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Dostarlimab in Advanced/Recurrent Mismatch Repair Deficient/Microsatellite Instability High or Proficient/Stable Endometrial Cancer: The GARNET Study

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Declaration of Interests

Dr. Oaknin reports consulting fees from AstraZeneca, Deciphera Pharmaceuticals, Genmab, GlaxoSmithKline, Immunogen, Mersana Therapeutics, MSD, Roche, and Sutro; institutional grants from Abbie Deutchland, Ability Pharmaceuticals, Advaxis Inc, Aeterna Zentaris, Amgen SA, Aprea Therapeutics AB, Bristol Meyers Squibb, Clovis Oncology Inc, Eisai Ltd, F. Hoffmann - La Roche Ltd, GlaxoSmithKline, Immunogen Inc, Merck Sharp & Dohme de Espana SA, Millennium Pharmaceuticals Inc, PharmaMar, and Regeneron Pharmaceuticals; and travel support from AstraZeneca, Clovis Oncology Inc, PharmaMar, and Roche.

Dr. Gilbert reports honoraria from AstraZeneca, Merck, and Pfizer. **Dr. Tinker** reports institutional grants from AstraZeneca; and personal fees from AstraZeneca and Eisai. **Dr. Brown** reports honoraria from Olympus; consulting or advisory role at AstraZeneca, Caris, Clovis, Genentech, and GlaxoSmithKline; and speakers' bureau at Clovis. **Dr. Mathews** reports institutional grants from GlaxoSmithKline. **Dr. Press** reports speaker's bureau compensation from AstraZeneca. **Dr. Sabatier** reports institutional grants from AstraZeneca and Eisai; personal fees from AstraZeneca, GlaxoSmithKline, Novartis, Pfizer, and Roche; and nonfinancial support from Amgen, AstraZeneca, Pfizer, and Roche. **Dr. O'Malley** reports personal fees from consulting and/or advisory board member from Abbvie, Agenus, Ambry, Amgen, AstraZeneca, Clovis, Eisai, Elevar, Genentech/Roche, GOG Foundation, Immunogen, Iovance Biotherapeutics, Janssen/J&J, Merck, Mersana, Myriad Genetics, Novartis, Novocure, Regeneron, Rubis, SeaGen, Tarveda, Tesaro/GSK; research funding (all funding to institution) from Abbvie, Agenus, Ajinomoto Inc., Amgen, Array Biopharma, AstraZeneca, BBI, Bristol Myers Squibb Co, Cerulean Pharma, Clovis, Eisai, EMD Serono, Ergomed, Genentech/Roche, GenMab, GOG Foundation, Immunogen, INC Research Inc, inVentiv Health Clinical, Iovance Biotherapeutics Inc, Janssen/J&J, Ludwig Cancer Research, Merck, Mersana, NCI, New Mexico Cancer Care Alliance, Novocure, PRA Intl, Regeneron, SeaGen, Serono Inc, Stemcentrx Inc, Tesaro/GSK, Tracon Pharmaceuticals, VentiRx, and Yale University. **Dr. Samouëlian** has nothing to disclose. **Dr. Boni** reports consulting or advisory roles at Guidepoint Global and OncoArt; speakers' bureau fees from Solti; travel support from START; honoraria from IDEAYA Biosciences and Loxo; and institutional grants from Abbvie, Adaptimmune, Alkermes, Amgen, Array BioPharma, AstraZeneca, Bayer, BioNTech AG, Boehringer Ingelheim, Boston Biomedical, Bristol Myers Squibb, CytomX Therapeutics, Genmab, GlaxoSmithKline, Incyte, Janssen Oncology, Kura Oncology, Lilly, Loxo, Menarini, Merck, Merus, Novartis, Pfizer, Pumo Biotechnology, Roche/Genentech, Sanofi, Seattle Genetics, Synthon, and Zenith Epigenetics. **Dr. Duska** reports personal fees from Advance Medical, ASCO, AstraZeneca, British Journal of OB/GYN, ClearView Health Care, Cue Biopharma, Elsevier, Genentech/Roche, Innovio, JB Learning, Merck, MorphoTek, National Cancer Institute, Parexel, State of California, and UpToDate; and institutional grants from Abbvie, Aduro BioTech, Advaxis, Cerulean/NextGen, Eisai, Genentech/Roche, GlaxoSmithKline, Inovio, LEAP Therapeutics, Ludwig, Lycera, Merck, Morab, Morphotek, Novartis, Pfizer, and Syndax. **Dr. Ghamande** reports consulting or advisory roles at Seattle Genetics; speakers' bureau fees from GlaxoSmithKline; and institutional research funding from Abbvie, Advaxis, Bristol Myers Squibb, Clovis, Genentech, GlaxoSmithKline, Merck, Roche, Seattle Genetics, and Takeda. **Dr. Ghatage** received an institutional grant from AstraZeneca; and personal fees from AstraZeneca, Eisai, and GSK. **Dr. Kristeleit** reports personal fees from GlaxoSmithKline. **Dr. Leath** reports contracted research for GlaxoSmithKline; and scientific advisory board fees from AbbVie, Clovis Oncology, Eisai, GlaxoSmithKline, and Seattle Genetics. **Drs. Veneris, Duan, and Im** are employees of GlaxoSmithKline. **Dr. Pothuri** reports institutional grants support from AstraZeneca, Clovis Oncology, Genentech/Roche, Karyopharm, Merck, Celsion, Mersana, and Tesaro/GSK; and advisory board fees from Arquer Diagnostics, AstraZeneca, Clovis Oncology, Eisai, Elevar Therapeutics, Merck, Mersana, Sutro Biopharma, Tesaro/GSK, and Toray.

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Background

- EC is the most common gynaecologic malignancy in the US and EU[1]
- Treatment options are limited for patients with disease progression that occurs on or after first-line therapy, and overall survival is typically <1 year
- Dostarlimab is an anti–PD-1 monoclonal antibody
  - In the EU, dostarlimab is approved as a monotherapy in adult patients with recurrent or advanced dMMR/MSI-H EC that has progressed on or after treatment with a platinum-containing regimen
  - In the US, dostarlimab is approved as a monotherapy in adult patients with the following:
    - dMMR recurrent or advanced EC that has progressed on or after a platinum-containing regimen
    - a dMMR solid tumour that has progressed on or after prior treatment and who have no satisfactory alternative treatment options
- Today, we present GARNET Trial outcomes from the 2 endometrial cancer cohorts:
  - The cohort A1 data presented are the data that were used to support the EU approval in dMMR/MSI-H EC

dMMR, mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability high; PD-1, programmed death 1.

1. Siegel RL, et al. *CA Cancer J Clin*. 2016;66:7–30.

GARNET Trial Design

- GARNET is a phase 1, single-arm study of dostarlimab monotherapy in multiple tumour types
- In part 2B, dostarlimab was dosed at the recommended therapeutic dose determined from parts 1 and 2A
  - 500 mg IV Q3W for 4 cycles, then 1000 mg Q6W until disease progression or discontinuation
- Primary endpoints were ORR and DOR
- Data cutoff date was March 1, 2020

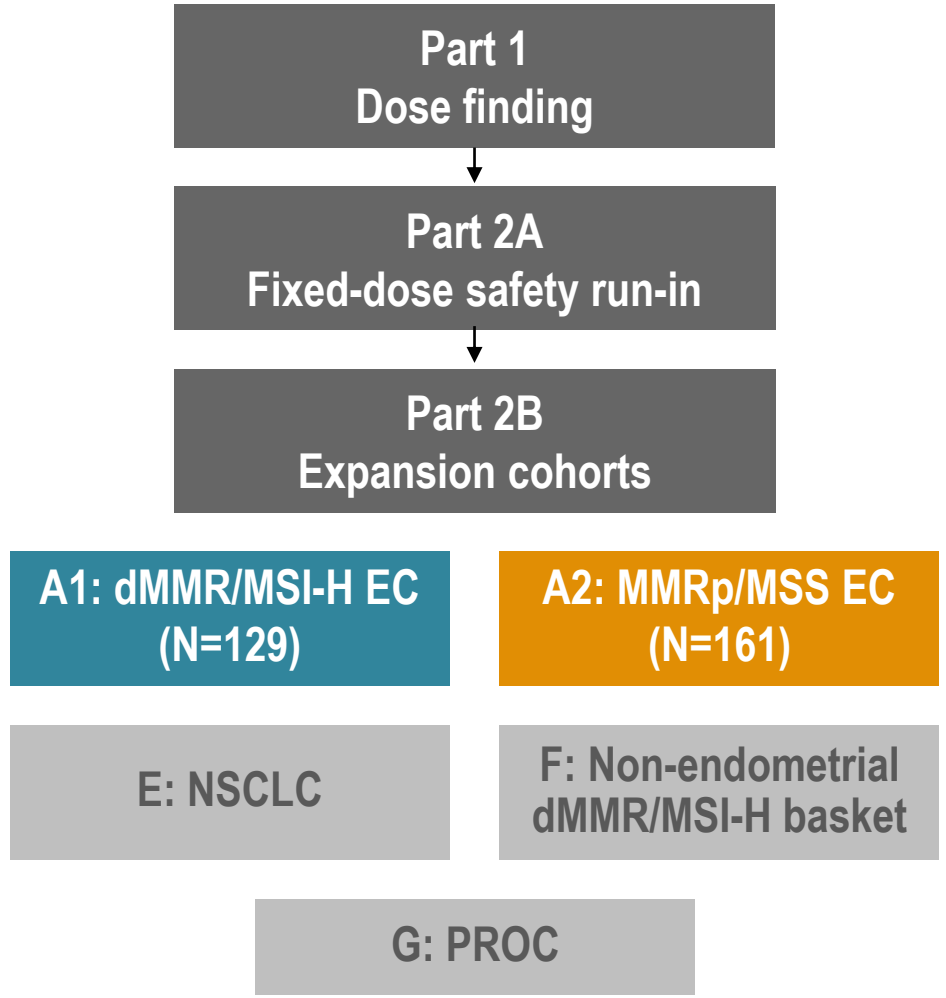
Key inclusion criteria:

– Patients must have progression on or after platinum doublet therapy

– Patients must have received ≤2 prior lines of treatment for recurrent or advanced disease

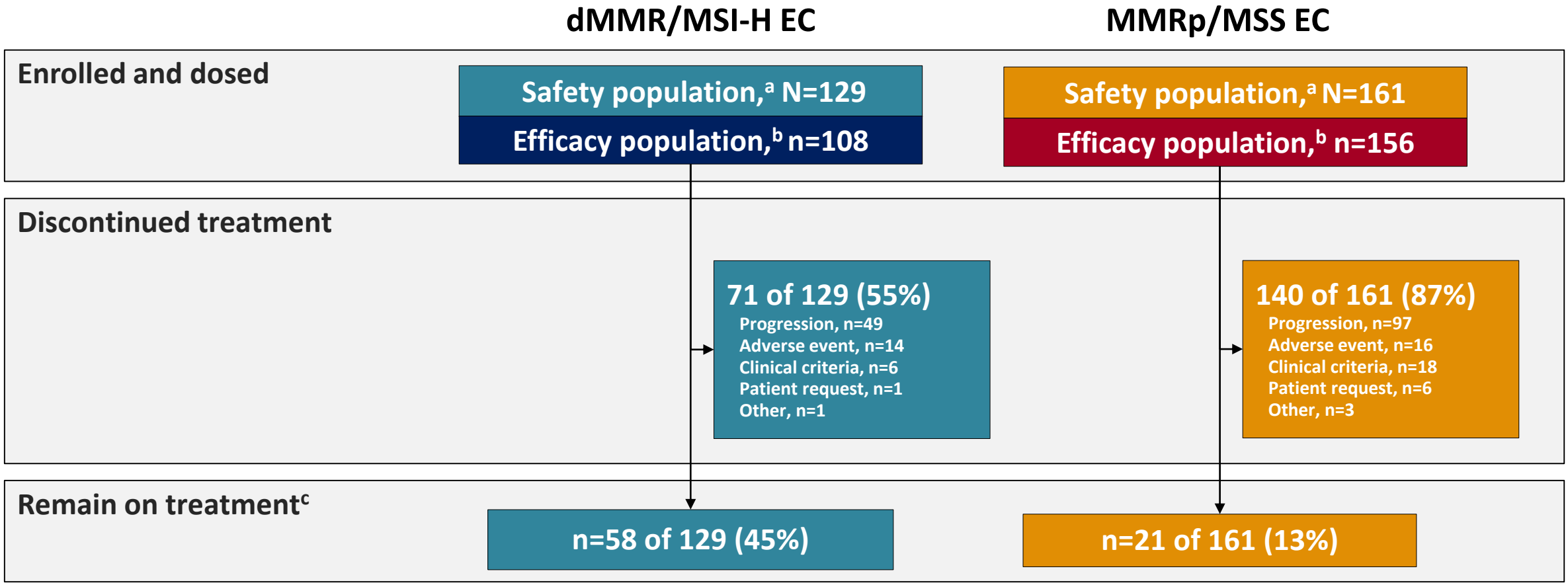
– Patients must have measurable disease at baseline

– Patients must be anti–PD-(L)1 naive



dMMR, mismatch repair deficient; MMRp, mismatch repair proficient; MSI-H, microsatellite instability high; MSS, microsatellite stable; NSCLC, non–small cell lung cancer; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PROC, platinum-resistant ovarian cancer.

Enrolment and Outcomes



[a]Safety population includes all patients who received ≥1 dose of dostarlimab; [b]Efficacy population includes all patients with measurable disease at baseline and ≥24 weeks of follow-up and an additional 3 patients with <24 weeks of follow-up who had discontinued treatment prior to 24 weeks; [c]Data cutoff date: March 1, 2020.
dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; MSI-H, microsatellite instability high; MSS, microsatellite stable.

Demographics and Baseline Characteristics

Characteristic	dMMR/MSI-H EC (n=108)	MMRp/MSS EC (n=156)
Age, median (IQR), years	64.5 (58.5–69.5)	64.5 (30–86)
FIGO stage at primary diagnosis, n (%)		
Stage I	41 (38.0)	46 (29.5)
Stage II	9 (8.3)	11 (7.1)
Stage III	38 (35.2)	43 (27.6)
Stage IV	20 (18.5)	55 (35.3)
Unknown	0	1 (0.6)
Histologic subtype, n (%)		
Grade 1 or 2 endometrioid carcinoma	71 (65.7)	35 (22.4)
Serous	5 (4.6)	59 (37.8)
Clear cell	1 (0.9)	10 (6.4)
Squamous	1 (0.9)	3 (1.9)
Undifferentiated	4 (3.7)	3 (1.9)
Carcinosarcoma	0	2 (1.3)
Mixed carcinoma	6 (5.6)	11 (7.1)
Type II EC, NOS	14 (13.0)	24 (15.4)
Adenocarcinoma	5 (4.6)	9 (5.8)
Unknown	1 (0.9)	0
Prior lines of therapy, n (%)[a]		
1	69 (63.9)	72 (46.2)
2	27 (25.0)	67 (42.9)
≥3	12 (11.1)	17 (10.9)
Prior radiation, n (%)	77 (71.3)	95 (60.9)

[a]Includes lines of the therapy in the adjuvant setting.
dMMR, mismatch repair deficient; EC, endometrial cancer; FIGO, International Federation of Gynaecology and Obstetrics; IQR, interquartile range; MMRp, mismatch repair proficient; MSI-H, microsatellite instability high; MSS, microsatellite stable; NOS, not otherwise specified.

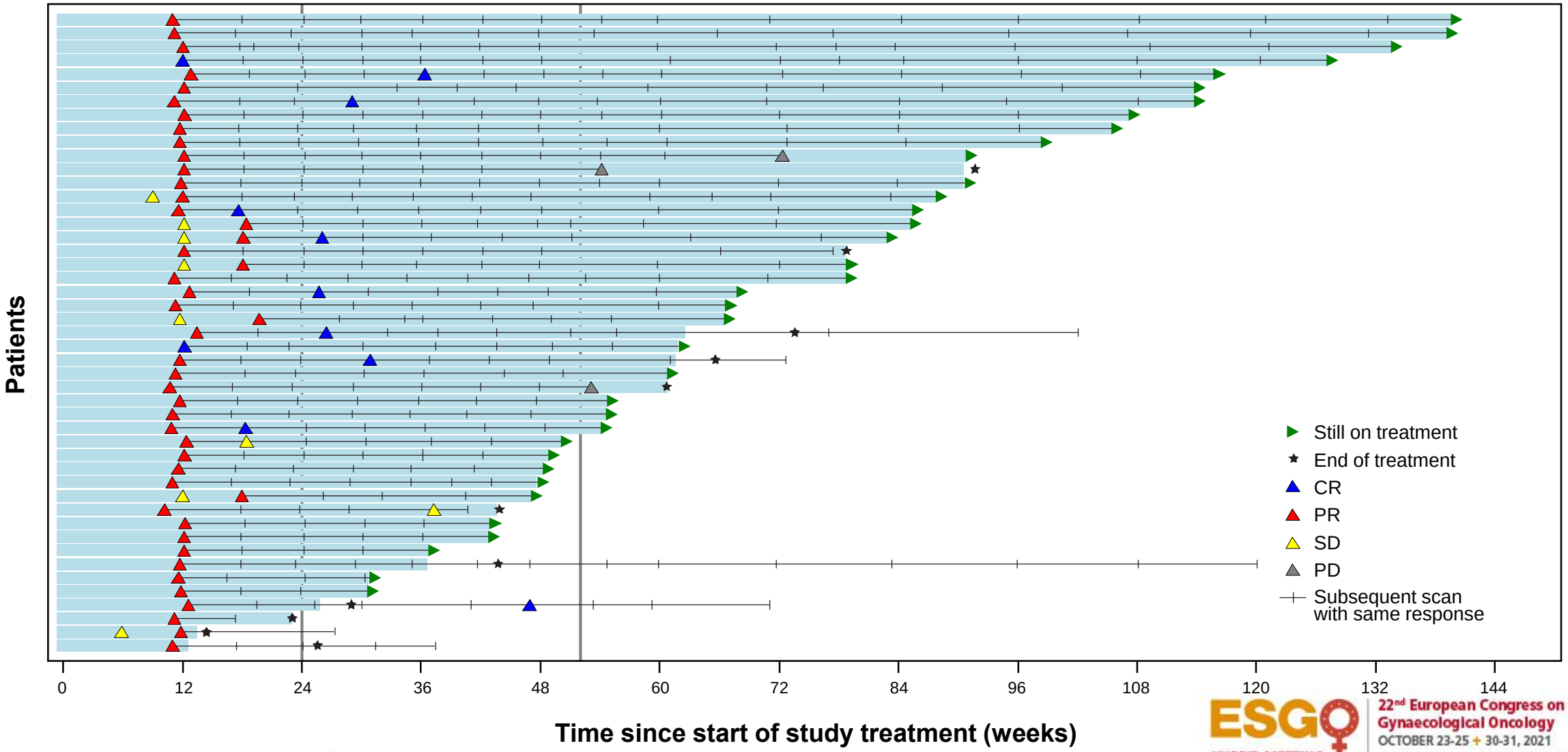
Primary Endpoint Analysis in the Efficacy-Evaluable Population*

Parameter	Cohort A1			Cohort A2		
	dMMR (n=106)	MSI-H and MMRunk (n=2)	Overall (n=108)	MMRp (n=142)	MSS and MMRunk (n=14)	Overall (n=156)
Median follow-up, mo	13.8	11.1	16.3	11.5	10.4	11.5
ORR, n (%)	46 (43.4%)	1 (50.0%)	47 (43.5%)	19 (13.4%)	3 (21.4%)	22 (14.1%)
(95% CI)	(33.8–53.4)	(1.3–98.7)	(34.0–53.4)	(8.3–20.1)	(4.7–50.8)	(9.1–20.6)
Best confirmed response, n (%)						
CR	11 (10.4)	0	11 (10.2)	3 (2.1)	0	3 (1.9)
PR	35 (33.0)	1 (50.0)	36 (33.3)	16 (11.3)	3 (21.4)	19 (12.2)
SD	13 (12.3)	0	13 (12.0)	31 (21.8)	1 (7.1)	32 (20.5)
PD	39 (36.8)	0	39 (36.1)	77 (54.2)	8 (57.1)	85 (54.5)
NE	8 (7.5)	1 (50.0)	9 (8.3)	15 (10.6)	2 (14.3)	17 (10.9)
DCR, n (%)	59 (55.7)	1 (50.0)	60 (55.6)	50 (35.2)	4 (28.6)	54 (34.6)
Response ongoing	41 of 46 (89.1%)	1 of 1 (100%)	42 of 47 (89.4%)	12 of 19 (63.2%)	2 of 3 (66.7%)	14 of 22 (63.6%)
Median DOR	Not reached	Not reached	Not reached	Not reached	Not reached	Not reached

*ORR was determined by blinded independent central review using REECIST v1.1; CR, complete response; DCR, disease control rate; dMMR, mismatch repair deficient; DOR, duration of response; IQR, interquartile range; K-M, Kaplan-Meier; MMRp, mismatch repair proficient; MMRunk, mismatch repair unknown; mo, month; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Duration of Treatment: dMMR/MSI-H EC

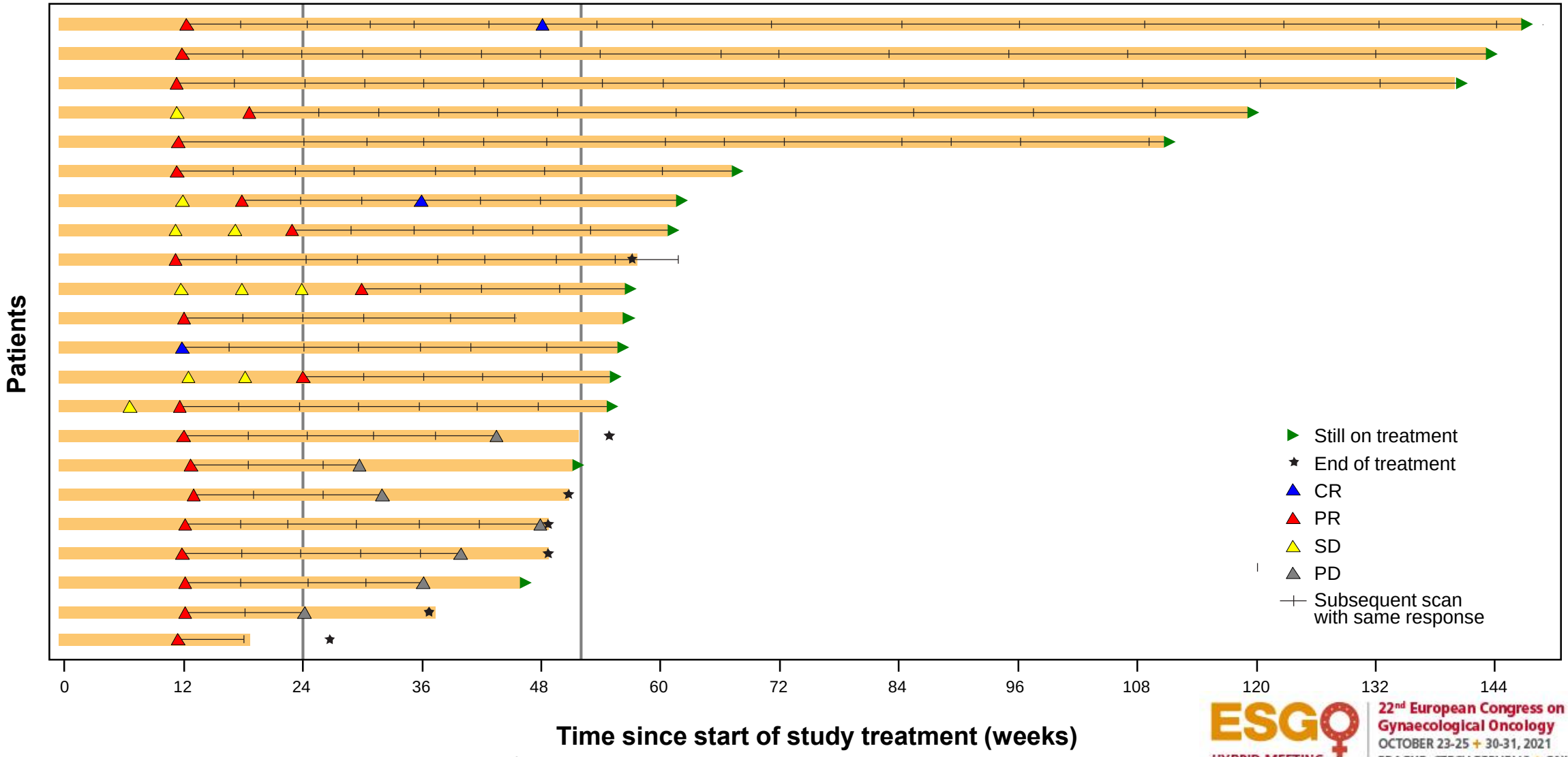
89.3% of responders remained in response as of the data cutoff date (March 1, 2020)
Median follow-up was 16.3 months



CR, complete response; dMMR, mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability-high; PD, progressive disease; PR, partial response; SD, stable disease.

Duration of Treatment: MMRp/MSS EC

63.6% of responders remained in response as of the data cutoff date (March 1, 2020)
Median follow-up was 11.5 months



CR, complete response; EC, endometrial cancer; MMRp, mismatch repair proficient; MSS, microsatellite stable; PD, progressive disease; PR, partial response; SD, stable disease.

Safety Overview

- Dostarlimab treatment was tolerable
  - Only 5.5% of patients discontinued due to a TRAE
  - No treatment related deaths were reported

Parameter, n (%)	dMMR/MSI-H EC (n=129)	MMRp/MSS EC (n=161)	Overall (N=290)
Any-grade TEAE	123 (95.3)	161 (100)	284 (97.9)
Grade ≥3 TEAE	62 (48.1)	90 (55.9)	152 (52.4)
Any-grade TRAE	82 (63.6)	114 (70.8)	196 (67.6)
Grade ≥3 TRAE	17 (13.2)	31 (19.3)	48 (16.6)
Treatment-related SAE	12 (9.3)	13 (8.1)	25 (8.6)
Any TRAE leading to discontinuation	5 (3.9)	11 (6.8)	16 (5.5)
TRAE leading to death	0	0	0

dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Treatment-Related Adverse Events

Parameter, n (%)	MMRp/MSS EC (n=161)	MMRp/MSS EC (n=161)	Overall (N=290)
Most common any-grade TRAE (≥10% cutoff)			
Fatigue	17 (13.2)	34 (21.1)	51 (17.6)
Diarrhoea	21 (16.3)	19 (11.8)	40 (13.8)
Nausea	16 (12.4)	24 (14.9)	40 (13.8)
Asthenia	18 (14.0)	13 (8.1)	31 (10.7)
Most common grade ≥3 TRAE (≥1.4% cutoff)			
Anaemia	5 (3.9)	3 (1.9)	8 (2.8)
Alanine aminotransferase increased	2 (1.6)	2 (1.2)	4 (1.4)
Diarrhoea	2 (1.6)	2 (1.2)	4 (1.4)
Fatigue	0	4 (2.5)	4 (1.4)
Amylase increased	1 (0.8)	3 (1.9)	4 (1.4)
Lipase increased	3 (2.3)	1 (0.6)	4 (1.4)

dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; TRAE, treatment-related adverse event.

Immune-Related Treatment-Related Adverse Events[a]

Parameter, n (%)	dMMR/MSI-H EC (n=129)	MMRp/MSS EC (n=161)	Overall (N=290)
Most common irTRAEs (≥1.4% cutoff)			
Hypothyroidism	8 (6.2)	12 (7.5)	20 (6.9)
Diarrhoea	6 (4.7)	5 (3.1)	11 (3.8)
Amylase increased	3 (2.3)	4 (2.5)	7 (2.4)
Aspartate transaminase increased	2 (1.6)	4 (2.5)	6 (2.1)
Alanine aminotransferase increased	3 (2.3)	2 (1.2)	5 (1.7)
Lipase increased	4 (3.1)	1 (0.6)	5 (1.7)
Hyperthyroidism	3 (2.3)	2 (1.2)	5 (1.7)
Colitis	3 (2.3)	1 (0.6)	4 (1.4)
Hyperglycaemia	0	4 (2.8)	4 (1.4)
Most common grade ≥3 irTRAE (≥1.0% cutoff)			
Alanine aminotransferase increased	2 (1.6)	2 (1.2)	4 (1.4)
Diarrhoea	2 (1.6)	2 (1.2)	4 (1.4)
Amylase increased	1 (0.8)	3 (1.9)	4 (1.4)
Aspartate transaminase increased	0	3 (1.9)	3 (1.0)
Hyperglycaemia	0	3 (1.9)	3 (1.0)
Lipase increased	3 (2.3)	1 (0.6)	4 (1.4)

[a]Grade 2 or higher event from a prespecified list of preferred terms.
dMMR, mismatch repair deficient; EC, endometrial cancer; irTRAE, immune-related treatment-related adverse event; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable.

Conclusions

- Dostarlimab demonstrated an ORR of 43.5% in dMMR/MSI-H EC, and 14.1% in MMRp/MSS EC
  - dMMR/MSI-H status was associated with a higher response rate
  - Responses were durable both dMMR/MSI-H and MMRp/MSS advanced/recurrent EC
- Dostarlimab demonstrated a notable disease control rate (34.6%; 1.9% complete response, 12.2% partial response, 20.5% stable disease) in patients with MMRp/MSS EC
  - The A2 cohort was composed of a higher percentage of patients with non-endometrioid ECs, which is historically associated with a worse prognosis compared with endometrioid EC and limited treatment options
- Safety was consistent with prior experience with dostarlimab
  - No new safety concerns emerged
  - There was low incidence of grade ≥3 TRAES
  - No deaths were attributed to dostarlimab
- Dostarlimab is being evaluated in first-line EC in the RUBY clinical trial (NCT03981796) in combination with standard-of-care chemotherapy

dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable.

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