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Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient (dMMR) or proficient (MMRp) endometrial cancer: Results from GARNET

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DISCLOSURE INFORMATION

Personal financial interests:

Advisory boards: Roche, AstraZeneca, PharmaMar, Clovis Oncology, GlaxoSmithKline, Immunogen, Genmab, Deciphera and Mersana Therapuetics

Support for travel and/or accommodation: Roche, AstraZeneca, Clovis Oncology, GlaxoSmithKline, and PharmaMar

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Leadership roles:

GEICO Executive Board member as a co-chair

GCIG Phase II Committee and Cervix Cancer Committee representative on behalf of GEICO

ESMO 2018 faculty member, Gynaecological Track

ESMO 2019 chair, Gynaecological Track

ESMO 2020 faculty member, Gynaecological Track

Membership: ESMO, ASCO, GCIG, SEOM, GOG

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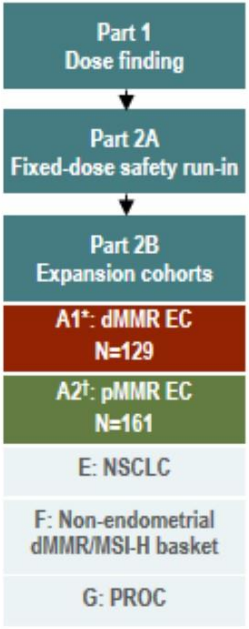
The GARNET Study

GARNET (NCT02715284) is a phase 1, single-arm study of dostarlimab monotherapy in multiple tumor types

- In part 2B, dostarlimab was dosed at the RTD determined from Part 1 and 2A
  - 500 mg IV Q3W for 4 cycles, then 1000 mg IV Q6W until disease progression
- MMR status was determined by local immunohistochemistry
- Primary endpoint: ORR and DOR



Key inclusion/exclusion criteria for cohorts A1 and A2:

- Patients must have progressed 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 naïve
- Patients could be screened based on local MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but patient eligibility needs to be confirmed by MMR IHC results

DOR, duration of response; IHC, immunohistochemistry; MMR, mismatch mutation repair; MSI, microsatellite instability; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; PCR, polymerase chain reaction; PD-(L)1, programmed cell death (ligand) 1; PROC, platinum-resistant ovarian cancer; Q3W, every 3 weeks; Q6W, every 6 weeks; RTD, recommended therapeutic dose.

*Cohort enrollment includes 3 patients with MMRunk/MSI-H disease; †Cohort enrollment includes 16 patients with MMRunk/MSS disease

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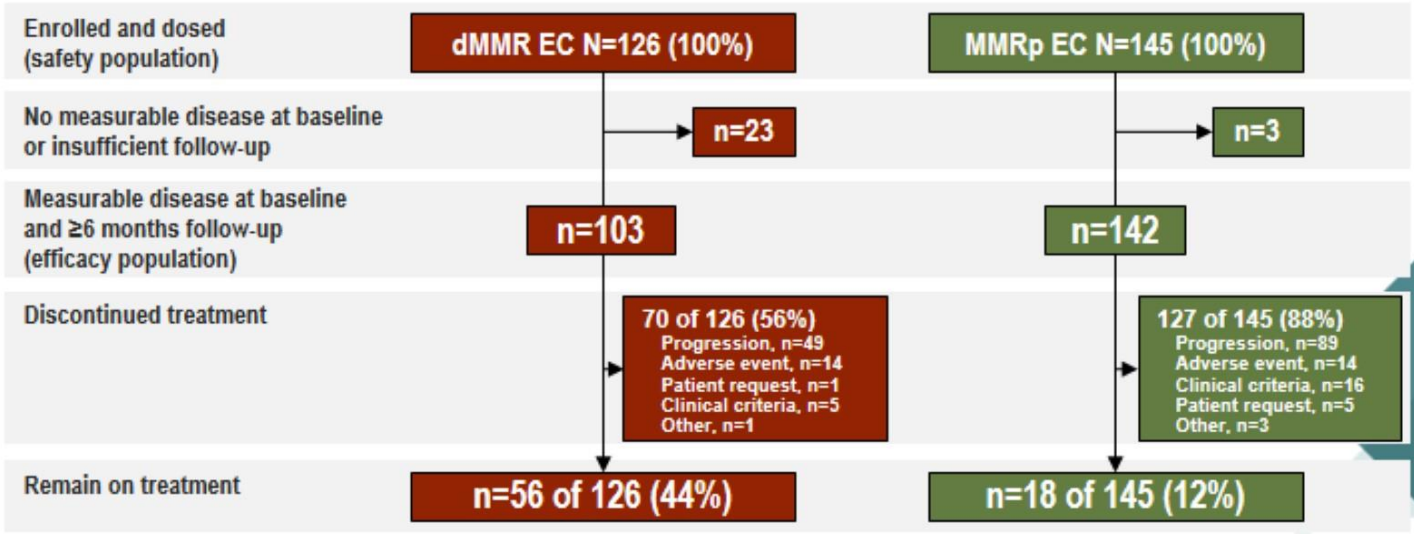
Enrollment and Outcomes



dMMR, mismatch mutation repair deficient; EC, endometrial cancer; MMRp, mismatch mutation repair proficient.

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Demographics and Baseline Characteristics

Characteristic, n (%)	dMMR EC, n=103	MMRp EC, n=142
Age, median (range)	**65 (39–80)**	**66 (30–86)**
Disease stage*		
Stage III or IV at primary diagnosis	56 (54.4)	88 (62.0)
Stage I or II at primary diagnosis	47 (45.6)	53 (37.3)
Histology		
Endometrioid carcinoma Type I (grade 1 and 2)	**70 (68.0)**	**33 (23.2)**
Endometrial carcinoma Type II	**32 (31.1)**	**109 (76.8)**
Serous	4 (3.9)	54 (38.0)
Clear Cell	1 (<1)	9 (6.3)
Squamous	1 (<1)	3 (2.1)
Undifferentiated	4 (3.9)	3 (2.1)
Carcinosarcoma	0	2 (1.4)
Mixed Carcinoma	4 (3.9)	9 (6.3)
Unspecified	14 (13.6)	22 (15.5)
Adenocarcinoma†	4 (3.9)	7 (4.9)
Prior lines of therapy		
1	65 (63.1)	65 (45.8)
2	27 (26.2)	62 (43.7)
≥3	11 (10.7)	15 (10.6)
Prior Radiation	**73 (70.9)**	**88 (62.0)**

*One patient with MMRp EC had disease status/stage unknown; †Includes adenocarcinoma, and adenocarcinoma with ambiguous differentiation.

dMMR, mismatch mutation repair deficient; EC, endometrial cancer; MMRp, mismatch mutation repair proficient.

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Primary Endpoint Analysis

ORR was 44.7% in patients with dMMR EC, and 13.4% in patients with MMRp EC

Variable	dMMR EC, n=103	MMRp EC, n=142
Median follow-up time, mo	16.3	11.5
Objective response rate*, n (%, 95% CI)	46 (44.7%, 34.9–54.8)	19 (13.4%, 8.3–20.1)
Complete response, n (%)	11 (10.7)	3 (2.1)
Partial response, n (%)	35 (34.0)	16 (11.3)
Stable disease, n (%)	13 (12.6)	31 (21.8)
Progressive disease, n (%)	39 (37.9)	77 (54.2)
Not evaluable, n (%)	3 (2.9)	0
Not done, n (%)	2 (1.9)	15 (10.6)
Disease control rate†, n (%, 95% CI)	59 (57.3%, 47.2–67.0)	50 (35.2%, 27.4–43.7)
Response ongoing, n (%)	41 (89.1)	12 (63.2)
Median duration of response, (range) mo	Not reached (2.63–28.09+)	Not reached (1.54+–30.36+)
Kaplan–Meier estimated probability of remaining in response		
at 6 mo, %	97.8	83.0
at 12 mo, %	90.6	61.3
at 18 mo, %	79.2	61.3

*Responses required confirmation at a subsequent scan; SD had to be observed at ≥12 weeks on study to qualify as SD; †Includes confirmed CR, PR or SD at ≥12 weeks.

CR, complete response; dMMR, mismatch mutation repair deficient; EC, endometrial cancer; MMRp, mismatch mutation repair proficient; ORR, objective response rate; PR, partial response; SD, stable disease.

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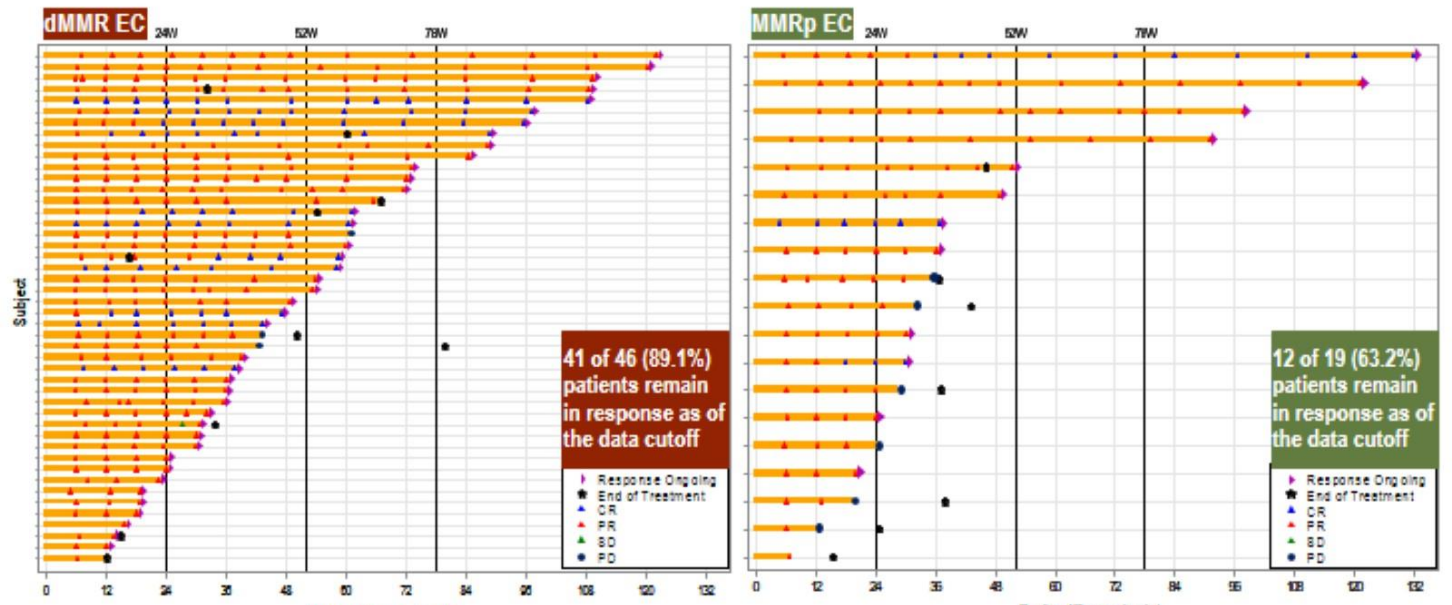
Duration of Response

Measured from first observed response (PR or CR), this response is not shown on the figure



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

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Safety (top 3 adverse events in each category)

- There were 2 (1%) reports of grade ≥3 treatment-related colitis, and no reports of grade ≥3 pneumonitis
- No deaths were attributed to dostarlimab

Safety Summary, n (%)	dMMR EC N=126	MMRp EC N=145
Any TEAE	120 (95.2)	145 (100)
Grade ≥3 TEAE	61 (48.4)	81 (55.9)
Any grade TRAE	80 (63.5)	104 (71.7)
Grade ≥3 TRAE	17 (13.5)	28 (19.3)
Treatment-related SAE	12 (9.5)	13 (9.0)
Any TRAE leading to discontinuation	5 (4.0)	10 (6.9)
TRAE leading to death	0	0

TRAEs leading to discontinuation, n (%)	dMMR EC N=126	MMRp EC N=145
ALT increased	1 (0.8)	2 (1.4)
AST increased	1 (0.8)	1 (0.7)
Transaminases increased	2 (1.6)	0

Any grade TRAEs, n (%)	dMMR EC N=126	MMRp EC N=145
Fatigue	17 (13.5)	30 (20.7)
Diarrhea	20 (15.9)	19 (13.1)
Nausea	16 (12.7)	21 (14.5)
Grade ≥3 TRAEs, n (%)		
Anemia	5 (4.0)	2 (1.4)
ALT increased	2 (1.6)	2 (1.4)
Diarrhea	2 (1.6)	2 (1.4)

Any grade irTRAEs, n (%)	dMMR EC N=126	MMRp EC N=145
Hypothyroidism	7 (5.6)	11 (7.6)
Diarrhea	6 (4.8)	5 (3.4)
AST increased	2 (1.6)	4 (2.8)
Grade ≥3 irTRAEs, n (%)		
ALT increased	2 (1.6)	2 (1.4)
Diarrhea	2 (1.6)	2 (1.4)
Amylase increased	1 (0.8)	2 (1.4)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; dMMR, mismatch mutation repair deficient; EC, endometrial cancer; MMRp, mismatch mutation repair proficient; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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Conclusions

- Dostarlimab demonstrated durable antitumor activity in both dMMR and MMRp advanced/recurrent EC
- dMMR status by IHC was associated with a higher response rate
  - These data support the use of MMR testing as predictive of response to dostarlimab
- Dostarlimab demonstrated a notable disease control rate (35.2%; 2.1% CR, 11.3% PR, 21.8% SD) in patients with MMRp EC, was comprised of a higher percentage of patients with Type II EC which is historically associated with a worse prognosis
- No new safety signals were detected, and only 5.5% of patients discontinued dostarlimab due a TRAE
  - Most adverse events were grade 1 or 2
  - Safety was consistent between dMMR and MMRp cohorts
- These cohorts are the largest prospective evaluation of a PD-(L)1 therapy in EC to date

CR, complete response; dMMR, mismatch mutation repair deficient; EC, endometrial cancer; IHC, immunohistochemistry MMRp, mismatch mutation repair proficient; PD-(L)1, programmed cell death (ligand) 1; PR, partial response; SD, stable disease.

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GARNET Cohort A1 and A2 Investigators

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