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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

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HIGHLIGHTS

- We evaluated safety and anti-tumor activity of retifanlimab in patients with recurrent MSI-H/dMMR endometrial cancer.
- Retifanlimab was generally well tolerated and demonstrated a safety profile typical of the PD-(L)1 inhibitor class.
- Objective response rate of 51% (95% CI, 39.6–63.0%) was observed with retifanlimab; median DOR was not reached.
- Retifanlimab represents a potential new treatment option for patients with recurrent MSI-H/dMMR endometrial cancer.

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ABSTRACT

Objective. Retifanlimab is a humanized immunoglobulin G4 monoclonal antibody against programmed death 1 being investigated in several solid tumor types. We report final results from patients with recurrent microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) endometrial cancer treated with retifanlimab in a POD1UM-101 expansion cohort.

Methods. Eligible patients (≥18 years; histologically proven/unresectable/recurrent, MSI-H/dMMR endometrial cancer; checkpoint inhibitor naive) received retifanlimab 500 mg intravenously every 4 weeks for ≤2 years. Primary endpoint was safety/tolerability.

Results. At data cutoff (May 17, 2023), 76 patients had received at least one retifanlimab dose. Median (range) age was 67 (49–88) years; 88.2% of patients had recurrent metastatic disease and 80.3% had visceral metastases. Seventy-five patients (98.7%) had received at least one prior systemic therapy. Median retifanlimab exposure was 10.0 (0.03–25.9) months; 23 patients completed treatment. 38 patients (50.0%) had grade ≥3 treatment-emergent adverse events (TEAEs), most commonly anemia ($n = 10$ [13.2%]). 63 patients (82.9%) had treatment-related AEs (TRAEs; grade ≥3, $n = 14$ [18.4%]); most common was fatigue ($n = 14$ [18.4%]). Two patients had TEAEs that led to death; no TRAEs were fatal. 39 patients had objective responses (51.3%; 95% CI, 39.6−63.0%); 19 patients (25.0%) had complete response and 20 (26.3%) had partial response. Median progression-free survival was 12.2 months; 30 patients (76.9%) had duration of response (DOR) ≥12 months. Median DOR was not reached after median follow-up time of 26.0 months.

Conclusions. Retifanlimab was generally well tolerated and demonstrated encouraging anti-tumor activity in patients with pre-treated recurrent MSI-H/dMMR endometrial cancer.

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1. Introduction

Endometrial cancer is the sixth most common cancer in women and the most common gynecologic cancer in developed countries [1,2], with a rising incidence among the aging and increasingly obese population [1,3]. Patients with advanced or metastatic endometrial cancer generally have a poor prognosis, with a 5-year survival rate of ~20% [4]. Historically, the first-line treatment for recurrent or metastatic endometrial carcinoma has been carboplatin plus paclitaxel [1,5], which is not curative. Patients who progress after first-line therapy (including those with microsatellite instability-high [MSI-H] and mismatch repair deficient [dMMR] disease) derive minimal benefit from second-line chemotherapies, with responses lasting <6 months and response rates averaging <15% [6]. Around 30% of primary endometrial cancers and 13–30% of recurrent endometrial cancers are MSI-H/dMMR [7], which demonstrate deficient proteins in the DNA mismatch repair pathway [7] and are associated with more aggressive prognostic features and worse outcomes than other molecular subtypes (i.e. intact/proficient MMR or DNA polymerase-ε [POLE] mutations/p53 wild-type, depending on the study) [8–10].

Immune checkpoint inhibitors represent a major advance in the treatment of various malignancies, including MSI-H/dMMR endometrial cancers [11,12]. The immune checkpoint protein programmed death 1 (PD-1) and its ligand (PD-L1) are overexpressed in 75% and 25%–100% of cases of endometrial cancer, respectively [7,13,14]. PD-L1 binds to PD-1 on cluster of differentiation (CD)-4 and CD8 T cells, leading to their inactivation within the tumor microenvironment [13]. POLE-mutated and MSI-H tumors frequently display many tumor-specific neoantigens, a high number of tumor-infiltrating lymphocytes, and upregulation of the PD-1 pathway in endometrial cancer cells [13,14]. For these reasons, targeting the PD-1 pathway is a promising treatment option for patients with MSI-H/dMMR endometrial cancer. The phase I single-arm GARNET study with dostarlimab [15] and the phase II KEYNOTE-158 study with pembrolizumab [16] demonstrated improved efficacy compared with chemotherapy- and hormone-based treatments (reported objective response rates [ORRs] of 43.5% and 48%, respectively, with median duration of response [DOR] not reached in either study). Based on these results, dostarlimab and pembrolizumab are currently approved by the US Food and Drug Administration and European Medicines Agency for the treatment of MSI-H/dMMR endometrial cancer in patients who have disease progression on or after platinum-based chemotherapy [17–20].

Retifanlimab (INCMGA00012) is a humanized immunoglobulin G4 monoclonal antibody against human PD-1. Preclinical studies demonstrated that retifanlimab had similar activity to replicas of nivolumab or pembrolizumab [21]. In ongoing early-phase clinical studies in advanced solid tumors, retifanlimab has demonstrated pharmacology as well as clinical safety and efficacy that are representative of the PD-1 class of inhibitors [22–26]. POD1UM-101 (NCT03059823) was a first-in-human study that aimed to evaluate safety and tolerability of retifanlimab monotherapy in multiple advanced solid tumor types [24]. At the interim analysis, retifanlimab monotherapy demonstrated acceptable tolerability and durable clinical activity in multiple advanced solid tumor types, including pre-treated biomarker-unselected and recurrent endometrial cancer [24]. Subsequently, safety and anti-tumor activity of retifanlimab at the recommended phase II dose (RP2D) of 500 mg every 4 weeks was investigated in a large expansion cohort of patients with recurrent MSI-H/dMMR endometrial cancer in POD1UM-101, with interim and primary analysis results demonstrating a manageable safety profile and encouraging anti-tumor activity [22,26]. Here we report final safety and efficacy results for a large cohort of patients with centrally confirmed recurrent MSI-H/dMMR endometrial cancer enrolled and treated in POD1UM-101.

2. Methods

2.1. Study design

POD1UM-101 (NCT03059823) was a phase I, open-label, dose-escalation, and cohort expansion study that evaluated safety, tolerability, pharmacokinetics, immunogenicity, and preliminary anti-tumor activity of retifanlimab in patients with advanced solid tumors. Results from the dose-escalation and completed expansion cohorts have been previously reported at congresses [22,24–27]. The study was conducted in accordance with the International Council for Harmonisation Guidelines for Good Clinical Practice and other applicable local and ethical legal requirements, including the principles of the Declaration of Helsinki. The study protocol and amendments were approved by institutional review boards or independent ethics committees of all participating sites, and all patients provided written informed consent before enrollment.

Based on results from the dose-finding part of the study, the selected dosing regimen for patients with MSI-H/dMMR endometrial cancer was retifanlimab 500 mg administered as an intravenous infusion every 28 days (4 weeks [Q4W]) [24,25]. Patients received retifanlimab for up to 2 years (26 cycles) unless they discontinued due to disease progression, unacceptable toxicity, withdrawal of consent, or other reasons specified in the protocol. Patients who achieved confirmed immune-related complete response (irCR) by Response Evaluation Criteria in Solid Tumors (RECIST), who had received retifanlimab for a minimum of 6 months, could discontinue treatment after receiving two additional cycles of study treatment after irCR or continue treatment up to 2 years, at the investigator's discretion. After the last dose of retifanlimab, patients were followed for overall safety (30 days), adverse events (AEs; 90 days), and survival (every 6 months for up to 2 years). Because blinded independent central radiographic review (ICR) was used for determination of ORR, scans continued to be collected beyond investigator's assessment of disease progression until the start of a new anti-cancer therapy or study withdrawal for any other reason. Patients who discontinued the study drug due to AEs or for any other reason continued with disease assessments per protocol schedule until the start of new anti-cancer therapy.

2.2. Patients

Full eligibility criteria are detailed in the Supplementary Methods. Briefly, eligible patients were ≥18 years of age with histologically proven, unresectable, recurrent MSI-H/dMMR endometrial cancer based on local testing (either by immunohistochemistry [IHC] or polymerase chain reaction [PCR]) and must have had a tumor specimen for retrospective central confirmation of MSI-H/dMMR status and PD-L1 expression assessment. Patients must also have progressed following at least one or up to five prior systemic therapies (prior neoadjuvant chemotherapy, adjuvant chemotherapy, or definitive chemoradiation therapy were considered a prior line of treatment if the time to disease recurrence was <12 months from the start of the corresponding therapy; prior hormonal therapy was considered a separate line of therapy), had measurable disease per RECIST v1.1, had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, had a life expectancy ≥12 weeks, and had adequate liver and renal function.

Patients were excluded if they had symptomatic or untreated central nervous system metastases; known or suspected autoimmune disease; clinically significant cardiovascular, gastrointestinal, or pulmonary conditions; or active infection (including hepatitis B or C virus or known human immunodeficiency virus). Patients previously treated with an immune checkpoint inhibitor (e.g. anti–PD-1, anti–PD-L1, or anti–cytotoxic T-lymphocyte associated protein 4) were excluded from this study, as were patients treated with anti-neoplastic therapy, investigational therapy, major surgery, live virus–based vaccination within 4 weeks, or radiation therapy or systemic corticosteroids (excluding

topical, ophthalmic, inhaled, or nasal administration) within 2 weeks of receiving retifanlimab.

2.3. Biomarker screening

Pre-treatment archival or fresh tumor tissue samples (paraffin-embedded tissue blocks or formalin-fixed paraffin-embedded slides) were retrospectively tested by a central laboratory facility (NeoGenomics Laboratories, Fort Myers, FL, USA; Clinical Laboratories Improvement Amendment number 05D1021650) for confirmation of MSI-H/dMMR status. For MSI-H testing, multiplex PCR with MSI Analysis System (Promega, Madison, WI, USA) was used to amplify five mononucleotide repeat markers (*BAT-25*, *BAT-26*, *NR-21*, *NR-24*, *MONO-27*) from tumor and matched non-tumor DNA. MSI was reported as MSI-H (at least two of five markers unstable) or MSI-low (one of five markers unstable). Samples that were not MSI-H were evaluated by IHC for MMR protein expression (MLH1, MSH2, MSH6, PMS2); detection of up to three of four proteins by IHC indicated dMMR. Available tissue was also centrally analyzed for PD-L1 expression using the Ventana PD-L1 (SP263) assay (Roche Diagnostics, Indianapolis, IN, USA) to determine tumor cell positivity and was scored by a pathologist.

2.4. Enrollment sites

POD1UM-101 was conducted at 48 international study sites across Asia-Pacific, Europe, and the United States.

2.5. Outcomes and assessments

The primary endpoint was safety and tolerability of retifanlimab in patients with centrally confirmed MSI-H/dMMR unresectable locally advanced or metastatic endometrial cancer. Secondary endpoints were ORR (defined as the percentage of patients with complete response [CR] or partial response [PR] according to RECIST v1.1, as determined by ICR), DOR, progression-free survival (PFS), and overall survival (OS).

Safety and tolerability were assessed by monitoring frequency and severity of AEs (using Common Terminology Criteria for Adverse Events v4.02) and by evaluating clinical laboratory assessments and changes in vital signs and electrocardiograms. Sponsor-defined infusion-related reactions (IRRs) included diagnosis of infusion reactions occurring any time during the treatment period, symptoms of potential infusion reactions occurring within 1 day of infusion (and resolving within 2 days of onset), and investigator-assessed infusion reactions. Sponsor-assessed immune-related AEs (irAEs) were programmatically identified, predefined preferred terms. Assessments took place at each visit from the first dose of retifanlimab until the end of treatment visit or 90 days after the last dose (whichever was last).

Tumor assessments were evaluated by computed tomography (CT) and/or magnetic resonance imaging at screening and every 8 weeks for the first 24 weeks, then every 12 weeks thereafter until death, withdrawal of consent, lost to follow-up, or initiation of alternative cancer treatment. Objective response status was determined at each tumor assessment time point, and survival status was determined every 6 months for 2 years following final dose of study drug, or until withdrawal of consent, lost to follow-up, or death.

2.6. Statistical analyses

Sample size considerations were based on safety (primary study endpoint) because this was the first evaluation of retifanlimab at the RP2D of 500 mg Q4W. The planned sample size of 70 patients was selected to give a >95% probability of seeing at least one irAE of interest if the underlying rate of such events was 5%, along with a preliminary estimation of response. Efficacy analysis was assessed on all patients with centrally confirmed MSI-H/dMMR endometrial cancer who received at least one dose of retifanlimab.

Patient disposition, demographics, and baseline characteristics were summarized using descriptive statistics. Objective responses (CR, PR, progressive disease [PD], stable disease [SD]) were categorized using RECIST v1.1. ORR was determined by the proportion of patients achieving CR and PR, and associated two-sided 95% exact binomial confidence intervals [CIs] were calculated [3]. Disease control rate was determined by the proportion of patients achieving at least one best response of CR, PR, or SD at any post-baseline visit (at least 8 weeks after the start of treatment) until the first PD or new anti-cancer therapy. The Kaplan-Meier method was used to estimate DOR, PFS, and OS curves; median DOR, PFS, and OS times; PFS rates at 6 and 12 months; and OS rates at 1 and 2 years. The 95% CIs were calculated using the Brookmeyer and Crowley method [28] for median DOR, PFS, and OS times. The 95% CIs for PFS rates at 6 and 12 months and OS rate at 1 year were calculated using normal approximation after log(−log) transformation. Subgroup analyses of ORR were performed based on the following intrinsic and extrinsic factors in the primary efficacy population: age group, race, ethnicity, PD-L1 tumor proportion score (TPS) by central laboratory testing, ECOG PS, number of prior systemic lines of therapy, number of prior platinum therapies, tumor biomarker status (MSI-H vs. dMMR), and number of organs with metastatic disease at baseline.

3. Results

3.1. Patient characteristics and disposition

As of May 17, 2023 (data cutoff date), recruitment into the MSI-H/dMMR endometrial cancer cohort was complete, with 88 patients enrolled at 28 sites. Of these, 76 patients had centrally confirmed MSI-H ($n = 65$ [85.5%])/dMMR ($n = 11$ [14.5%]) status and comprised the efficacy and safety population for the primary analysis; 12 patients were locally tested for MSI-H/dMMR status but did not have central confirmation and therefore were excluded. Patient baseline characteristics are summarized in Table 1. Median (range) age of patients with centrally confirmed MSI-H/dMMR endometrial cancer was 67.0 (49–88) years and 73.7% were White. Overall, 88.2% had metastatic and 11.8% had locally advanced unresectable cancer. The most common cancer histology subtype was endometrioid carcinoma (92.1%) and 72.4% of patients had a PD-L1 TPS <1%. Most patients (65.8%) had at least two metastatic sites reported; visceral metastases were reported in 80.3% of patients, of which 22.4% had liver metastases. Seventy-five patients (98.7%) had received at least one prior anti-cancer systemic therapy, which included chemotherapy (93.4%), hormonal therapy (28.9%), investigational therapy (2.6%), and targeted therapy (1.3%). Seventy-three patients (96.1%) had prior systemic palliative therapy for recurrent disease, 23 (30.3%) of whom received at least two therapies. Majority of patients (64.5%) had low hemoglobin at baseline.

At data cutoff, 23 patients (30.3%) had completed the protocol-specified 2-year treatment period and 53 (69.7%) had discontinued treatment. The most common reason for treatment discontinuation was disease progression in 34 patients (44.7%; radiographic disease progression, $n = 32$; clinical progression, $n = 2$), followed by AEs in atients (17.1%). Additional reasons for discontinuation were death ($n = 3$ [3.9%]), withdrawal by patient ($n = 1$ [1.3%]), and other (confirmed immune-related CR after 6 months of treatment, overall deterioration of patient's general condition; $n = 1$ each). Patients received a median (range) of 11.5 (1–26) infusions of retifanlimab 500 mg; median duration of treatment was 10.0 (0.03–25.9) months.

3.2. Safety and tolerability

Overall, 75 patients (98.7%) experienced a treatment-emergent AE (TEAE); the most common TEAEs included asthenia (32.9%), diarrhea and urinary tract infection (26.3% each), fatigue (21.1%), and anemia,

Table 1
Baseline characteristics of the centrally confirmed MSI-H/dMMR endometrial cancer cohort.[a]

Variable	$N = 76$
Age, median (range), years	67 (49–88)
Race, *n* (%)	
White	56 (73.7)
Asian	1 (1.3)
Other[b]	18 (23.7)
Unknown	1 (1.3)
ECOG PS,[c] *n* (%)	
0	29 (38.2)
1	44 (57.9)
Tumor stage at study entry, *n* (%)	
Locally advanced	9 (11.8)
Metastatic	67 (88.2)
Visceral metastases, *n* (%)	61 (80.3)
Most common sites of metastases at study entry,[d] *n* (%)	
Lymph node	49 (64.5)
Peritoneal carcinomatosis	21 (27.6)
Lung	20 (26.3)
Liver	17 (22.4)
Cancer histology, *n* (%)	
Endometrioid carcinoma	70 (92.1)
Mixed carcinoma	2 (2.6)
Other[e]	2 (2.6)
Clear cell carcinoma	1 (1.3)
Serous carcinoma	1 (1.3)
PD-L1 TPS, *n* (%)[f]	
<1%	55 (72.4)
≥1%	20 (26.3)
Unknown	1 (1.3)
Prior systemic therapy in any disease setting, *n* (%)[g]	75 (98.7)
Prior systemic therapy with palliative intent, *n* (%)	73 (96.1)
1 line	50 (65.8)
2 lines	17 (22.4)
≥3 lines	6 (7.9)
Prior radiotherapy, *n* (%)	54 (71.1)
Prior surgery, *n* (%)	68 (89.5)

dMMR = mismatch repair deficient; ECOG PS = Eastern Cooperative Oncology Group performance status; MSI-H = microsatellite instability-high; PD-L1 = programmed death ligand 1; TPS = tumor proportion score.

[a] Twelve patients with only locally confirmed MSI-H/dMMR status were excluded from this analysis and are not represented in the baseline characteristics.

[b] "Other," includes patients in France where race data could not be collected due to local privacy regulations ($n = 18$).

[c] Two patients had ECOG PS of 1 at time of enrollment but had a baseline ECOG PS of 2 recorded at the time of initiation of therapy (Cycle 1, Day 1), and 1 patient's status was missing.

[d] Most common sites of metastases.

[e] "Other" includes anaplastic ($n = 1$), subtype not available ($n = 1$).

[f] Based on central testing.

[g] All received platinum-based therapy except for 5 patients.

decreased appetite, and pruritus (19.7% each) (Table 2). Grade ≥3 TEAEs occurred in 38 patients (50%), the most common being anemia in 10 patients (13.2%). All the patients in whom treatment-emergent worsening of hemoglobin to grade 3 occurred had grade ≥1 low hemoglobin at baseline (2 with baseline grade 1, 5 with baseline grade 2, and 1 with baseline grade 3 low hemoglobin). TRAEs were reported in 63 patients (82.9%), of whom 14 (18.4%) experienced grade ≥3 TRAEs. Fatigue was the most common TRAE of any grade, reported in 14 patients (18.4%), followed by pruritus, diarrhea (15.8% each), and asthenia (14.5%) (Supplementary Table S1).

TEAEs leading to dose discontinuations occurred in 13 patients (17.1%) and included uveitis, diarrhea, dry mouth, autoimmune hepatitis, hepatitis, increased lipase, arthralgia, myositis, polymyalgia rheumatica, and tubulointerstitial nephritis ($n = 1$ [1.3% each], considered treatment related), and transitional cell carcinoma, renal failure, and muscular weakness ($n = 1$ [1.3% each], not considered treatment related). TEAEs leading to dose interruption (defined as delay of next scheduled dose or infusion interruption) occurred in 28 patients (36.8%), the most common being diarrhea ($n = 3$ [3.9%]). Most TEAEs leading to interruptions resolved completely or resolved with sequelae.

Table 2
TEAEs occurring in >10% of patients by MedDRA preferred term in decreasing order of total frequency.

Adverse event, *n* (%)	$N = 76$	
	Any grade	Grade ≥3
Any TEAE	75 (98.7)	38 (50.0)
Asthenia	25 (32.9)	0
Diarrhea	20 (26.3)	1 (1.3)
Urinary tract infection	20 (26.3)	3 (3.9)
Fatigue	16 (21.1)	1 (1.3)
Anemia	15 (19.7)	10 (13.2)
Decreased appetite	15 (19.7)	0
Pruritus	15 (19.7)	0
Nausea	14 (18.4)	0
Abdominal pain	14 (18.4)	2 (2.6)
Constipation	12 (15.8)	0
Rash	12 (15.8)	1 (1.3)
Peripheral edema	11 (14.5)	0
Back pain	10 (13.2)	2 (2.6)
Arthralgia	10 (13.2)	0
Pyrexia	8 (10.5)	0
Hyperthyroidism	8 (10.5)	0
Muscle spasm	8 (10.5)	0

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Dose reduction of retifanlimab was not permitted for patients enrolled in the MSI-H/dMMR confirmed cohort. Two patients experienced fatal TEAEs (large intestinal stenosis and renal failure), neither of which was considered related to retifanlimab by the investigator.

Sponsor-defined irAEs occurred in 31 patients (40.8%), of which 10 (13.2%) were grade ≥3 (Table 3). The most common any-grade irAEs were hyperthyroidism (10.5%), hypothyroidism (9.2%), and pruritus (6.6%). Per sponsor assessment, 7 patients (9.2%) experienced a treatment-emergent infusion reaction, 3 (3.9%) by diagnosis and 4 (5.3%) by potential symptoms of IRR; all IRRs were of grade 1 or 2 severity. Investigator-identified AEs of special interest are summarized in Supplementary Table S2.

3.3. Efficacy

Efficacy was assessed in the 76 patients with centrally confirmed MSI-H/dMMR tumors. Best percentage change from baseline in target lesion size among evaluable patients is shown in Fig. 1. Based on confirmed tumor responses assessed by ICR according to RECIST v1.1, ORR (95% CI) was 51.3% (39.6–63.0%). By study cutoff, best overall response of CR and PR was observed in 19 (25.0%) and 20 (26.3%) patients, respectively; 20 patients (26.3%) had SD; at 7 weeks post first dose of retifanlimab, 15 patients (19.7%) had PD. Disease control rate (95% CI) was 77.6% (66.6–86.4%).

Duration of treatment with response assessment is shown in Fig. 2. Median (range) time to first confirmed response was 2.2 (1.6–27.3) months. Of note, 6 responders maintained prolonged tumor response (ranging from 3.0 to >24.9 months) following treatment discontinuation. Median DOR (determined by ICR) was not reached at data cutoff (Fig. 3), with a median (range) follow-up time of 26.0 (2.3–42.5) months. Thirty-four responders (87.2%) and 30 (76.9%) had a DOR of ≥6 months and ≥12 months by landmark analysis.

ICR-determined median (range) PFS was 12.2 (6.0–33.4) months (Fig. 3); 6-month and 12-month PFS rates (95% CI) were 62.6% (50.6–72.4%) and 51.4% (39.5–62.1%), respectively. Median (95% CI) OS was 30.2 months (19.3–not estimable) following a median (range) follow-up time of 27.5 (0.4–46.3) months (Fig. 3), and estimated probability of surviving for ≥1 year was 77.3% (95% CI, 66.1–85.2%) based on Kaplan-Meier analysis.

Tumor responses were seen in all subgroups of interest; ORRs were generally consistent with numerical differences observed for age group (<65 vs. ≥65 years), ECOG PS (0 vs. 1), number of prior systemic

Table 3
Sponsor-assessed immune-related TEAEs occurring in ≥1 patient (safety population).[a]

Preferred term, *n* (%)	*N* = 76	
	Any grade	Grade ≥3
Any event	31 (40.8)	10 (13.2)
Hyperthyroidism[b,c]	8 (10.5)	0
Hypothyroidism[c,d]	7 (9.2)	0
Pruritus	5 (6.6)	0
Acute kidney injury	3 (3.9)	3 (3.9)
Hepatitis[e]	2 (2.3)	1 (1.3)
Polyneuropathy	2 (2.6)	0
Pneumonitis	2 (2.6)	1 (1.3)
Rash	2 (2.6)	1 (1.3)
Autoimmune hepatitis	1 (1.3)	1 (1.3)
Interstitial lung disease	1 (1.3)	0
Ocular keratitis	1 (1.3)	0
Lung infiltration	1 (1.3)	0
Myositis	1 (1.3)	1 (1.3)
Polyarthritis	1 (1.3)	0
Polymyalgia rheumatica	1 (1.3)	0
Rash papular	1 (1.3)	0
Rash pruritic	1 (1.3)	0
Toxic skin eruption	1 (1.3)	0
Thyroiditis	1 (1.3)	0
Tubulointerstitial nephritis	1 (1.3)	1 (1.3)
Uveitis	1 (1.3)	1 (1.3)

AE = adverse event; TEAE = treatment-emergent adverse event.
Immune-related AEs were identified using pre-defined preferred terms, and patients were counted only once under each group term and preferred term.
[a] No immune-related TEAEs with fatal outcome occurred in the study.
[b] Four patients had hyperthyroidism without preceding or subsequent hypothyroidism.
[c] Hypothyroidism preceded hyperthyroidism in 2 patients. Hyperthyroidism preceded hypothyroidism in 2 patients.
[d] Three patients had hypothyroidism without preceding or subsequent hyperthyroidism.
[e] One case of autoimmune hepatitis is listed as a separate entry and is therefore excluded.

therapies for endometrial cancer (<2 vs. ≥2), and number of prior platinum therapies (≤1 vs. >1); however, no statistically significant differences were observed (Supplementary Fig. S1).

4. Discussion

MSI/dMMR endometrial cancer represents an important subset of the disease with a unique biology responsive to immunotherapy. In POD1UM-101, retifanlimab 500 mg Q4W was evaluated in patients with pre-treated, locally advanced or metastatic centrally confirmed MSI-H/dMMR endometrial cancer. Retifanlimab was generally well tolerated, with a safety profile consistent with the PD-(L)1 therapy class, and demonstrated deep and durable responses, with 39 patients (51.3%) achieving an objective response, and by landmark analysis 34 (87.2%) and 30 (76.9%) of them had a DOR of ≥6 and ≥12 months, respectively. All patients had disease progression on or after prior platinum-based therapy (93.4%), 43.4% had received at least two lines of systemic therapy for advanced disease before enrollment and 80.3% of patients had visceral metastatic spread. These characteristics are consistent with those of the intended population and clinical setting, and the observed clinical benefit with retifanlimab is comparable with what has previously been reported with dostarlimab and pembrolizumab [15,16], both of which are approved for the treatment of MSI-H/dMMR endometrial cancer in this population [15–20]. Responses were also quite durable, underscoring the clinical benefit of retifanlimab.

Despite the high ORR, a significant proportion of patients did not respond to retifanlimab treatment. This is similar to what is experienced with other PD-1 inhibitors [15,16]. Although patients enrolled in this study cohort all had centrally confirmed MSI-H/dMMR endometrial cancer, it is possible that inter-patient heterogeneity in tumor mutational burden (TMB) [15] and tumor immune microenvironment may be the underlying reason for the differential responses to retifanlimab observed in our study [29]. Of note, interim analysis of GARNET, a phase I study of dostarlimab for the treatment of endometrial cancer reported that among the 103 patients harboring MSI-H/dMMR tumors with known TMB statuses, ORR for the TMB-high and TMB-low subgroups were 43.8% and 21.4%, respectively [15]. Future experiments evaluating TMB, tumor lymphocyte infiltration, and serum cytokine levels may identify biomarkers predictive of retifanlimab response.

Historically, second-line treatment options for patients with advanced or recurrent endometrial cancer have included single-agent chemotherapies (paclitaxel or doxorubicin); however, little benefit has been derived from these [5,6,30]. For patients with hormone-sensitive endometrial cancer, endocrine-based therapy regimens can be considered [5,30]. Results from the current study show that retifanlimab has a favorable efficacy profile compared with salvage chemotherapy or targeted therapies in patients with pre-treated advanced endometrial cancer who have high disease burden [31,32], with 76.9% of patients having a DOR of >12 months. In addition, tumor responses were observed in all subgroups of interest, including in patients with less than two or at least two lines of prior systemic therapy for endometrial cancer and less than one or at least one line of prior platinum chemotherapy.

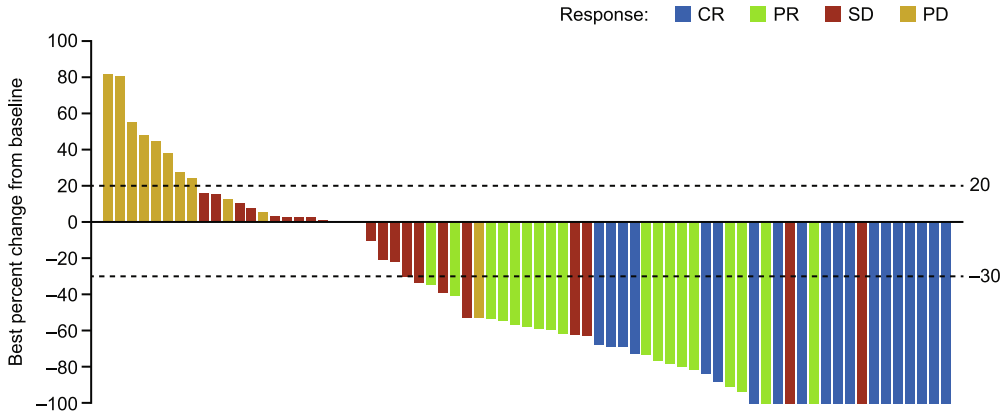

Fig. 1. Best percentage change from baseline in sum of target lesion size by ICR (full analysis set). Out of 76 patients enrolled in the study, 5 patients are not included in the plot: 2 patients had missing post-baseline target lesion assessments (1 patient withdrew from the study after one infusion, 1 patient died before lesion assessment after two infusions), and 3 patients had a change in imaging method and were therefore non-evaluable. Confirmed best objective response is shown for each patient in the figure; 4 patients with best percentage change in target lesion size of 0% had best objective responses of SD, SD, SD, and PD, respectively. 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). CR = complete response; ICR = independent central review; PD = progressive disease; PR = partial response; SD = stable disease.

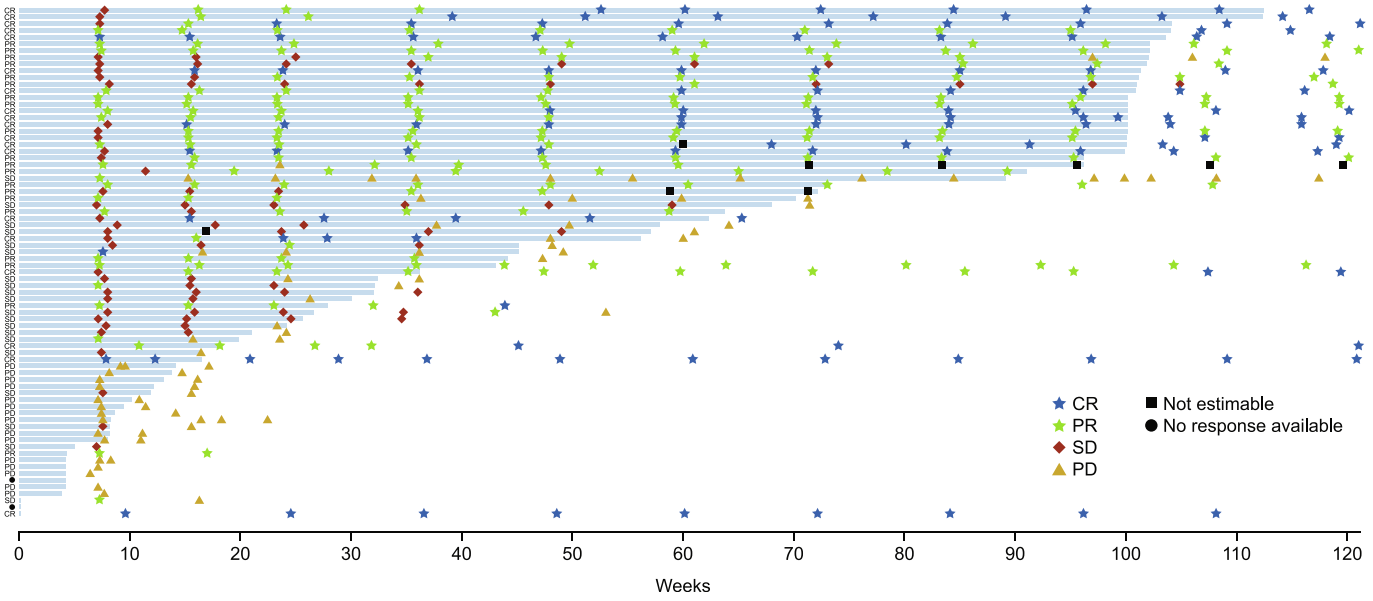

Fig. 2. Duration of treatment and best objective response by ICR according to RECIST v1.1 (full analysis set). Out of 76 patients, 2 did not have any post-baseline tumor assessments and are not included in the plot. Confirmed best objective response is shown for each patient. CR = complete response; ICR = independent central review; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

The safety of retifanlimab was characteristic of the PD-(L)1 inhibitor class and manageable using standard guidelines, and was consistent with the safety profile seen across other tumor types in POD1UM-101 [24]. The most frequently occurring TEAEs among patients with centrally confirmed MSI-H/dMMR endometrial cancer were asthenia (32.9%) and diarrhea and urinary tract infection (both 26.3%), and toxicities were predominantly of mild to moderate severity. Grade ≥3 anemia was reported in 13.2% of patients, potentially owing to the fact that majority of patients had low hemoglobin at baseline, which is consistent with a chemotherapy-pretreated, advanced cancer population. TEAEs leading to drug interruptions occurred in 36.8% of patients, with most resolving or resolving with sequelae; discontinuation rate due to TEAEs was 17.1%. Results from subgroup analyses demonstrated that baseline characteristics (age, race, baseline ECOG PS) do not affect the safety profile of retifanlimab. Incidence of irAEs was consistent with that observed in previous studies using PD-1 inhibitors across a range of cancer types [33,34]; in this study, any-grade and grade ≥3 irAEs based on sponsor assessment occurred in 40.8% and 13.2% of patients, respectively, with no unique irAEs reported. The most frequent irAEs (hyperthyroidism, hypothyroidism, pruritus) are consistent with those reported in previous phase II studies with PD-1 inhibitors.

It should be noted that one trial patient in the study who was a non-responder to retifanlimab treatment had not received prior systemic anticancer therapy before enrolment; while this represents a major protocol violation, her inclusion in the analyzed population presents a conservative assessment of overall efficacy. Another limitation of our study was that no comparator arm was included because the primary endpoint was safety. Therefore, a direct comparison of efficacy with other available therapies is not possible. However, there is no evidence that the POD1UM-101 study population had more favorable characteristics than patients included in pivotal trials for other PD-1 inhibitors. The POD1UM-101 design also included central confirmation of MSI-H/dMMR status and independent radiology assessment of ORR, both of which provide added confidence in the observed results.

Retifanlimab received accelerated approval in March 2023 by the US Food and Drug Administration for adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma [35]. Based on the results of POD1UM-101, retifanlimab represents a potential therapeutic option for patients with previously treated recurrent or metastatic MSI-H/dMMR endometrial cancer who have not previously received immunotherapy. Pembrolizumab and dostarlimab have shown efficacy when combined with standard chemotherapy in the first-line setting [36,37] and promising preliminary efficacy has been reported with atezolizumab and durvalumab in the same setting [38,39]. Although pembrolizumab (as single agent) is approved in the second-line setting and dostarlimab (in combination with chemotherapy) is now approved in the first-line setting for patients with dMMR/MSI-H disease [17,20], there still remains a need for safe and effective therapies for patients who have comorbidities and experience relapse following platinum-based chemotherapy alone. The results of POD1UM-101 provide the basis for further exploration of retifanlimab-based combinations for relapsed disease and ongoing studies, such as the POD1UM-204 phase II umbrella study (NCT04463771) [40], will further characterize the role for retifanlimab as monotherapy or in novel chemotherapy-sparing combinations in additional settings of recurrent endometrial cancer.

Ethics statement and informed consent

The study was approved by institutional review boards or independent ethics committees in Belgium (Commissie Medische ethiek UZ Leuven; Ethics Committee of Hospital-Faculty University of Liège); Bulgaria (Ethics Committee for Clinical Trials, Sofia); Finland (HUS Tutkimuseettiset toimikunnat Biomedicum Helsinki); France (CPP Île-de-France X Hôpital, Aulnay-sous-Bois cedex); Germany (Ethik-Kommission der Albert-Ludwigs-Universität Freiburg, Freiburg; Ethics Committee at the Technical University of Dresden, Dresden; Ethics Committee of the State of Berlin, Berlin); Italy (Comitato Etico del Policlinico Gemelli Fondazione Policlinico Universitario "Agostino Gemelli", Roma [RM]; Comitato Etico IRCCS di Candiolo, Candiolo-TO); Latvia (Ethics Committee for Clinical Research at Development Society of Pauls Stradins Clinical University Hospital, Riga); Lithuania (Lithuanian Bioethics Committee, Vilnius); Poland (Komisja Bioetyczna przy Uniwersytecie Medycznym, Poznań); Spain (Comité de Ética de Investigación con Medicamentos, Madrid Centro Actividades Ambulatoria); Ukraine (Ethical Committee at Prykarpatsky Regional Clinical Oncology Center of Ivano-Frankivsk Regional Rada, Ivano-Frankivsk); United States (IntegReview IRB, Austin, TX; The University of Texas MD Anderson Cancer Center Institutional Review Board,

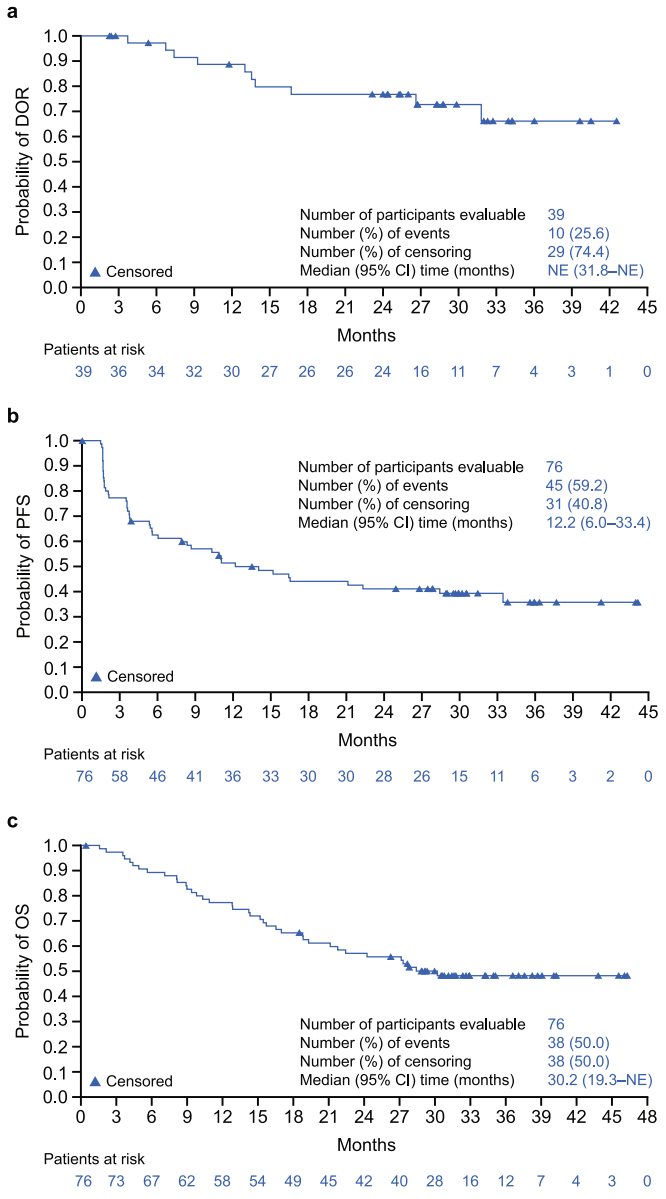

Fig. 3. Kaplan-Meier estimates of a) DOR, b) PFS, and c) OS in patients with centrally confirmed MSI-H/dMMR endometrial cancer. DOR and PFS were determined by IRC according to RECIST v1.1. CI = confidence interval; dMMR = mismatch repair deficient; DOR = duration of response; IRC = independent review committee; MSI-H = microsatellite instability-high; NE = not estimable; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

Houston, TX). All patients provided written informed consent before enrolling in the study.

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CRediT authorship contribution statement

Dominique Berton: Writing – review & editing, Investigation, Data curation. **Patricia Pautier:** Writing – review & editing, Investigation, Data curation. **Domenica Lorusso:** Writing – review & editing, Investigation, Data curation. **Christine Gennigens:** Writing – review & editing, Investigation, Data curation. **Laurence Gladieff:** Writing – review & editing, Investigation, Data curation. **Anna Kryzhanivska:** Writing – review & editing, Investigation, Data curation. **Jill Bowman:** Writing – review & editing, Writing – original draft, Formal analysis. **Chuan Tian:** Writing – review & editing, Formal analysis. **Mark Cornfeld:** Writing – review & editing, Writing – original draft, Formal analysis. **Toon Van Gorp:** Writing – review & editing, Investigation, Data curation.

Data availability

Incyte Corporation (Wilmington, DE, USA) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymized datasets owned by Incyte for the purpose of conducting legitimate scientific research. Researchers may request anonymized datasets from any interventional study (except phase I studies) for which the product and indication have been approved on or after January 1, 2020 in at least one major market (eg, US, EU, JPN). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte's clinical trial data sharing policy and instructions for submitting clinical trial data requests are available at: https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trial-data-sharing.pdf?ver=2020-05-21-132838-960.

Declaration of competing interest

Patricia Pautier received travel funding from Amgen, AstraZeneca, GlaxoSmithKline, MSD, Novartis, PharmaMar, and Tesaro; had an advisory role with AstraZeneca, Genmab, MSD, Onxeo, PharmaMar, and Roche; and received honoraria from AstraZeneca, Eisai, MSD, and PharmaMar. **Domenica Lorusso** had consultancy roles with Novartis and PharmaMar; had advisory and invited speaker roles with AstraZeneca, Clovis Oncology, Genmab, GlaxoSmithKline, ImmunoGen, MSD, and Seagen; received institutional support from Clovis Oncology, Corcept, Genmab, ImmunoGen, and MSD; and received grants for academic trials from Clovis Oncology, GlaxoSmithKline, and MSD. **Christine Gennigens** received a grant from AstraZeneca, GlaxoSmithKline; received consulting fees from Ispen, GlaxoSmithKline, and MSD; received honoraria for lectures from AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Ipsen, MSD, Pfizer, and PharmaMar; received support for meetings and/or travel from GlaxoSmithKline, Ipsen, MSD, Pfizer, and PharmaMar; and participated in a data safety monitoring board/advisory board for AstraZeneca, Bristol Myers Squibb, Eisai, GlaxoSmithKline, Ipsen, and MSD. **Laurence Gladieff** participated in an advisory board for AstraZeneca, Clovis Oncology, GlaxoSmithKline, and MSD; received honoraria from AstraZeneca, GlaxoSmithKline, MSD, PharmaMar, and Roche; and received congress funding from GlaxoSmithKline, PharmaMar, Roche, and Viatris. **Jill Bowman**, **Chuan Tian**, and **Mark Cornfeld** have employment and stock ownership at Incyte Corporation. **Toon Van Gorp** received consulting fees from AstraZeneca, BionTech, Eisai, GlaxoSmithKline, ImmunoGen, Incyte, Karyopharm, MSD, OncXerna, Seagen, Tubulis, and Zentalis; had corporate-sponsored research from Amgen, AstraZeneca, and Roche; and received honoraria for lectures from GlaxoSmithKline, ImmunoGen, and MSD. All payments were via the institution. **Dominique Berton** and **Anna Kryzhanivska** have no conflict of interest related to this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2024.05.025.

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