Dostarlimab in Advanced/Recurrent Mismatch Repair Deficient/Microsatellite Instability–High or Proficient/Stable Endometrial Cancer: the GARNET study

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Background

Endometrial cancer is the most common gynecologic malignancy in the US and EU[1,2]

The incidence of endometrial cancer is rising globally[1–3]

Overall survival is typically <1 year for patients with disease progression that occurs on or after first-line therapy

There is no standard second-line therapy, and new therapeutics options are needed

Dostarlimab

Dostarlimab is an anti–PD-1 monoclonal antibody that blocks interaction with the ligands PD-L1 and PD-L2

In the US, dostarlimab is approved as a monotherapy in adult patients with the following:

- dMMR recurrent or advanced endometrial cancer that has progressed on or after a platinum-containing regimen[4]
- dMMR solid tumors that have progressed on or after prior treatment, with no satisfactory alternative treatment options[4]
  - The US indications are approved under accelerated approval based on tumor response rate and durability of response[4]

In the EU, dostarlimab is approved as a monotherapy in patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed on or after treatment with a platinum-containing regimen[5]

Objective

We report efficacy and safety of dostarlimab monotherapy in the 2 expansion cohorts of the GARNET trial that enrolled patients with advanced/recurrent endometrial cancer

Data are from the third prespecified interim analysis and provide long-term follow-up on enrolled patients (Data cutoff date: November 1, 2021)

Methods

GARNET is a phase 1, multicenter, open-label, single-arm study of dostarlimab monotherapy in patients with advanced or recurrent solid tumors

Patients were enrolled to cohort A1 (dMMR/MSI-H) or cohort A2 (MMRp/MSS) based on MMR IHC assessment

Patients received 500 mg IV dostarlimab every 3 weeks for 4 cycles, followed by 1000 mg IV every 6 weeks until disease progression, discontinuation, or withdrawal

Primary endpoints were evaluation of antitumor activity (in terms of ORR and DOR by BICR per RECIST v1.1), safety, and tolerability

GARNET Trial Design

Part 1
Dose finding

Part 2A
Fixed-dose safety run-in

Part 2B
Expansion cohorts

A1: dMMR/MSI-H EC N=153

A2: MMRp/MSS EC N=161

E: NSCLC

F: Non-endometrial dMMR/MSI-H basket

G: PROC

Key Inclusion and Exclusion Criteria

Patients must have had 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

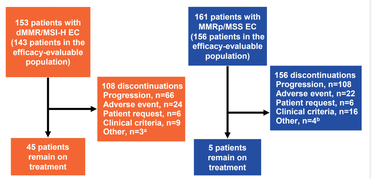
Patients must be anti–PD-(L)1 naïve

Patients could be screened based on local MMR/MSI testing using IHC, PCR or NGS performed in a certified local laboratory, but patient cohort assignment was by MMR IHC results

Patients must submit 2 scans demonstrating PD on or after the latest systemic anticancer therapy based on RECIST v1.1 per BICR prior to the first dose of dostarlimab

Results

Figure 1. Enrollment and outcomes



10 (cohort A1) and 5 (cohort A2) patients were excluded from the efficacy-evaluable population because they had no measurable disease at baseline per BICR. [a]3 patients in cohort A1 died of disease progression. [b]2 patients in cohort A2 died of disease progression, 1 patient was sent to hospice care, 1 patient discontinued because of a joint decision between patient and investigator.

Table 1. Demographics and baseline characteristics

Characteristic, n (%)	dMMR/MSI-H EC N=143	MMRp/MSS EC N=156
Age, median (range), years	65.0 (39–85)	66.0 (30–86)
FIGO disease stage at diagnosis[a]		
Stage I or II	62 (43.4)	57 (36.5)
Stage III or IV	81 (56.6)	98 (62.8)
Histology		
Grade 1 or 2 endometrioid carcinoma	92 (64.3)	36 (23.1)
Serous	7 (4.9)	63 (40.4)
Grade 3 endometrioid	21 (14.7)	14 (9.0)
Clear cell	1 (0.7)	11 (7.1)
Squamous	1 (0.7)	3 (1.9)
Undifferentiated	4 (2.8)	3 (1.9)
Carcinosarcoma	0	2 (1.3)
Mixed carcinoma	7 (4.9)	11 (7.1)
Unspecified	4 (2.8)	9 (5.8)
Other[b]	4 (2.8)	4 (2.6)
Unknown	2 (1.4)	0
Prior anticancer treatment	143 (100)	156 (100)
Prior lines of therapy, n (%)[c]		
1	90 (62.9)	72 (46.2)
2	35 (24.5)	67 (42.9)
≥3	18 (12.6)	17 (10.9)
Patients with only adjuvant or neoadjuvant therapy	49 (34.3)	42 (26.9)
Neoadjuvant setting only	3 (2.1)	3 (1.9)
Adjuvant setting only	44 (30.8)	39 (25.0)
Only adjuvant and neoadjuvant	2 (1.4)	0
Prior radiation, n (%)	101 (70.6)	95 (60.9)

[a]One patient with MMRp EC had disease status/stage unknown. [b]Other includes dedifferentiated, endometrial adenocarcinoma, endometrial adenocarcinoma NOS, endometrial neuroendocrine carcinoma, high grade uterine carcinoma, and undifferenciated clear cell carcinoma. [c]Includes lines of therapy in the adjuvant setting.

Figure 2. Best Volume Change in Target Lesions Based on BICR per RECIST v1.1

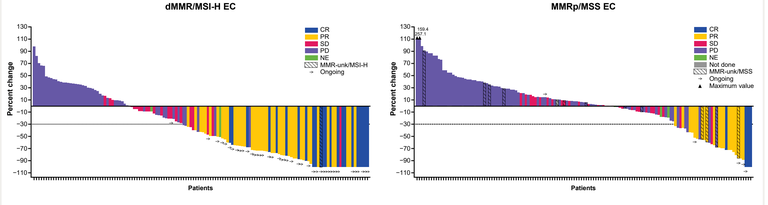


Table 2. Primary endpoint analysis

	dMMR/MSI-H EC N=143	MMRp/MSS EC N=156
Median follow-up time, months	27.6	33.0
ORR, % (95% CI; n/N)	45.5% (37.1–54.0; 65/143)	15.4% (10.1–22.0; 24/156)
Complete response, n (%)	23 (16.1)	4 (2.6)
Partial response, n (%)	42 (29.4)	20 (12.8)
Stable disease, n (%)	21 (14.7)	29 (18.6)
Progressive disease, n (%)	51 (35.7)	88 (56.4)
Not evaluable, n (%)	6 (4.2)	15 (9.6)
Median time from cycle 1 day 1 to best overall response, mo		
Complete response	2.79	2.81
Partial response	2.69	2.79
Disease control rate, % (95% CI; n/N)	60.1% (51.6–68.2; 86/143)	34.0% (26.6–42.0; 53/156)
Response ongoing, n (%)	54 (83.1)	9 (37.5)
Median duration of response (range), months	NR (1.18+ to 47.21+)	19.4 (2.8 to 47.18+)
Probability of maintaining response, %		
6 months	96.8	82.6
12 months	93.3	60.3
24 months	83.7	44.2

Safety Summary

The safety population included all patients with EC who had received ≥1 dose of dostarlimab

Most TRAEs were grade 1 or 2 and were manageable

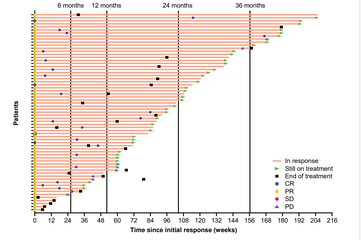
27 (8.6%) patients discontinued treatment because of a TRAE

No deaths associated with dostarlimab were reported in these cohorts

Table 3. Safety summary

Parameter, n (%)	dMMR/MSI-H EC N=153	MMRp/MSS EC N=161	Overall N=314
Any TEAE	152 (99.3)	161 (100)	313 (99.7)
Grade ≥3 TEAE	87 (56.9)	95 (59.0)	182 (58.0)
Any-grade TRAE	108 (70.6)	115 (71.4)	223 (71.0)
Grade ≥3 TRAE	27 (17.6)	33 (20.5)	60 (19.1)
Any irTRAE	42 (27.5)	31 (19.3)	73 (23.2)
Grade ≥3 irTRAE	16 (10.5)	9 (5.6)	25 (8.0)
Treatment-related SAE	18 (11.8)	14 (8.7)	32 (10.2)
Any TRAE leading to discontinuation	13 (8.5)	14 (8.7)	27 (8.6)
TRAE leading to death	0	0	0

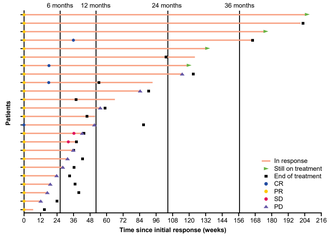
Figure 3. Duration of Response in Responders: dMMR/MSI-H



Responses in dMMR/MSI-H patients were durable, as shown with increased median duration of follow-up of 27.6 months

- Median duration of response was not reached
- Probability of remaining in response at 24 months was 83.7%

Figure 4. Duration of Response in Responders: MMRp/MSS



Responses in MMRp/MSS patients were durable, as shown with increased median duration of follow-up of 33.0 months

- Median duration of response was 19.4 months
- Probability of remaining in response at 24 months was 44.2%

Figure 5. Probability of Progression-Free Survival: dMMR/MSI-H

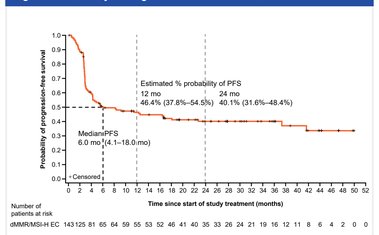


Figure 6. Probability of Progression-Free Survival: MMRp/MSS

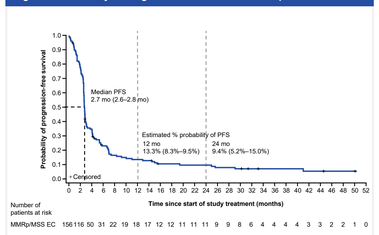


Figure 7. Probability of Overall Survival: dMMR/MSI-H

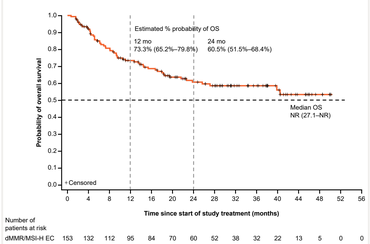


Figure 8. Probability of Overall Survival: MMRp/MSS

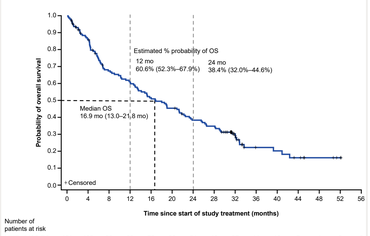


Table 4. TRAEs and irTRAEs

Preferred term, n (%)	dMMR/MSI-H EC N=153	MMRp/MSS EC N=161	Overall N=314
Any-grade TRAEs occurring in ≥10% of patients			
Fatigue	21 (13.7)	35 (21.7)	56 (17.8)
Diarrhea	25 (16.3)	21 (13.0)	46 (14.6)
Nausea	19 (12.4)	24 (14.9)	43 (13.7)
Asthenia	24 (15.7)	13 (8.1)	37 (11.8)
Grade ≥3 TRAEs occurring in ≥1% of patients			
Anemia	7 (4.6)	3 (1.9)	10 (3.2)
Alanine aminotransferase increased	3 (2.0)	3 (1.9)	6 (1.9)
Amylase increased	1 (0.7)	4 (2.5)	5 (1.6)
Diarrhea	3 (2.0)	2 (1.2)	5 (1.6)
Aspartate aminotransferase increased	0	4 (2.5)	4 (1.3)
Fatigue	1 (0.7)	3 (1.9)	4 (1.3)
Hyperglycemia	1 (0.7)	3 (1.9)	4 (1.3)
Lipase increased	3 (2.0)	1 (0.6)	4 (1.3)
Pneumonitis	2 (1.3)	1 (0.6)	3 (1.0)
Grade ≥2 irTRAEs occurring in ≥2% of patients[a]			
Hypothyroidism	13 (8.5)	13 (8.1)	26 (8.3)
Alanine aminotransferase increased	5 (3.3)	3 (1.9)	8 (2.5)
Aspartate aminotransferase increased	2 (1.3)	5 (3.1)	7 (2.2)
Arthralgia	6 (3.9)	4 (2.5)	10 (3.2)
Grade ≥3 irTRAEs occurring in ≥1% of patients			
Alanine aminotransferase increased	3 (2.0)	3 (1.9)	6 (1.9)
Aspartate aminotransferase increased	0	4 (2.5)	4 (1.3)
Pneumonitis	2 (1.3)	1 (0.6)	3 (1.0)
Any-grade TRAE leading to discontinuation in ≥1% of patients			
Alanine aminotransferase increased	2 (1.3)	3 (1.9)	5 (1.6)
Aspartate aminotransferase increased	1 (0.7)	2 (1.2)	3 (1.0)
Pneumonitis	2 (1.3)	1 (0.6)	3 (1.0)

[a]Immune-related AEs were defined as grade 2 and above from a predefined list.

Conclusions

Cohort A1 is the largest cohort of patients with dMMR/MSI-H endometrial cancer studied with an anti–PD-1 monotherapy to date

- The probability of remaining in response at 24 months was 83.7%

Dostarlimab demonstrated durable antitumor activity in both dMMR/MSI-H and MMRp/MSS advanced or recurrent endometrial cancer

- Median follow-up time is 27.6 (dMMR/MSI-H) and 33.0 (MMRp/MSS) months

Dostarlimab is the only PD-1 therapy clinically tested with a Q6W dosing schedule in endometrial cancer

The safety profile was manageable

- The majority of TRAEs were grade 1 or 2
- Discontinuation rates were low
- 8.6% of patients discontinued treatment because of a TRAE

Abbreviations

AE, adverse event; BICR, blinded independent central review; CR, complete response; dMMR, mismatch repair deficient; DOR, duration of response; EC, endometrial cancer; EU, European Union; FIGO, International Federation of Gynecology and Obstetrics; IHC, immunohistochemistry; ir, immune related; IV, intravenous; MMR, mismatch repair; MMRp, MMR proficient; MMR-unk, MMR unknown; MSI, microsatellite instability; MSI-H, microsatellite instability–high; MSS, microsatellite stable; NE, not evaluated; NGS, next-generation sequencing; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PCR, polymerase chain reaction; PD, progressive disease; PD-(L)1, programmed death (ligand) 1/2; PFS, progression-free survival; PR, partial response; PROC, platinum-resistant ovarian cancer; QW, every 6 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event; SD, stable disease; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; US, United States.

Disclosures

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