Progression-Free Survival and Overall Survival in Patients with Mismatch Repair Deficient Solid Tumours Treated with Dostarlimab in the GARNET Study

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[*]Employed by GSK at the time the study was conducted.

Background

- Precision cancer medicine has led to biomarker-driven tumour-agnostic treatments[1]
  - In mismatch repair deficient (dMMR) tumours, DNA mismatches accumulate and result in genomic instability with many mutations in microsatellite regions, leading to microsatellite instability (MSI)[2]
  - dMMR/MSI-high (MSI-H) tumours demonstrate increased neoantigen expression, making these tumours attractive candidates to respond to anti–programmed death 1 (anti–PD-1) therapy[2–5]
- dMMR/MSI-H can be found across solid tumours, but the frequency varies by tumour type
  - Endometrial cancer (EC) and colorectal cancer (CRC) have been reported to have a high prevalence of dMMR/MSI-H, at 25%–30% and 10%–15%, respectively[4–7]
- Patients with advanced dMMR/MSI-H tumours who experience disease progression despite standard systemic therapy have limited treatment options[8]
- Dostarlimab is an anti–PD-1 monoclonal antibody that blocks interaction with the ligands PD-L1 and PD-L2 and is being investigated in multiple tumor types

Conclusions

- In 341 patients with dMMR solid tumours, dostarlimab demonstrated durable antitumour activity and a 44% overall objective response rate (ORR) across 16 tumour types
- The landmark estimates at 12, 24, and 36 months (45.8%, 40.6%, and 39.7%, respectively) demonstrate the stability of PFS benefits for responders in this study
- With a median follow-up of 27.7 months, median overall survival (OS) was not reached, suggesting a survival benefit in this biomarker-selected patient population
- As previously reported, the safety profile was manageable, with only 7.3% of patients discontinuing treatment because of a treatment-related adverse event (TRAE)
  - Overall, adverse events were generally similar across both dMMR cohorts (EC and non-EC solid tumours)

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Objectives

- To report on the secondary endpoints of progression-free survival (PFS) and OS in the 2 expansion cohorts of the GARNET trial that enrolled patients with dMMR solid tumours
- To report on updated results of primary endpoints: ORR and duration of response (DOR) by blinded independent central review per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), safety, and tolerability
- Data are from the third prespecified interim analysis and provide long-term follow-up on enrolled patients

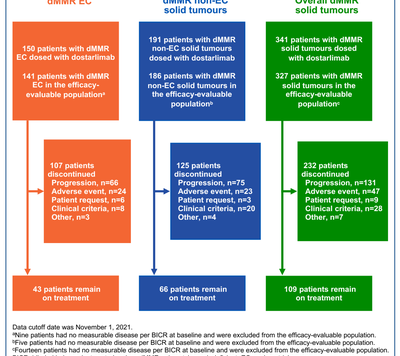
Methods

- GARNET is a phase 1, multicentre, open-label, single-arm study of dostarlimab monotherapy in patients with advanced or recurrent solid tumours (**trial design available via QR code**)
- 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
- All patients were required to be PD-(L)1 naive
- Cohort A1 included patients with dMMR EC
  - Patients were required to have progression on or after platinum doublet therapy
- Cohort F included patients with dMMR non-EC solid tumours
  - Patients with CRC must have progression after, or been intolerant to, fluoropyrimidine, oxaliplatin, and irinotecan
  - Patients with ovarian cancer with platinum-resistant disease were allowed to receive up to 1 line of systemic therapy after becoming platinum resistant
- 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 tumours were enrolled and dosed
  - 141 patients with dMMR EC and 186 patients with dMMR non-EC solid tumours (including 105 patients with dMMR CRC and 81 patients with other tumour types) who had measurable disease at baseline and who enrolled on or before June 1, 2021, constituted the efficacy-evaluable population (**Figure 1**; **Table 1**)

Figure 1. Enrolment and Outcomes



Data cutoff date was November 1, 2021.
[a]Nine patients had no measurable disease per BICR at baseline and were excluded from the efficacy-evaluable population.
[b]Five patients had no measurable disease per BICR at baseline and were excluded from the efficacy-evaluable population.
[c]Fourteen 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.

Results *(cont'd)*

Table 1. Demographics and Baseline Characteristics

Characteristic	dMMR EC N=141	dMMR non-EC solid tumours N=186	Overall dMMR solid tumours 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)
Race			
White	108 (76.6)	98 (52.7)	206 (63.0)
Asian	5 (3.5)	2 (1.1)	7 (2.1)
Black or African American	4 (2.8)	2 (1.1)	6 (1.8)
American Indian or Alaska Native	3 (2.1)	0	3 (0.9)
Other, unknown, or not reported	21 (14.9)	84 (45.2)	105 (32.1)
Ethnicity			
Hispanic or Latino	6 (4.3)	4 (2.2)	10 (3.1)
Not Hispanic or Latino	109 (77.3)	96 (51.6)	205 (62.7)
Unknown or not reported	26 (18.4)	86 (46.2)	112 (34.3)
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 systemic 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)
Tumour 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, oesophageal cancer, mesothelioma, breast cancer, malignant neoplasm of the female genitals, renal cell carcinoma, sarcoma, and thymic tumour.
dMMR, mismatch repair deficient; EC, endometrial cancer; ECOG, Eastern Cooperative Oncology Group.

- ORR was 44.0% in all patients with dMMR solid tumours (**Tables 2 and 3**)
- Disease control rate was 58.4% in all patients with dMMR solid tumours
- At a median duration of follow-up of 27.7 months, responses were durable, with median DOR not reached
  - The probability of maintaining a response for ≥12 months was 92.4% (**Table 2**)

Table 2. Primary Endpoint Analysis

Variable	dMMR EC N=141	dMMR non-EC solid tumours N=186	Overall dMMR solid tumours N=327
Median follow-up time, months	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 (6.7)
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)
DOR, median (range), months	NR (1.18+ to 47.21+)	NR (2.76 to 41.49+)	NR (1.18+ to 47.21+)
Probability of maintaining a response, % (95% CI)[a]			
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]Kaplan-Meier estimated probability of DOR; 95% CIs were generated using the method of Brookmeyer and Crowley.
CR, complete response; dMMR, mismatch repair deficient; DOR, duration of response; EC, endometrial cancer; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

- The median PFS for all patients was 6.9 months; the probability of PFS at 12 months, 2 years, and 3 years was 45.8%, 40.6%, and 39.7%, respectively (**Table 4, Figure 2**)
  - Median PFS for patients with EC was 5.6 months and for patients with non-EC was 7.0 months
- With 38.7% of patients experiencing an event, median OS for all patients was not reached; the 3-year probability of OS was 55.9% (**Table 5, Figure 3**)
  - Median OS was not reached in either the dMMR EC or non-EC cohort
- Most TRAEs were grade 1 or 2 and manageable (**Table 6**)
- 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
- The most frequent irTRAEs were hypothyroidism (6.2%), alanine aminotransferase increased (4.4%), and arthralgia (3.2%)
- 8.8% of patients had grade ≥3 irTRAEs
- Two deaths were attributed by investigators to study treatment, both in patients with dMMR non-EC solid tumours
  - One patient with biliary neoplasm had hepatic ischemia, and 1 patient with CRC completed suicide
- There were no deaths from irTRAEs

Table 3. Antitumour Activity by Tumour Type

		Confirmed ORR (RECIST v1.1)		DOR (RECIST v1.1)
Tumour type	Patients, N	n (%)	95% CI, %	Median (range), months
Overall	327	144 (44.0)	38.6–49.6	NR (1.18+ to 47.21+)
EC	141	64 (45.4)	37.0–54.0	NR (1.18+ to 47.21+)
Non-EC	186	80 (43.0)	35.8–50.5	NR (2.76 to 41.49+)
CRC	105	45 (42.9)	33.2–52.9	NR (2.8 to 41.5+)
Non-CRC	81	35 (43.2)	32.3–54.7	NR (2.8+ to 39.4+)
Gastric cancer	21	10 (47.6)	25.7–70.2	NR (2.8+ to 27.7+)
Small-intestinal cancer	19	7 (36.8)	16.3–61.6	NR (4.1+ to 39.4+)
Pancreatic carcinoma	11	5 (45.5)	16.7–76.6	NR (8.4+ to 19.8+)
Biliary neoplasm	10	4 (40.0)	12.2–73.8	NR (16.5+ to 27.9+)
Ovarian cancer	7	3 (42.9)	9.9–81.6	NR (6.0+ to 36.4+)
Adrenal cortical cancer	2	PR, PD		
Cancer of unknown origin	2	PR, PD		
Oesophageal 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 tumour	1	PD		

CR, complete response; CRC, colorectal cancer; DOR, duration of response; EC, endometrial cancer; NR, not reached; 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.

Table 4. Progression-Free Survival

Variable	dMMR EC N=141	dMMR non-EC solid tumours N=186	Overall dMMR solid tumours N=327
Median follow-up time, months	27.6	29.8	27.7
PFS events observed, n (%)	83 (58.9)	105 (56.5)	188 (57.5)
Median PFS (95% CI), months	5.6 (4.1–16.6)	7.0 (3.6–16.5)	6.9 (4.2–13.6)
Estimated probability of PFS, % (95% CI)			
6 months	49.2 (40.6–57.2)	51.5 (44.0–58.5)	50.5 (44.9–55.9)
12 months	46.0 (37.4–54.1)	45.6 (38.2–52.8)	45.8 (40.2–51.2)
24 months	39.6 (31.2–48.0)	41.4 (34.0–48.7)	40.6 (35.0–46.1)
36 months	39.6 (31.2–48.0)	39.6 (31.8–47.4)	39.7 (33.9–45.3)

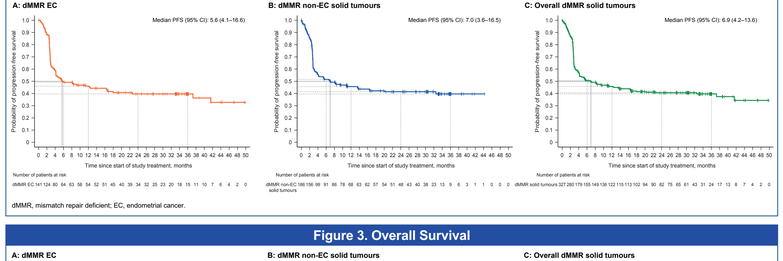
dMMR, mismatch repair deficient; EC, endometrial cancer; non-EC, non-endometrial cancer; PFS, progression-free survival.

Table 5. Overall Survival

Variable	dMMR EC N=150	dMMR non-EC solid tumours N=191	Overall dMMR solid tumours N=341
Median follow-up time, months	27.6	29.8	27.7
OS events observed	57 (38.0)	75 (39.3)	132 (38.7)
Median OS (95% CI), months	NR (25.7–NR)	NR (21.7–NR)	NR (31.6–NR)
Estimated probability of survival, % (95% CI)			
6 months	84.7 (77.7–89.7)	80.9 (74.5–85.8)	82.6 (78.0–86.2)
12 months	72.9 (64.7–79.5)	68.7 (61.4–75.0)	70.6 (65.3–75.3)
24 months	59.9 (50.8–67.8)	57.3 (49.3–64.5)	58.4 (52.5–63.9)
36 months	57.7 (48.5–65.9)	54.4 (45.9–62.2)	55.9 (49.7–61.7)

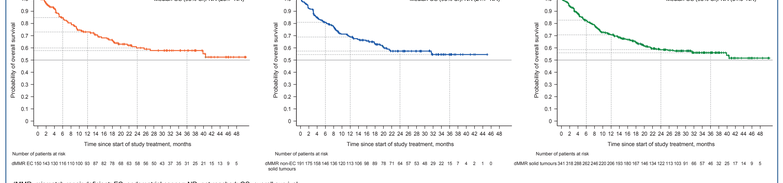
dMMR, mismatch repair deficient; EC, endometrial cancer; non-EC, non-endometrial cancer; NR, not reached; OS, overall survival.

Figure 2. Progression-Free Survival



dMMR, mismatch repair deficient; EC, endometrial cancer.

Figure 3. Overall Survival



dMMR, mismatch repair deficient; EC, endometrial cancer; NR, not reached; OS, overall survival.

Table 6. Safety

	dMMR EC N=150	dMMR non-EC solid tumours N=191	Overall dMMR solid tumours 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	0	2 (1.0)	2 (0.6)
Any irTRAE leading to death	0	0	0
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 occurring in ≥10% of patients, n (%)			
Diarrhoea	24 (16.0)	27 (14.1)	51 (15.0)
Asthenia	24 (16.0)	28 (14.7)	52 (15.2)
Pruritis	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 (%)			
Anaemia	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)
irTRAEs in ≥2% of patients, n (%)[a]			
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)
Pruritis	4 (2.7)	4 (2.1)	8 (2.3)
Rash	3 (2.0)	5 (2.6)	8 (2.3)
Grade ≥3 irTRAEs in ≥1% of patients, n (%)			
Alanine aminotransferase increased	3 (2.0)	4 (2.1)	7 (2.1)

[a]rAEs were defined as grade 2 and above from a predefined list.
AE, adverse event; dMMR, mismatch repair deficient; EC, endometrial cancer; ir, immune-related; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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Conflicts of Interest

Dr. André reports serving in a consulting/advisory role and/or received honoraria from Amgen, Astellas Pharma, AstraZeneca, Bristol Myers Squibb, GSK, Gritstone Oncology, Haliodx, Kaleido Biosciences, Merck & Co. Inc., Pierre Fabre, RocheVentana, Sanofi, Seagen, Servier, and Transgene; travel, accommodation, and expenses from Bristol Myers Squibb and MSD & Co., Inc.