Antitumor Activity of Dostarlimab in Patients with Mismatch Repair–Deficient (dMMR) Tumors: a Combined Analysis of 2 Cohorts in the GARNET Study

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**Employed by GlaxoSmithKline when the study was conducted.*

Background

- Dostarlimab is a humanized programmed death 1 (PD-1) receptor monoclonal antibody that blocks interaction with the PD-1 ligands, PD-L1 and PD-L2
  - In the US, dostarlimab is approved as a monotherapy in adult patients with dMMR recurrent or advanced endometrial cancer that has progressed on or after a platinum-containing regimen
  - In the EU, dostarlimab is approved as a monotherapy in adult patients with recurrent or advanced dMMR/microsatellite instability–high endometrial cancer that has progressed on or after treatment with a platinum-containing regimen

Conclusions

- Dostarlimab has demonstrated antitumor activity across multiple tumor types in patients with dMMR advanced/recurrent solid tumors, with an objective response rate of 41.6% (34.9%–48.6%) in the combined cohort A1 + F population
  - Consistent antitumor activity was seen across endometrial and non-endometrial tumor types, such as colorectal cancer
  - The median duration of response was 34.7 (2.63 to 35.78+) months in the combined cohort A1 + F population
- Dostarlimab demonstrated a manageable safety profile across different tumor types

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Conflicts of Interest

Dr. Berton has nothing to disclose. **Dr. Banerjee** reports honoraria and institutional grants from AstraZeneca and GlaxoSmithKline; consulting fees from Amgen, AstraZeneca/MedImmune, Clovis Oncology, GenMab, GlaxoSmithKline, Immunogen, Merck, Mersana, MSD Oncology, and Roche; institutional consulting fees from Carrick Therapeutics; travel support from NuCana BioMed; and honoraria from Pfizer. **Dr. Curigliano** reports personal fees from BMS, Ellipsis, Pfizer, Roche, and Seattle Genetics. **Dr. Cresta** has nothing to disclose. **Dr. Arkenau** reports consulting fees from iOncologi; honoraria from Bayer, BeiGene, Bicycle Therapeutics, Guardant Health, Merck KGaA, Roche, and Servier; and research funding from Sarah Cannon Research Institute. **Dr. Abdeddaim** has nothing to disclose. **Dr. Kristeleit** reports personal fees from GlaxoSmithKline. **Dr. Redondo** reports institutional grants from Eisai, PharmaMar, and Roche; and advisory roles at AstraZeneca, GlaxoSmithKline, PharmaMar, and Roche. **Dr. Leath** reports contracted research for GlaxoSmithKline; and scientific advisory board fees from AbbVie, Clovis Oncology, Eisai, GlaxoSmithKline, and Seattle Genetics. **Dr. Torres** has nothing to disclose. **Drs. Guo** and **Im** are former employees of GlaxoSmithKline. **Dr. André** reports personal fees from Amgen, Astellas, AstraZeneca, BMS, GlaxoSmithKline, Gritstone Oncology, Haliodx, Kaleido Biosciences, MSD Oncology, Pierre Fabre, Roche, Sanofi, Servier, and Vantana.

Objective

- To report objective response rate (ORR) and duration of response (DOR), by individual cohort and as an overall population, in patients with dMMR tumors

Methods

- GARNET (NCT02715284) is a phase 1, single-arm study of dostarlimab monotherapy in multiple tumor types
- In part 2B, dostarlimab was administered at the recommended therapeutic dose determined from parts 1 and 2A (Figure 1)

Figure 1. GARNET Study Dosing Schedule

	500 mg Q3W (1 cycle = 3 weeks)				1000 mg Q6W until disease progression or unacceptable toxicity (1 cycle = 6 weeks)			
Cycle	1	2	3	4	5	6	7	Continue dosing Q6W
Week	1	4	7	10	13	19	25	

Q3W, every 3 weeks; Q6W, every 6 weeks.

- MMR status was determined by immunohisto-chemistry
- Primary endpoints were ORR and DOR
- 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 (GARNET Trial Design)
- Patients were required to be PD-(L)1 naive
- Patients were scanned at baseline, 12 weeks (±10 days) after the first dose of dostarlimab, then every 6 weeks (±10 days) for the first year, and every 12 weeks (±10 days) thereafter
- Data cutoff date was March 1, 2020, with an update on duration of response and safety taken on November 1, 2020

Results

- 143 patients in cohort A1 and 173 patients in cohort F were enrolled and treated as of the data cutoff date; these patients constitute the safety population
- The efficacy population included those patients with ≥6 months of follow-up time as of March 1, 2020, and with ≥1 measurable lesion at baseline (Table 1)
  - Additional follow-up on duration of response and safety was taken on November 1, 2020
  - 103 patients in cohort A1 and 106 patients in cohort F met this criteria (Figure 2)

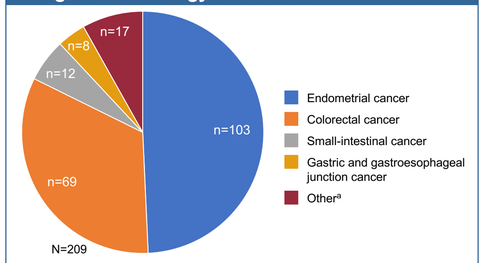
Results

Table 1. Demographics and Baseline Characteristics

Characteristic	Cohort A1 (n=103)	Cohort F (n=106)	Cohorts A1 + F (n=209)
Age, median (range), y	65.0 (39–80)	61.5 (24–85)	63.0 (24–85)
ECOG performance status, n (%)			
0	40 (38.8)	42 (39.6)	82 (39.2)
1	63 (61.2)	64 (60.4)	127 (60.8)
Disease stage at study entry,[a] n (%)			
I	12 (11.7)	0	—
II	3 (2.9)	0	—
III	16 (15.5)	3 (2.8)	—
IV	70 (68.0)	103 (97.2)	—
Prior lines of therapy,[b] n (%)			
1	65 (63.1)	25 (23.6)	90 (43.1)
2	27 (26.2)	48 (45.3)	75 (35.9)
≥3	11 (10.7)	33 (31.1)	44 (21.1)
Prior therapy type, n (%)			
Surgery	93 (90.3)	92 (86.8)	185 (88.5)
Radiotherapy	73 (70.9)	21 (19.8)	94 (45.0)
Chemotherapy	103 (100)	106 (100)	209 (100)

[a]Includes 2 patients with dMMR EC and unknown disease stage at study entry; [b]Includes all prior lines of chemotherapy, not only those for advanced or recurrent disease.
dMMR, mismatch repair deficient; EC, endometrial cancer; ECOG, Eastern Cooperative Oncology Group.

Figure 2. Histology of Cohorts A1 + F Tumors



[a]Includes adrenal cortical carcinoma, biliary neoplasm, breast cancer, esophageal cancer, hepatocellular carcinoma, malignant neoplasm of the female genitals, ovarian cancer, pancreatic carcinoma, pleural cancer, renal cell carcinoma, and unknown origin.

- ORR was 44.7% in cohort A1 and 38.7% in cohort F (Tables 2 and 3; Figure 3)
- Responses were durable, with 95.4% of responders having a response that lasted ≥6 months (Figure 4)

Table 2. Primary Endpoint Analysis

Variable	Cohort A1 (n=103)	Cohort F (n=106)	Cohorts A1 + F (n=209)
Median follow-up time, mo[a]	20.4	16.7	17.5
Confirmed responses, n	46	41	87
ORR, % (95% CI)[b]	44.7 (34.9–54.8)	38.7 (29.4–48.6)	41.6 (34.9–48.6)
CR, n (%)	11 (10.7)	8 (7.5)	19 (9.1)
PR, n (%)	35 (34.0)	33 (31.1)	68 (32.5)
SD, n (%)	13 (12.6)	26 (24.5)	39 (18.7)
PD, n (%)	39 (37.9)	32 (30.2)	71 (34.0)
NE, n (%)	5 (4.9)	7 (6.6)	3 (1.4)
Disease control rate, % (95% CI)[c]	57.3 (47.2–67.0)	63.2 (53.3–72.4)	60.3 (53.3–67.0)
Duration of response, median (range), mo	34.7 (2.63 to 35.78+)	NR (5.59 to 30.13+)	34.7 (2.63 to 35.78+)

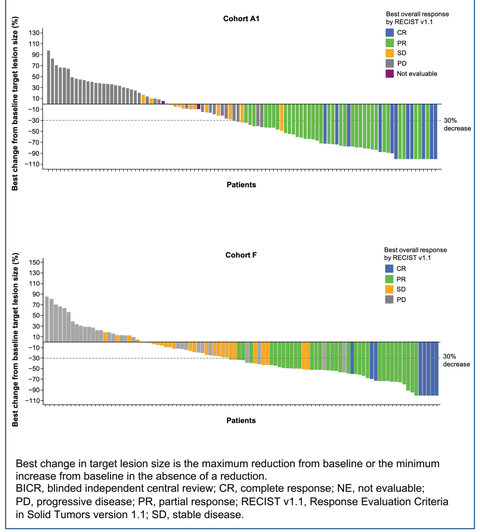
[a]Median follow-up time is a post hoc analysis of time since initial response; [b]Responses required confirmation at a subsequent scan: SD had to be observed at ≥12 wk on study to qualify as SD; [c]Includes confirmed CR, PR, or SD at ≥12 wk.
CR, complete response; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3. Antitumor Activity by Tumor Type

		Confirmed ORR (RECIST v1.1)	
Tumor type	**Patients, N**	**n (%)**	**95% CI, %**
Overall	**209**	**87 (41.6)**	**(34.9–48.6)**
EC	**103**	**46 (44.7)**	**(34.9–54.8)**
CRC	**69**	**25 (36.2)**	**(25.0–48.7)**
Non-CRC	**37**	**16 (43.2)**	**(27.1–60.5)**
Small-intestinal cancer	12	4 (33.3)	(9.9–65.1)
Gastric and gastroesophageal junction cancer	8	3 (37.5)	(8.5–75.5)
Pancreatic carcinoma	4	SD, 3 PD	
Ovarian cancer	2	PR, SD	
Hepatocellular carcinoma	2	PR, PD	
Biliary neoplasm	2	2 CR	
Breast cancer	1	CR	
Adrenal cortical carcinoma	1	PR	
Malignant neoplasm of the female genitals	1	PR	
Pleural cancer	1	PR	
Unknown origin	1	PR	
Renal cell carcinoma	1	SD	
Esophageal cancer	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.

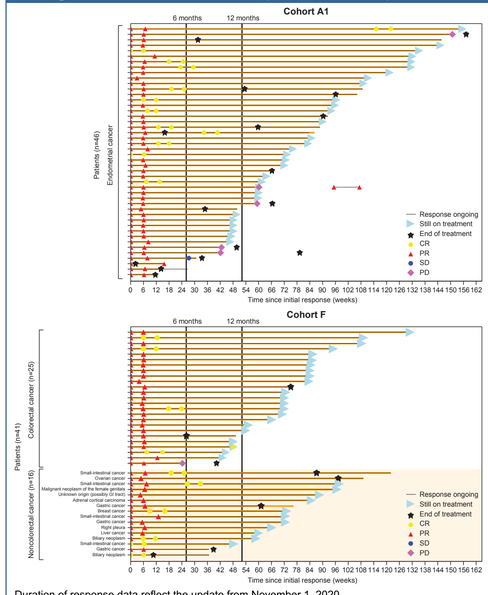
Figure 3. Best Volume Change in Target Lesions, Based on BICR per RECIST v1.1



Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
BICR, blinded independent central review; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

- Dostarlimab was well tolerated, with an adverse event profile similar to others in the drug class (Table 4)
- The grade ≥3 immune-related treatment-related adverse events had an incidence of ≤1.6% each
  - There were 2 (0.6%) reports of grade ≥3 treatment-related colitis

Figure 4. Duration of Response in Responders



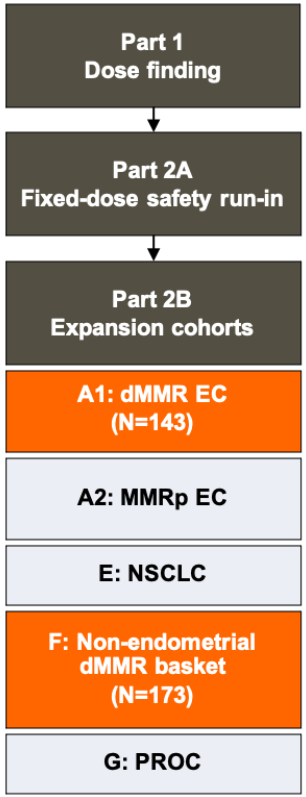
Duration of response data reflect the update from November 1, 2020.
CR, complete response; GI, gastrointestinal; PD, progressive disease; PR, partial response; SD, stable disease.

Table 4. Safety Summary

	Cohort A1 (N=143)	Cohort F (N=173)	Cohorts A1 + F (N=316)
Safety summary, n (%)			
Any TEAE	140 (97.9)	167 (96.5)	307 (97.2)
Any-grade TRAE	100 (69.9)	119 (68.8)	219 (69.3)
Grade ≥3 TEAE	72 (50.3)	85 (49.1)	157 (49.7)
Grade ≥3 TRAE	23 (16.1)	20 (11.6)	43 (13.6)
Treatment-related SAE	15 (10.5)	13 (7.5)	28 (8.9)
Any TRAE leading to discontinuation	8 (5.6)	8 (4.6)	16 (5.1)
TRAE leading to death[a]	0	2 (1.2)	2 (0.6)
TEAEs in ≥1% of patients leading to discontinuation, n (%)			
ALT increased	2 (1.4)	2 (1.2)	4 (1.3)
Any-grade TEAEs in ≥20% of patients, n (%)			
Anemia	45 (31.5)	55 (31.8)	100 (31.6)
Diarrhea	40 (28.0)	43 (24.9)	83 (26.3)
Asthenia	35 (24.5)	42 (24.3)	77 (24.4)
Nausea	45 (31.5)	26 (15.0)	71 (22.5)
Fatigue	36 (25.2)	28 (16.2)	64 (20.3)
Grade ≥3 TEAEs in ≥2% of patients, n (%)			
Anemia	21 (14.7)	13 (7.5)	34 (10.8)
Abdominal pain	7 (4.9)	6 (3.5)	13 (4.1)
Hyponatremia	6 (4.2)	5 (2.9)	11 (3.5)
Sepsis	4 (2.8)	6 (3.5)	10 (3.2)
ALT increased	3 (2.1)	5 (2.9)	8 (2.5)
Acute kidney injury	4 (2.8)	3 (1.7)	7 (2.2)
Lipase increased	3 (2.1)	4 (2.3)	7 (2.2)
Grade ≥2 irTEAEs in ≥5% of patients, n (%)			
Diarrhea	12 (8.4)	11 (6.4)	23 (7.3)
Hypothyroidism	11 (7.7)	9 (5.2)	20 (6.3)
ALT increased	4 (2.8)	12 (6.9)	16 (5.1)
Grade ≥3 irTEAEs in ≥1% of patients, n (%)			
ALT increased	3 (2.1)	5 (2.9)	8 (2.5)
Lipase increased	3 (2.1)	4 (2.3)	7 (2.2)
AST increased	1 (0.7)	4 (2.3)	5 (1.6)
Diarrhea	3 (2.1)	2 (1.2)	5 (1.6)
Hyperglycemia	1 (0.7)	3 (1.7)	4 (1.3)

[a]1 hepatic ischemia and 1 suicide.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ir, immune-related; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

GARNET Trial Design



Key inclusion/exclusion criteria for cohorts A1 and F:

- Patients with dMMR/MSI-H solid tumors (cohort F was also open to patients with POLε-mutated solid tumors)
- Patients could be screened based on MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but patient eligibility was determined by MMR IHC results for this analysis
- Patients must have measurable disease at baseline
- Patients must be anti–PD-(L)1 naive
- Patients must submit 2 scans demonstrating PD based on BICR per RECIST v1.1 prior to the first dose of dostarlimab

Additional key inclusion/exclusion criteria for cohort A:

- Patients must have progression on or after platinum doublet therapy
- Patients must have received ≤2 prior lines of treatment for recurrent or advanced disease

Additional key inclusion/exclusion criteria for cohort F:

- Patients must have progression following systemic therapy and have no satisfactory alternative treatment options
- Patients with CRC must have PD after, or been intolerant to, fluoropyrimidine, oxaliplatin, and irinotecan

BICR, blinded independent central review; CRC, colorectal cancer; dMMR, mismatch repair deficient; EC, endometrial cancer; IHC, immunohistochemistry; MMR, mismatch repair; MMRp, mismatch repair proficient; MSI, microsatellite instability; MSI-H, microsatellite instability high; NGS, next-generation sequencing; NSCLC, non–small cell lung cancer; PCR, polymerase chain reaction; PD, progressive disease; PD-(L)1, programmed death (ligand) 1; PROC, platinum-resistant ovarian cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.