

Retifanlimab (INCMGA00012) in Patients With Recurrent MSI-H or dMMR Endometrial Cancer: Results From the POD1UM-101 Study

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Introduction

- Recurrent or metastatic endometrial cancer has limited treatment options and poor prognosis, with 5-year survival rate around 17%¹
- Approximately 25% of endometrial cancers are microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)²
 - Tumors characterized by abnormalities in DNA repair are associated with high numbers of neoantigens, making immunotherapy with programmed cell death protein 1 (PD-1) inhibitors an attractive option³
- Retifanlimab (INCMGA00012) is an investigational humanized immunoglobulin G4 monoclonal antibody against human PD-1,⁴ with safety and preliminary clinical activity representative of the PD-1 inhibitor class^{5–8}
 - In the ongoing first-in-human POD1UM-101 study (NCT03059823), retifanlimab monotherapy demonstrated acceptable tolerability and durable clinical activity in multiple advanced tumor types, including pretreated endometrial cancer⁹
 - A preplanned interim analysis of patients in POD1UM-101 with recurrent MSI-H or dMMR endometrial cancer demonstrated that retifanlimab was well tolerated with encouraging antitumor activity⁶
- The present analysis reports safety and clinical activity from the full cohort of patients with MSI-H or dMMR recurrent endometrial cancer from POD1UM-101

Objectives

Primary

- Safety and tolerability

Secondary

- Antitumor activity assessed by objective response rate, duration of response (DOR), progression-free survival (PFS), and overall survival (OS)

Methods

Figure 1. POD1UM-101 Cohort H: Enrolled Patients and Treatment

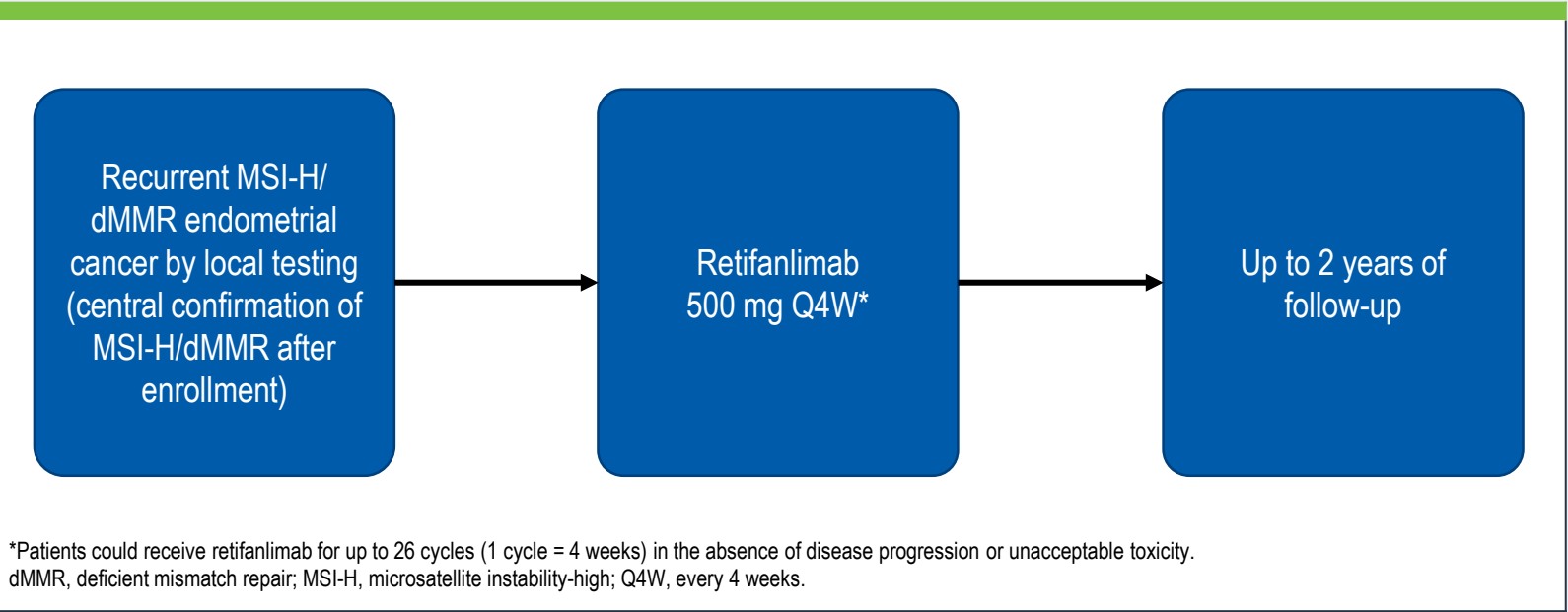


Table 1. Patient Eligibility Criteria (MSI-H or dMMR Endometrial Cancer Cohort)

Inclusion	Patients ≥18 years of age with histologically proven, unresectable recurrent endometrial cancer that was MSI-H or dMMR based on local testing (either by PCR or IHC)	Patients ≥18 years of age with histologically proven, unresectable recurrent endometrial cancer that was MSI-H or dMMR based on local testing (either by PCR or IHC)
Inclusion	Measurable disease per RECIST v1.1	Measurable disease per RECIST v1.1
	Disease progression during or following 1 to ≤5 prior systemic treatments	Disease progression during or following 1 to ≤5 prior systemic treatments
Exclusion	Tumor specimen collection for retrospective central confirmation of MSI-H/dMMR status and testing PD-L1 expression	Tumor specimen collection for retrospective central confirmation of MSI-H/dMMR status and testing PD-L1 expression
	Eastern Cooperative Oncology Group performance status 0 or 1	Eastern Cooperative Oncology Group performance status 0 or 1
Exclusion	Adequate liver and renal laboratory parameters	Adequate liver and renal laboratory parameters
	Symptomatic or untreated central nervous system metastases	Symptomatic or untreated central nervous system metastases
Exclusion	Prior treatment with an immune checkpoint inhibitor	Prior treatment with an immune checkpoint inhibitor
	Clinically significant cardiovascular, gastrointestinal, or pulmonary conditions	Clinically significant cardiovascular, gastrointestinal, or pulmonary conditions
Exclusion	Systemic corticosteroids (prednisone ≥10 mg/day) or immunosuppressant drugs within 14 days prior to study drug initiation	Systemic corticosteroids (prednisone ≥10 mg/day) or immunosuppressant drugs within 14 days prior to study drug initiation
	History of suspected autoimmune disease	History of suspected autoimmune disease
Exclusion	Known positive HIV status, or active HBV or HCV infection	Known positive HIV status, or active HBV or HCV infection

dMMR, deficient mismatch repair; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IHC, immunohistochemistry; MSI-H, microsatellite instability-high; PCR, polymerase chain reaction; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors.

Assessments

- Safety and tolerability were evaluated based on adverse events (AEs) per Common Terminology Criteria for Adverse Events version 4.03
 - AEs of special interest include grade ≥3 infusion-related reactions or cytokine release syndrome, grade ≥2 immune-related AEs, and abnormal liver enzymes that meet the criteria for potential Hy's law
- Evaluation of disease response was done every 8 weeks for the first 24 weeks and every 12 weeks thereafter. Response was assessed by independent central review (ICR) per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1

Statistical Analyses

- Kaplan-Meier methods were used to estimate DOR, PFS, and OS curves, and median DOR, PFS, and OS times
- The Brookmeyer and Crowley method was used to construct 95% confidence intervals for median DOR, PFS, and OS times

Results

Patients

- As of the cutoff date of July 6, 2021, 76 patients had received ≥1 dose of retifanlimab; centrally confirmed with MSI-H (65 [85.5%], by polymerase chain reaction) or dMMR (11 [14.5%], by immunohistochemistry)
- Patient demographics and disease characteristics are presented in Table 2
- At the data cutoff, 2 patients (2.6%) had completed treatment and 30 (39.5%) remained on treatment
 - Forty-four of 76 patients (57.9%) discontinued treatment; primary reasons for discontinuation were radiographic disease progression (n = 29, 38.2%) and AEs (n = 9, 11.8%). Other reasons for discontinuation were clinical progression (n = 2, 2.6%), death (n = 2, 2.6%), withdrawal by patient (n = 1, 1.3%), and other (confirmed immune-related complete response after 6 months of treatment; n = 1, 1.3%)

Drug Exposure

- Patients received a median of 9 (range, 1–26) infusions of retifanlimab 500 mg every 4 weeks
- Median duration of treatment was 7.4 (range, 0.03–23.0) months

Table 2. Baseline Characteristics of MSI-H or dMMR Endometrial Cancer Cohort

Variable	N = 76
Age, median (range), years	67 (49–88)
Race, n (%)	
White	56 (73.7)
Other*	20 (26.3)
ECOG PS, [†] n (%)	
0 / 1	28 (36.8) / 45 (59.2)
Tumor stage at study entry, n (%)	
Locally advanced	9 (11.8)
Metastatic	67 (88.2)
Visceral metastases, n (%)	61 (80.3)
Histology, n (%) [‡]	
Endometrioid carcinoma	70 (92.1)
Mixed carcinoma	2 (2.6)
MSI-H / dMMR, n (%) [§]	65 (85.5) / 11 (14.5)
PD-L1 TPS, n (%) [§]	
<1% / ≥1%	55 (72.4) / 20 (26.3)
Prior systemic therapy in any disease setting, n (%)	75 (98.7)
Prior systemic therapy for advanced disease, n (%)	73 (96.1)
1 line of prior systemic therapy for advanced disease, n (%)	50 (65.8)
2 lines of prior systemic therapy for advanced disease, n (%)	17 (22.4)
≥3 lines of prior systemic therapy for advanced disease, n (%)	6 (7.9)
Prior radiotherapy, n (%)	54 (71.1)
Prior surgery, n (%)	68 (89.5)

*Includes Asian (n = 1). Other including patients in France where race data could not be collected (n = 18), and Unknown (n = 1). [†]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. [‡]One patient each had clear cell carcinoma and serous carcinoma, and 2 patients had "other." [§]Based on central testing. ^{||}All received platinum-based therapy except for 5 patients. dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group performance status; MSI-H, microsatellite instability-high; PD-L1, programmed death ligand 1; TPS, tumor proportion score.

Safety and Tolerability

- Seventy-four patients (97.4%) had at least 1 treatment-emergent adverse event (TEAE; all-grade, regardless of causality; Table 3), with asthenia being the most common AE (n = 23, 30.3%)
- Eleven patients (14.5%) experienced grade ≥3 treatment-related TEAEs (Table 4); none were reported in more than 1 patient
- Immune-related AEs (Table 5) led to study drug discontinuation in 4 patients (5.3%; n = 1 each of autoimmune hepatitis, hepatitis, myositis, and polymyalgia rheumatica)

Table 3. Summary of Adverse Events

Adverse Event, n (%)	N = 76
Adverse events (all grade, treatment-related and -unrelated)	74 (97.4)
Treatment-related adverse event	62 (81.6)
Grade ≥3 adverse events (treatment-related and -unrelated)	33 (43.4)
Grade ≥3 treatment-related adverse event	11 (14.5)
Serious adverse events (all grade, treatment-related and -unrelated)	30 (39.5)
Serious treatment-related adverse event	4 (5.3)
Adverse events leading to drug discontinuation*	9 (11.8)
Adverse events leading to drug interruption [†]	21 (27.6)
Adverse events leading to death (all unrelated to treatment) [‡]	2 (2.6)
Adverse events of special interest (all immune-related)	18 (23.7)
Grade ≥3 treatment-related adverse events of special interest	7 (9.2)
Serious treatment-related adverse events of special interest	4 (5.3)

*Diarrhea, dry mouth, autoimmune hepatitis, hepatitis, myositis, polymyalgia rheumatica (n = 1 patient each, considered treatment related); large intestinal stenosis, renal failure, and transitional cell carcinoma (n = 1 patient each, not considered treatment related). [†]Diarrhea and erysipelas led to interruption in 2 patients each. The rest of the adverse events that led to drug interruption occurred in 1 patient each. [‡]One patient had a fatal adverse event of large intestinal stenosis and 1 had a fatal adverse event of renal failure.

Table 4. Treatment-Related Adverse Events Occurring in ≥5% of Patients

Adverse Event, n (%)	N = 76	
	Any Grade	Grade ≥3
Any event	62 (81.6)	11 (14.5)*
Fatigue	14 (18.4)	0
Pruritus	12 (15.8)	0
Diarrhea	11 (14.5)	1 (1.3)
Asthenia	11 (14.5)	0
Rash	8 (10.5)	1 (1.3)
Arthralgia	7 (9.2)	0
Hypothyroidism	7 (9.2)	0
Hyperthyroidism	6 (7.9)	0
Decreased appetite	5 (6.6)	0
Rash pruritic	4 (5.3)	0

*Includes 1 patient with alanine aminotransferase increased, aspartate aminotransferase increased, lymphopenia, and myositis; 1 patient with amylase increased and lipase increased; 1 patient with arthritis, diarrhea, and pneumonitis; 1 patient with hepatitis; 1 patient with acute kidney injury; 1 patient with anemia; 1 patient with autoimmune hepatitis; 1 patient with dry mouth; 1 patient with hypertension; 1 patient with hypokalemia; and 1 patient with rash.

Table 5. Potential Immune-Related TEAEs Occurring in ≥2 Patients*

Adverse Event, n (%)	N = 76	
	Any Grade	Grade ≥3
Any event	29 (38.2)	7 (9.2)
Hyperthyroidism	8 (10.5)	0
Skin reactions [†]	8 (10.5)	1 (1.3)
Hypothyroidism	7 (9.2)	0
Hepatitis [‡]	3 (3.9)	2 (2.6)
Pneumonitis [§]	3 (3.9)	1 (1.3)
Acute kidney injury	2 (2.6)	2 (2.6)

Immune-related TEAEs were identified using predefined preferred terms, and patients were counted only once under each group term and preferred term. [†]No immune-related TEAEs with fatal outcome have occurred in the study. [‡]Skin reactions includes the terms: pruritus (n = 4), rash (n = 2), rash pruritic (n = 1), and toxic skin eruption (n = 1). [§]Hepatitis includes the terms: hepatitis (n = 2) and autoimmune hepatitis (n = 1); 1 grade 3 hepatitis based on laboratory abnormalities without symptom after cycle 19 and assessed as possibly related to study treatment or to treatment with amoxicillin per the investigator. 1 autoimmune hepatitis based on isolated grade 2/3 liver function abnormalities 3 weeks after first dose assessed as possibly related to study treatment per the investigator (no pathological evidence of immune-mediated hepatitis observed in both cases). ^{||}Pneumonitis includes the terms: pneumonitis (n = 2) and interstitial lung disease (n = 1). TEAE, treatment-emergent adverse event.

Antitumor Activity

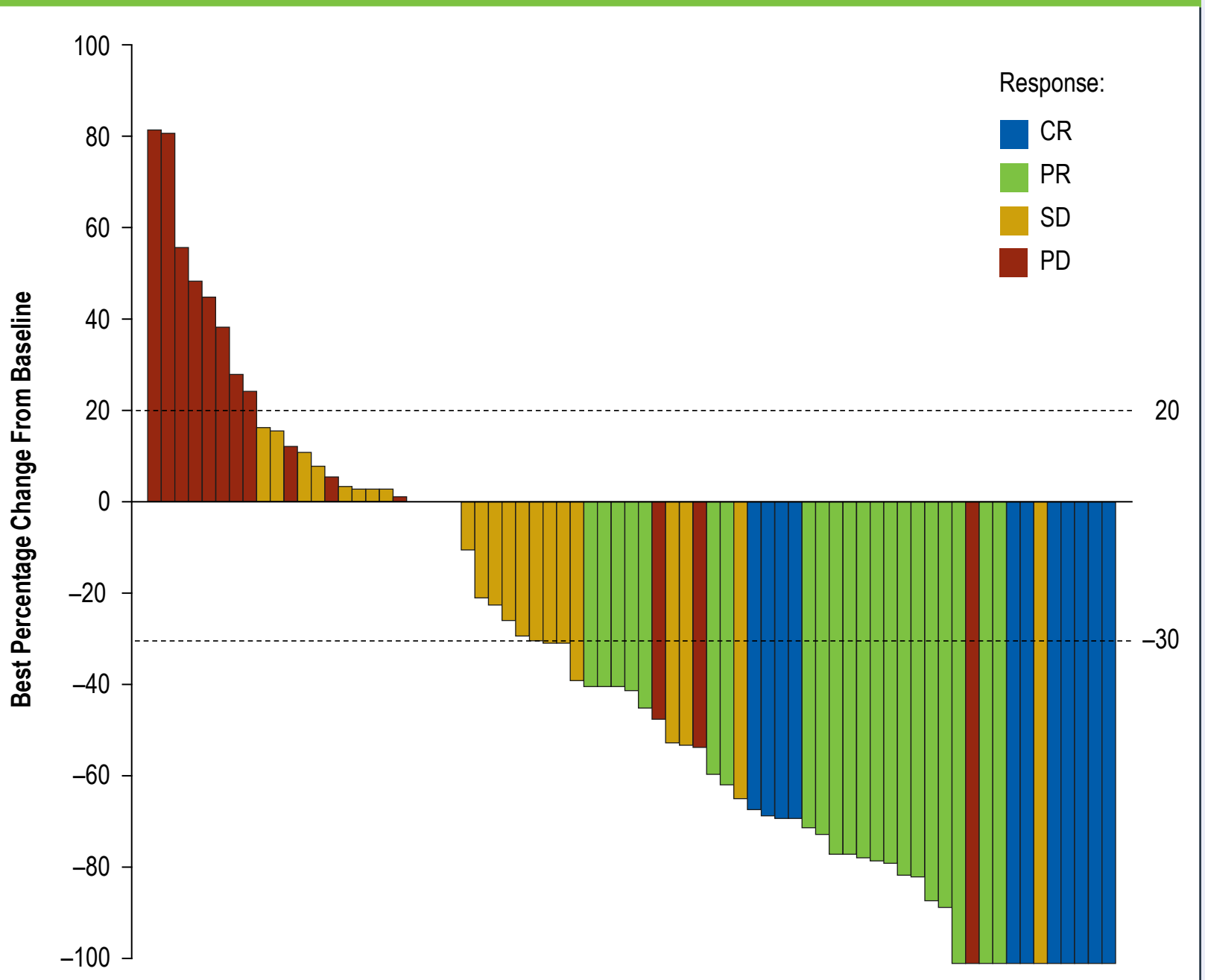
- Seventy-four patients were assessable for response by ICR at the time of this analysis
- After a median follow-up for response of 8.4 (range, 1.9–28.3) months, confirmed responses per RECIST were observed in 33 of 76 patients (Table 6)
- The best percentage change from baseline in target lesion size among evaluable patients is shown in Figure 2
 - Fourteen out of 22 patients (64%) with confirmed PR had over 70% tumor size reduction
- Treatment durations of individual evaluable patients are shown in Figure 3
 - Twenty-nine of 33 responders remain on treatment
- Six patients had sustained response after discontinuing treatment
 - At data cutoff (July 6, 2021), DORs by ICR from the time of treatment discontinuation ranged from 3.0 to 24.9 months for these 6 patients

Table 6. Summary of Overall Response by ICR According to RECIST v1.1

Variable	N = 76
Confirmed objective response rate (95% CI), %	43.4 (32.1–55.3)
Best objective response, n (%)	
Complete response	11 (14.5)
Partial response	22 (28.9)
Stable disease	25 (32.9)
Progressive disease	16 (21.1)
Missing*	2 (2.6)
DOR	
Median DOR	Not reached
DOR ≥6 months, n (%)	25 (75.8)
Disease control rate (95% CI), %	76.3 (65.2–85.3)
Median progression-free survival (95% CI), months	11.0 (5.6–NE)
Median overall survival (95% CI), months	NE (19.3–NE)

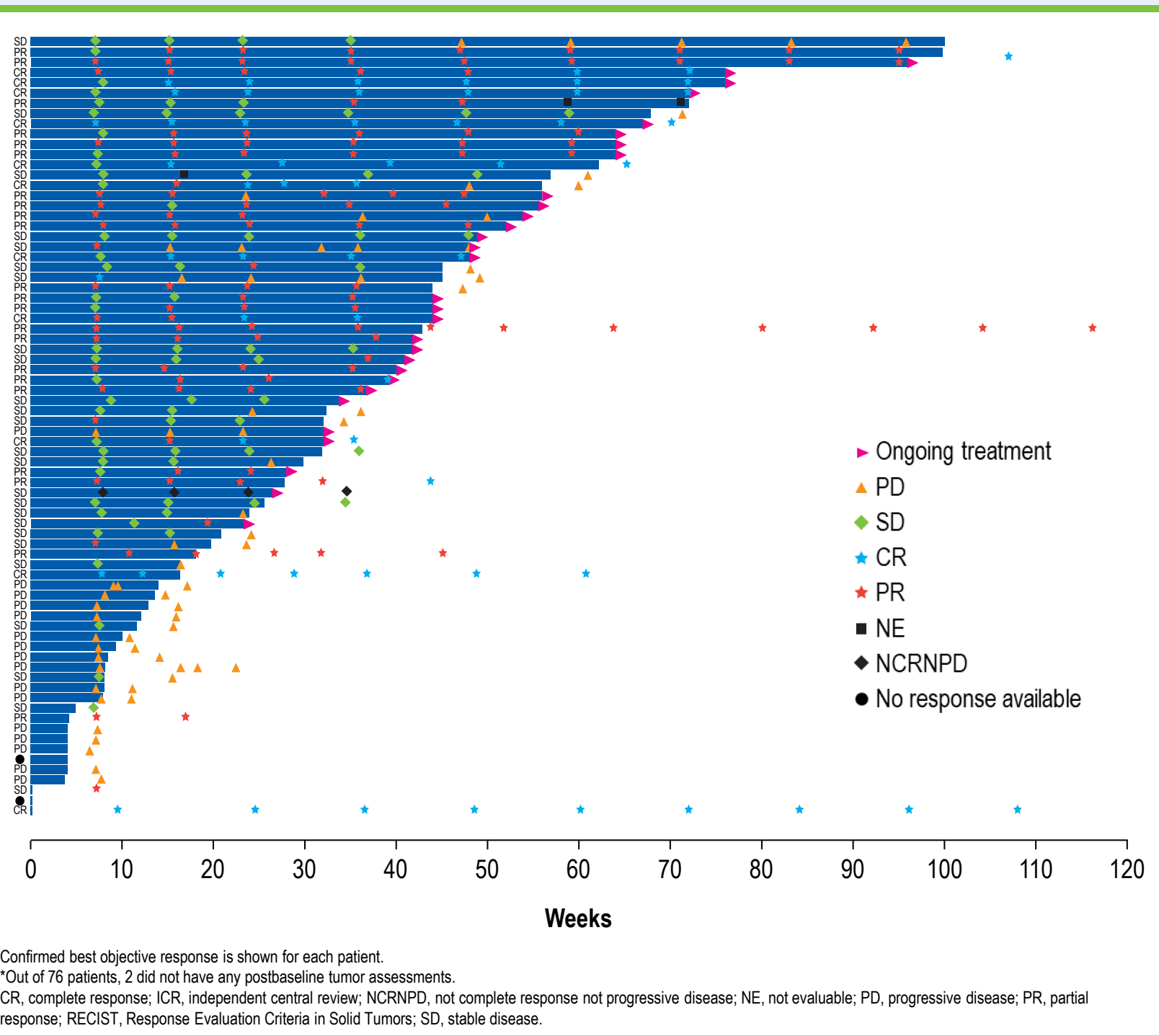
*Two patients had no postbaseline assessment available. CI, confidence interval; DOR, duration of response; ICR, independent central review; NE, not estimable; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 2. Best Percentage Change From Baseline in Sum of Target Lesion Size by ICR (Full Analysis Set)*



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). *Out of 76 patients enrolled in the study, 5 patients not included in the plot had either missing baseline or postbaseline target lesion assessments or different imaging methods were used. 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. CR, complete response; ICR, independent central review; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 3. Duration of Treatment and Best Objective Response by ICR According to RECIST v1.1 (Full Analysis Set)*



Confirmed best objective response is shown for each patient. *Out of 76 patients, 2 did not have any postbaseline tumor assessments. CR, complete response; ICR, independent central review; NCRNPD, not complete response not progressive disease; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Conclusions

- Retifanlimab was well tolerated in patients with pretreated, centrally confirmed recurrent MSI-H/dMMR advanced endometrial cancer, with no new safety signals^{5,6}
 - AEs of special interest, including immune-related AEs, are consistent with available clinical experience with PD-1/PD-L1 inhibitors^{9,10}
- Retifanlimab demonstrated encouraging antitumor activity that is consistent with previously reported activity from other immune checkpoint inhibitors in this population^{9,10}
 - With a median follow-up of 8.4 months, confirmed responses were observed in 43.4% of patients (including 11 CRs, 22 PRs)
 - DCR was 76.3%
 - Median DOR was not reached and 75.8% of patients had DOR ≥6 months
- These findings support further clinical investigation of retifanlimab, either alone or in combination therapy, in patients with endometrial cancer

Disclosures

Berton, Kryzhanivska: Nothing to disclose. Pautier: Travel – AstraZeneca, MSD, Novartis, Tesaro; Advisory board – AstraZeneca, Novartis, Tesaro; Honoraria – AstraZeneca, MSD, Tesaro. Lorusso: Consultancy – Amgen, PharmaMar; Advisory board and invited speaker – AstraZeneca, GSK, MSD; Invited speaker – Clovis Oncology; ENGOT trial with institutional support for coordination – Clovis Oncology, Genmab; Grant for founding academic trial – Clovis Oncology, GSK, MSD. Gennigens: Grants – AstraZeneca, MSD, PharmaMar, Roche; Personal fees – AstraZeneca, BMS, Eli Lilly & Company, GSK, Ipsen, MSD, Novartis, Pfizer, Roche; Non-financial support – Ipsen, Pfizer, PharmaMar, Roche, Gladiéff; Advisory board – AstraZeneca, Clovis Oncology, GSK, MSD, Honoraria – AstraZeneca, GSK, MSD, PharmaMar, Roche; Congress funding – GSK, PharmaMar, Roche, Viartis. Ranganathan, Tian, Bourayou: Employment and stock ownership – Incyte Corporation. Vergote: Consultant – Amgen (Europe) GmbH, AstraZeneca, Clovis Oncology, Carisq Therapeutics, Deciphera Pharmaceuticals, MSD, Octmet Oncology NV, Oncovient, PharmaMar, Solio, Tesaro, Verastem Oncology; Contracted research (via KU Leuven) – Genmab, Oncovient; Grant (corporate-sponsored research) – Amgen, Roche; Accommodation, travel expenses – Amgen, AstraZeneca, MSD, Roche, Tesaro.

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