Efficacy and Safety of Dostarlimab in Patients with Mismatch Repair Deficient Solid Tumors: Analysis of 2 Cohorts in the GARNET Study

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Background

- Precision cancer medicine has led to biomarker-driven tumor-agnostic treatments[1]
  - In mismatch repair deficient (dMMR) tumors, mismatches accumulate and result in genome instability with many mutations in microsatellites, leading to microsatellite instability (MSI)[2]
  - dMMR/MSI-high (MSI-H) tumors demonstrate increased neoantigen expression, making these tumors attractive candidates to respond to anti–programmed death 1 (anti–PD-1) therapy[2–5]
- dMMR/MSI-H can be found across solid tumors, but the frequency varies by tumor type
  - Endometrial cancer (EC) and colorectal cancer have been reported to have a high prevalence of dMMR/MSI-H, at 25%–30% and 10%–15%, respectively[4–7]
- 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 EC that has progressed on or after a platinum-containing regimen[8]
- dMMR solid tumors that have progressed on or after prior treatment, with no satisfactory alternative treatment options[8]
  - The US indications are approved under accelerated approval based on tumor response rate and durability of response[8]

In the EU, dostarlimab is approved as a monotherapy in patients with dMMR/MSI-H recurrent or advanced EC that has progressed on or after treatment with a platinum-containing regimen[9]

Conclusions

- In 341 patients with dMMR solid tumors, dostarlimab demonstrated durable antitumor activity and consistent response rate across 16 tumor types with extended follow-up of 2 or more years
  - Objective response rate (ORR) was 44%, with the majority of patients having reduction in tumor volume
  - Median duration of response was not reached (range, 1.18+ to 47.21+ months)
  - 72.2% of responders had a response lasting ≥12 months
- The safety profile was acceptable with manageable toxicities, with only 7.3% of patients discontinuing treatment because of a treatment-related adverse event (TRAE)

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Objective

- To report efficacy and safety of dostarlimab monotherapy in the 2 expansion cohorts of the GARNET trial that enrolled patients with dMMR solid tumors
- Data are from the third prespecified interim analysis and provide long-term follow-up on enrolled patients (Data cutoff date: November 1, 2021)

Methods

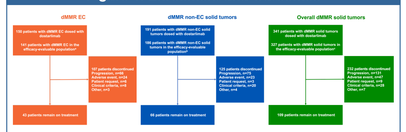
- GARNET is a phase 1, multicenter, open-label, single-arm study of dostarlimab monotherapy in patients with advanced or recurrent solid tumors
- Patients received 500 mg of intravenous dostarlimab every 3 weeks for 4 cycles, followed by 1000 mg every 6 weeks until disease progression, discontinuation, or withdrawal
  - Patient eligibility was determined by MMR immunohistochemistry
- Primary endpoints were evaluation of antitumor activity (in terms of ORR) and duration of response by blinded independent central review per Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]), safety, and tolerability
  - Cohort A1: Patients that had progression on or after a platinum regimen were included
  - Cohort F: Patients that had progression following systemic therapy and had no satisfactory alternative treatment options were included. Patients with colorectal cancer must have had progressive disease after, or been intolerant to, fluoropyrimidine, oxaliplatin, and irinotecan
  - Patients were required to be PD-(L)1 naive
- All patients who received ≥1 dose of dostarlimab were included in the safety analysis
- The data cutoff date for this third interim analysis was November 1, 2021

Results

- For this third interim analysis, 341 patients with dMMR solid tumors were enrolled and dosed
  - 141 patients with dMMR EC and 186 patients with dMMR non-EC solid tumors (including 105 patients with dMMR CRC and 81 patients with other tumor types) who had measurable disease at baseline and who enrolled on or before June 1, 2021, to allow sufficient follow-up time to assess response, constituted the efficacy-evaluable population (Figure 1; Table 1)
- ORR was 44.0% in all patients with dMMR solid tumors (Tables 2 and 3; Figure 2)
- Disease control rate was 58.4% in all patients with dMMR solid tumors
- Responses were durable, with 72.2% of responders having a response that lasted ≥12 months (Figure 3)
  - The probability of remaining in response at 6 months was 95.7% (95% CI, 90.6%–98.0%), at 12 months was 92.4% (95% CI, 86.4%–95.9%), and at 24 months was 84.7% (95% CI, 76.7%–90.2%)
- Median PFS for all patients was 6.9 months
- Median OS for all patients was not reached
- Most TRAEs were grade ≤2 and manageable (Table 4)
- 7.3% (n=25) of patients discontinued treatment because of a TRAE
  - The only TRAEs leading to discontinuation in ≥1% of patients were alanine aminotransferase increased (1.5%) and pneumonitis (1.2%)
- Treatment-related serious adverse events occurred in 10% of patients
- Immune-related TRAEs (irTRAEs) occurred in 27.0% of patients
  - 8.8% of patients had grade ≥3 irTRAEs
- There were no deaths from irTRAEs
  - The most frequent irTRAEs were hypothyroidism (6.2%), alanine aminotransferase increased (4.4%), and arthralgia (3.2%)
- There were 2 deaths attributed by investigators to study treatment, both in patients with dMMR non-EC solid tumors

Results *(cont'd)*

Figure 1. Enrollment and Outcomes



Data cutoff date was November 1, 2021.
[a]9 patients had no measurable disease per BICR at baseline and were excluded from the efficacy-evaluable population. [b]5 patients had no measurable disease per BICR at baseline and were excluded from the efficacy-evaluable population. [c]14 patients had no measurable disease per BICR at baseline and were excluded from the efficacy-evaluable population.
BICR, blinded independent central review; dMMR, mismatch repair deficient; EC, endometrial cancer.

Table 1. Demographics and Baseline Characteristics

Characteristic	Cohort A1 dMMR EC N=141	Cohort F dMMR non-EC solid tumors N=186	Overall dMMR solid tumors N=327
Age, median (range), years	65.0 (39–85)	61.0 (24–85)	63.0 (24–85)
Sex, n (%)			
Female	141 (100)	94 (50.5)	235 (71.9)
Male	—	92 (49.5)	92 (28.1)
ECOG performance status, n (%)			
0	54 (38.3)	75 (40.3)	129 (39.4)
1	87 (61.7)	111 (59.7)	198 (60.6)
Prior lines of therapy, n (%)[a]			
1	89 (63.1)	48 (25.8)	137 (41.9)
2	35 (24.8)	83 (44.6)	118 (36.1)
≥3	17 (12.1)	55 (29.6)	72 (22.0)
Prior therapy type, n (%)			
Surgery	125 (88.7)	154 (82.8)	279 (85.3)
Radiotherapy	100 (70.9)	40 (21.5)	140 (42.8)
Tumor types, n (%)			
Endometrial cancer	141 (100)	—	141 (43.1)
Colorectal cancer	—	105 (56.5)	105 (32.1)
Gastric and gastroesophageal junction cancer	—	21 (11.3)	21 (6.4)
Small-intestinal cancer	—	19 (10.2)	19 (5.8)
Pancreatic carcinoma	—	11 (5.9)	11 (3.4)
Biliary neoplasm	—	10 (5.4)	10 (3.1)
Ovarian cancer	—	7 (3.8)	7 (2.1)
Other[b]	—	13 (7.0)	13 (4.0)

[a]Includes lines of therapy in the adjuvant setting. [b]Includes adrenal cortical carcinoma, cancer of unknown origin, esophageal cancer, mesothelioma, breast cancer, malignant neoplasm of the female genitals, renal cell carcinoma, sarcoma, and thymic tumor.
dMMR, mismatch repair deficient; EC, endometrial cancer; ECOG, Eastern Cooperative Oncology Group.

Table 2. Primary Endpoint Analysis

Characteristic	Cohort A1 dMMR EC N=141	Cohort F dMMR non-EC solid tumors N=186	Overall dMMR solid tumors N=327[a]
Median follow-up time, mo	27.6	29.8	27.7
Confirmed responses, n	64	80	144
ORR, % (95% CI)	45.4 (37.0–54.0)	43.0 (35.8–50.5)	44.0 (38.6–49.6)
CR, n (%)	22 (15.6)	21 (11.3)	43 (13.1)
PR, n (%)	42 (29.8)	59 (31.7)	101 (30.9)
SD, n (%)	21 (14.9)	26 (14.0)	47 (14.4)
PD, n (%)	51 (36.2)	63 (33.9)	114 (34.9)
NE, n (%)	5 (3.5)	17 (9.1)	22 (6.8)
Disease control rate, % (95% CI)	60.3 (51.7–68.4)	57.0 (49.5–64.2)	58.4 (52.9–63.8)
Response ongoing, n (%)	53 (82.8)	70 (87.5)	123 (85.4)
Duration of response, median (range), mo	NR (1.18+ to 47.21+)	NR (2.76 to 41.49+)	NR (1.18+ to 47.21+)
Duration ≥12 months, n (%)	51 (79.7)	53 (66.3)	104 (72.2)
Probability of remaining in response, % (95% CI)			
6 months	96.7 (87.5–99.2)	94.8 (86.7–98.0)	95.7 (90.6–98.0)
12 months	93.1 (82.7–97.4)	92.0 (83.0–96.3)	92.4 (86.4–95.9)
24 months	83.4 (70.3–91.0)	86.3 (75.1–92.8)	84.7 (76.7–90.2)

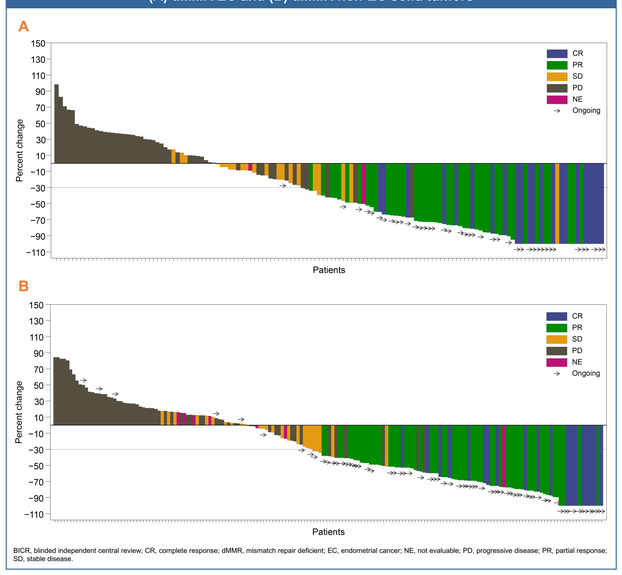
[a]341 patients were included in the overall safety population. 327 patients had measurable disease at baseline by BICR and ≥6 months of follow-up and were included in the efficacy-evaluable population. 14 patients were excluded from the efficacy-evaluable population because they had no measurable disease at baseline per BICR.
BICR, blinded independent central review; CR, complete response; dMMR, mismatch repair deficient; EC, endometrial cancer; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3. Antitumor Activity by Tumor Type

Tumor Type	Patients, N	Confirmed ORR (RECIST v1.1) n (%)	95% CI, %
Overall	327	144 (44.0)	38.6–49.6
EC	141	64 (45.4)	37.0–54.0
Non-EC	186	80 (43.0)	35.8–50.5
CRC	105	45 (42.9)	33.2–52.9
Non-CRC	81	35 (43.2)	32.3–54.7
Gastric cancer	21	10 (47.6)	25.7–70.2
Small-intestinal cancer	19	7 (36.8)	16.3–61.6
Pancreatic carcinoma	11	5 (45.5)	16.7–76.6
Biliary neoplasm	10	4 (40.0)	12.2–73.8
Ovarian cancer	7	3 (42.9)	9.9–81.6
Adrenal cortical cancer	2	PR, PD	
Cancer of unknown origin	2	PR, PD	
Esophageal cancer	2	PR, PD	
Mesothelioma	2	SD, PR	
Breast cancer	1	CR	
Malignant neoplasm of the female genitals	1	PR	
Renal cell carcinoma	1	SD	
Sarcoma	1	PD	
Thymic tumor	1	PD	

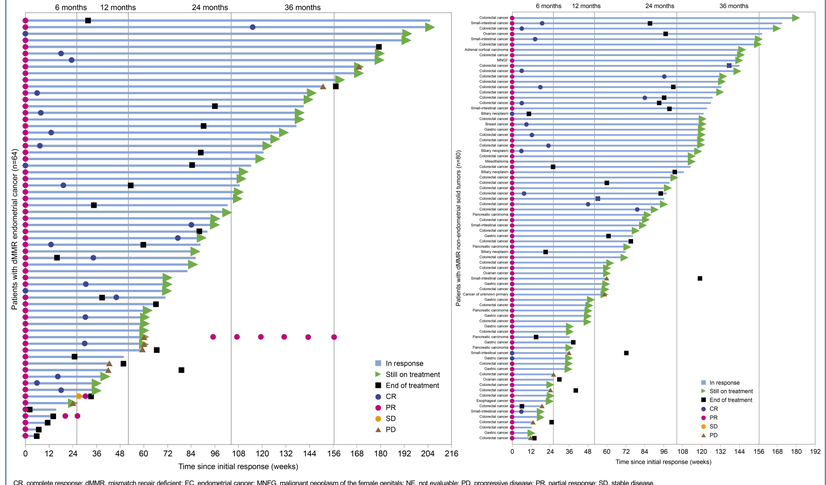
CR, complete response; CRC, colorectal cancer; EC, endometrial cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Figure 2. Best Volume Change in Target Lesions Based on BICR per RECIST 1.1 in (A) dMMR EC and (B) dMMR non-EC solid tumors



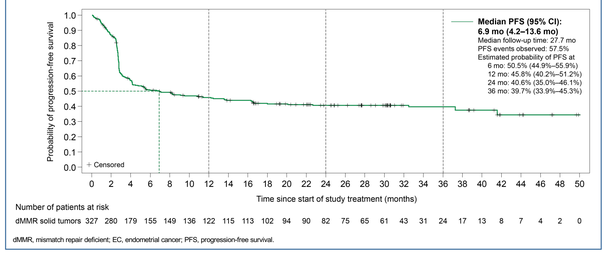
BICR, blinded independent central review; CR, complete response; dMMR, mismatch repair deficient; EC, endometrial cancer; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 3. Duration of Response in Responders in (A) dMMR EC and (B) dMMR non-EC solid tumors



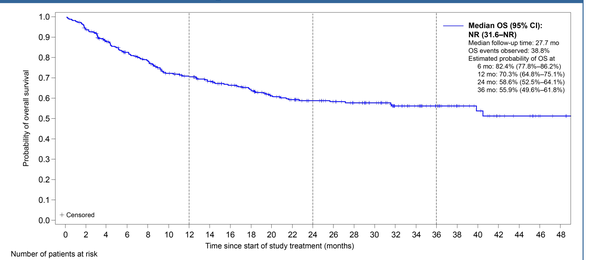
CR, complete response; dMMR, mismatch repair deficient; EC, endometrial cancer; MNFG, malignant neoplasm of the female genitals; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 4. Progression-Free Survival



dMMR, mismatch repair deficient; EC, endometrial cancer; PFS, progression-free survival.

Figure 5. Overall Survival



dMMR, mismatch repair deficient; OS, overall survival.

Table 4. Safety

	Cohort A1 dMMR EC N=150	Cohort F dMMR non-EC solid tumors N=191	Overall dMMR solid tumors N=341
Safety summary, n (%)			
Any TEAE	149 (99.3)	188 (98.4)	337 (98.8)
Grade ≥3 TEAE	84 (56.0)	103 (53.9)	187 (54.8)
Any-grade TRAE	106 (70.7)	137 (71.7)	243 (71.3)
Grade ≥3 TRAE	27 (18.0)	30 (15.7)	57 (16.7)
Any irAE	58 (38.7)	61 (31.9)	119 (34.9)
Grade ≥3 irAE	20 (13.3)	19 (9.9)	39 (11.4)
Any irTRAE	41 (27.3)	51 (26.7)	92 (27.0)
Grade ≥3 irTRAE	16 (10.7)	14 (7.3)	30 (8.8)
Treatment-related SAE	18 (12.0)	16 (8.4)	34 (10.0)
Any TRAE leading to discontinuation	13 (8.7)	12 (6.3)	25 (7.3)
TRAE leading to death[a]	0	2 (1.0)	2 (0.6)
TRAEs leading to discontinuation in ≥1% of patients, n (%)			
Alanine aminotransferase increased	2 (1.3)	3 (1.6)	5 (1.5)
Pneumonitis	2 (1.3)	2 (1.0)	4 (1.2)
Any-grade TRAEs in ≥10% of patients, n (%)			
Diarrhea	24 (16.0)	27 (14.1)	51 (15.0)
Asthenia	24 (16.0)	28 (14.7)	52 (15.2)
Pruritus	19 (12.7)	26 (13.6)	45 (13.2)
Fatigue	21 (14.0)	20 (10.5)	41 (12.0)
Hypothyroidism	16 (10.7)	19 (9.9)	35 (10.3)
Nausea	19 (12.7)	12 (6.3)	31 (9.1)
Grade ≥3 TRAEs in ≥1% of patients, n (%)			
Anemia	7 (4.7)	2 (1.0)	9 (2.6)
Alanine aminotransferase increased	3 (2.0)	4 (2.1)	7 (2.1)
Lipase increased	3 (2.0)	2 (1.0)	5 (1.5)
Grade ≥2 irTRAEs in ≥2% of patients, n (%)			
Hypothyroidism	12 (8.0)	9 (4.7)	21 (6.2)
Alanine aminotransferase increased	5 (3.3)	10 (5.2)	15 (4.4)
Arthralgia	6 (4.0)	5 (2.6)	11 (3.2)
Aspartate aminotransferase increased	2 (1.3)	6 (3.1)	8 (2.3)
Hyperthyroidism	4 (2.7)	4 (2.1)	8 (2.3)
Pneumonitis	4 (2.7)	4 (2.1)	8 (2.3)
Pruritus	4 (2.7)	4 (2.1)	8 (2.3)
Rash	3 (2.0)	5 (2.6)	8 (2.3)
Grade ≥3 irTRAEs in ≥1.0% of patients, n (%)			
Alanine aminotransferase increased	3 (2.0)	4 (2.1)	7 (2.1)

[a]1 patient with biliary neoplasm had hepatic ischemia, and 1 patient with colorectal cancer completed suicide; these events were attributed by investigators to study treatment.
dMMR, mismatch repair deficient; EC, endometrial cancer; ir, immune-related; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.