refractory (n = 5) Grade ≥3	Total (N = 40) Any Grade	Total (N = 40) Grade ≥3
Hypothyroidism	2 (5.7)	0	0	0	2 (5.0)	0
Pneumonitis*	2 (5.7)	0	0	0	2 (5.0)	0
Skin reactions†	2 (5.7)	0	0	0	2 (5.0)	0
Type 1 diabetes	1 (2.9)	1 (2.9)	0	0	1 (2.5)	1 (2.5)
Other rare immune-related TEAEs	1 (2.9)‡	0	1 (20.0)¶	1 (20.0)¶	2 (5.0)	1 (2.5)

Participants were counted once under the highest grade; TEAEs with missing severity are included under any grade only.
* Pneumonitis includes the following MedDRA terms: interstitial lung disease and pneumonitis.
† Skin reactions include the following MedDRA terms: pruritus and rash.
‡ Polyarthritis.
¶ Radiculopathy.
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Conclusions

- **As of this report, 35 of the planned 60 patients with advanced or metastatic chemotherapy-naive MCC have been enrolled and received retifanlimab 500 mg Q4W**
- **Confirmed responses by ICR, including complete responses, were observed in chemotherapy-naive and chemotherapy-refractory patients**
- **Initial results demonstrate promising activity with retifanlimab in chemotherapy-naive MCC**
- **Retifanlimab was generally well tolerated by patients with MCC**
- **Immune-related adverse events were consistent with reports of other PD-1/PD-L1 inhibitors**
- **Results support continued clinical investigation of retifanlimab in MCC**

Disclosures

Grignani: Honoraria – *Bayer, Eisai, Lilly, Merck, Novartis, Pfizer, and PharmaMar;* consulting or advisory role – *Bayer, Eisai, Lilly, Novartis, Pfizer, and PharmaMar;* research funding – *Bayer, Novartis, and PharmaMar.* **Burgess:** Advisor – *EMD Serono and Immune Design.* **Depenni** has no relationships to disclose. **Guida:** Advisory board member – *Bristol Myers Squibb, MSD, Novartis, and Pierre Fabre.* **Spagnolo:** Honoraria – *Bristol Myers Squibb, Merck, MSD, Novartis, Pierre Fabre, Roche, Sanofi, and Sun Pharma;* advisory board member – *MSD and Novartis;* travel expenses – *Bristol Myers Squibb, MSD, and Novartis.* **Spada:** Honoraria – *EMD Serono, Ipsen, Novartis, and Pfizer;* travel expenses – *Ipsen, Novartis, and Pfizer.* **De Braud:** Consulting or advisory role – *Amgen, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Dompé, Ignyta, Novartis, Pfizer, Servier, and Tiziana Life Sciences;* speakers' bureau participant – *Bristol Myers Squibb, Lilly, Menarini Group, MSD, Novartis, Pfizer, Roche, and Servier;* research funding – *Amgen, Bristol Myers Squibb, Ignyta, Lilly, MedImmune, Merck Serono, MSD, Nektar, Novartis, and Roche;* travel expenses – *Amgen, Bristol Myers Squibb, and Roche.* **Pulini, Shankar,** and **Tian:** Employment and stock ownership – *Incyte Corporation.* **Lebbé:** Honoraria – *Bristol Myers Squibb, Merck Serono, MSD, Novartis, Pierre Fabre, Roche, and Sanofi;* institutional support – *Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, and Roche;* participated in clinical trials – *Bristol Myers Squibb, Merck Serono, MSD, Novartis, Pierre Fabre, and Roche;* travel grants – *Bristol Myers Squibb and Roche.*

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