Analysis of the Immune-Related Endpoints of the Mismatch Repair–Deficient Non-endometrial Solid Cancers Cohort from 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 mismatch repair–deficient (dMMR) recurrent or advanced endometrial cancer that has progressed on or after prior treatment with 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
- The GARNET trial (NCT02715284) is assessing the antitumor activity and safety of dostarlimab in patients with advanced solid tumors
- Standard RECIST may underestimate the clinical benefit of immunotherapies[1,2]
  - To account for this, immune-related (ir) endpoints, including irORR, irDOR, and irDCR, per investigator assessment by irRECIST, were prespecified secondary endpoints in GARNET[3]
- Data reported are from an interim analysis, with a data cutoff date of March 1, 2020

Conclusions

- The GARNET trial assessed the antitumor activity and safety of dostarlimab in patients with advanced solid tumors
  - The analysis presented here looked at cohort F (non-endometrial dMMR pan tumor); most, 65%, were patients with colorectal cancer
  - The majority of patients were enrolled with advanced disease that had progressed on prior therapy
    - These patients have limited treatment options and represent a high unmet need
- Dostarlimab demonstrated durable antitumor activity per IA by irRECIST in patients with non-endometrial dMMR solid tumors
  - irORR was 45.0%; 87.8% of responders remained in response as of the data cutoff date
  - Results were consistent with the primary endpoint, RECIST v1.1 by BICR
  - The difference between irORR and ORR could suggest a component of pseudoprogression
- Dostarlimab was both convenient and tolerable across multiple tumor types
  - The schedule of administration allows for less frequent clinic visits after 12 weeks of treatment while maintaining efficacy (500 mg Q3W for 4 cycles, then 1000 mg Q6W thereafter)
  - Dostarlimab demonstrated a manageable safety profile across different tumor types that was consistent with the drug class

Presentation #SO-9

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Objective

- This presentation reports the efficacy endpoints by immune-related (ir)RECIST, based on investigator assessment (IA) of cohort F (non-endometrial mismatch repair–deficient [dMMR] pan tumor)

Methods

- GARNET is a phase 1, single-arm study of dostarlimab monotherapy in multiple tumor types
- In part 2B, dostarlimab was dosed at the recommended therapeutic dose determined from parts 1 and 2A (Figure 1)
  - Patients received 500 mg of dostarlimab IV every 3 weeks (Q3W) for 4 cycles, then 1000 mg IV every 6 weeks (Q6W) for up to 2 years or until disease progression or discontinuation

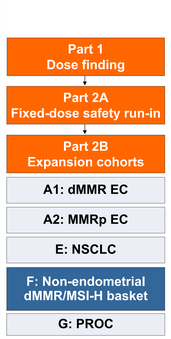
Figure 1. GARNET Study Dosing Schedule

	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
- Patients with dMMR solid tumors (cohort F) that progressed on or after a platinum regimen were included in this analysis (Figure 2)
- Secondary immune-related endpoints were irORR, irDOR, and irDCR

Figure 2. GARNET Part 2B



Key inclusion/exclusion criteria for cohort F:
- Patients with advanced dMMR or POLε-mutated solid tumors
- Patients must have measurable disease at baseline
- Patients must be anti–PD-(L)1 naive
- Patients must have PD following systemic therapy and have no satisfactory alternative treatment options. Patients must submit 2 scans demonstrating PD based on RECIST v1.1 for BICR prior to the first dose of dostarlimab
- Patients with colorectal cancer must have PD after, or been intolerant to, fluoropyrimidine, oxaliplatin, and irinotecan
- Patients were required to be PD-(L)1 naive
- Screening was based on testing results using IHC, polymerase chain reaction, or next-generation sequencing performed in a certified local laboratory, but patient eligibility needed to be determined by MMR IHC results for this analysis

dMMR, mismatch repair deficient; EC, endometrial cancer; IHC, immunohistochemistry; MSI-H, microsatellite instability high; MMRp, mismatch repair proficient; NSCLC, non–small cell lung cancer; 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.

Results

- The efficacy population included those patients with ≥6 months of follow-up time in the study and with ≥1 measurable lesion at baseline (Table 1)
  - 106 patients with dMMR non-endometrial cancer met these criteria and were included in the primary efficacy population

Table 1. Demographics and Baseline Characteristics: Primary Efficacy Population

Characteristic	dMMR NEC (n=106)
Age, median (range), years	61.5 (24–85)
Sex, n (%)	
Male	58 (55)
Female	48 (45)
ECOG performance status, n (%)	
0	42 (40)
1	64 (60)
Tumor type, n (%)	
Colorectal cancer	69 (65)
Small-intestinal cancer	12 (11)
Gastric and gastroesophageal junction cancer	8 (8)
Other[a]	17 (16)
Disease stage at restaging, n (%)	
Locally advanced	3 (3)
Metastatic	103 (97)
Prior lines of therapy, n (%)	
≥1	106 (100)
Prior therapy, n (%)	
Surgery	92 (87)
Radiotherapy	21 (20)
Chemotherapy	106 (100)

[a]Adrenal cortical cancer, biliary neoplasm, breast cancer, esophageal cancer, hepatocellular carcinoma, malignant neoplasm of the female genitals, ovarian cancer, pancreatic carcinoma, and unknown.
dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; NEC, non-endometrial cancer.

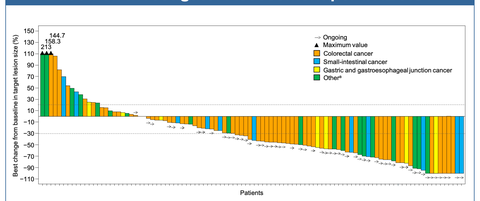
- The secondary efficacy population for the irRECIST analysis included 109 patients, with 3 patients assessed as having measurable disease at baseline per IA
- In patients with dMMR non-endometrial solid tumors, irORR was 45.0% based on IA using irRECIST, compared with a 38.7% ORR by blinded independent central review using RECIST v1.1 assessments (Table 2)
  - The difference between irRECIST and RECIST assessments may suggest pseudoprogression
- Responses were seen across tumor types and were durable, with the majority of responders (87.8%) remaining in response as of the data cutoff date of March 1, 2020 (Figures 3 and 4)

Table 2. irRECIST and RECIST v1.1 Analyses

Immune-related secondary endpoints (irRECIST by IA)		Primary endpoints[5] (RECIST v1.1 by BICR)	
Variable	Cohort F (N=109)	Variable	Cohort F (N=106)
irORR, n (%)	49 (45.0)	ORR, n (%)	41 (38.7)
irCR	6 (5.5)	CR	8 (7.5)
irPR	43 (39.4)	PR	33 (31.1)
irSD	27 (24.8)	SD	26 (24.5)
irPD	26 (23.9)	PD	32 (30.2)
NE	7 (6.4)	NE	7 (6.6)
irDCR,[a] n (%)	76 (69.7)	DCR,[a] n (%)	67 (63.2)
Follow-up, median, months	12.4	Follow-up, median, months	12.4
irDOR,[b] months	NR (1.74+ to 21.88+)	DOR,[b] months	NR (1.74+ to 21.88+)

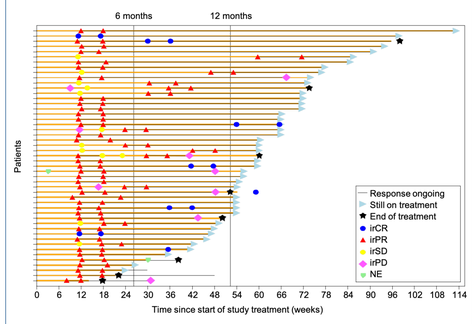
[a]Includes CR, PR, and SD ≥12 weeks; [b]Only includes responders.
CR, complete response; DCR, disease control rate; DOR, duration of response; IA, investigator assessment; ir, immune-related; ORR, objective response rate; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 3. Best Volume Change in Target Lesions, Based on Investigator Assessment per irRECIST



[a]Adrenal cortical carcinoma, biliary neoplasm, brain cancer, breast cancer, esophageal cancer, malignant neoplasm of the female genitals, liver cancer, ovarian cancer, pancreatic carcinoma, renal cell carcinoma, and unknown.
irRECIST, immune-related Response Evaluation Criteria in Solid Tumors.

Figure 4. Immune-Related Duration of Response



[a]Data cutoff date of March 1, 2020. CR, complete response; ir, immune-related; NE, nonevaluable; PD, progressive disease; PR, partial response; SD, stable disease.

- The safety population included 173 patients who had received ≥1 dose of dostarlimab
- Dostarlimab was well tolerated, with an adverse event profile similar to others in the drug class (Table 3)
  - 2 deaths associated with dostarlimab were reported

Table 3. Safety Summary

Characteristic	dMMR NEC (N=173)[a]
Safety summary, n (%)	
Any TEAE	167 (96.5)
Any-grade TRAE	119 (68.8)
Grade ≥3 TEAE	85 (49.1)
Grade ≥3 TRAE	20 (11.6)
Treatment-related SAE	13 (7.5)
Any TRAE leading to discontinuation	8 (4.6)
TRAE leading to death[b]	2 (1.2)
TEAEs in ≥1% of patients leading to discontinuation, n (%)	
ALT increased	2 (1.2)
AST increased	2 (1.2)
Any-grade TEAEs in ≥20% of patients, n (%)	
Anemia	55 (31.8)
Diarrhea	43 (24.9)
Asthenia	42 (24.3)
Grade ≥3 TEAEs in ≥2% of patients, n (%)	
Anemia	13 (7.5)
Abdominal pain	6 (3.5)
Sepsis	6 (3.5)
ALT increased	5 (2.9)
Hyponatremia	5 (2.9)
Asthenia	4 (2.3)
AST increased	4 (2.3)
Fatigue	4 (2.3)
Lipase increased	4 (2.3)
Vomiting	4 (2.3)
Grade ≥2 irTEAEs in ≥5% of patients, n (%)	
ALT increased	12 (6.9)
Diarrhea	11 (6.4)
AST increased	10 (5.8)
Hypothyroidism	9 (5.2)
Grade ≥3 irTEAEs in ≥1% of patients, n (%)	
ALT increased	5 (2.9)
AST increased	4 (2.3)
Lipase increased	3 (1.7)
Hyperglycemia	3 (1.7)
Diarrhea	2 (1.2)

[a]Safety population reflects a November 1, 2020, update; [b]1 hepatic ischemia and 1 suicide.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; dMMR, mismatch repair deficient; EC, endometrial cancer; ir, immune-related; NEC, non-endometrial cancer; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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Conflicts of Interest

Dr. André reports personal fees from Amgen, Astellas, AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Gritstone Oncology, Halliodx, Kaleido Biosciences, MSD Oncology, Pierre Fabre, Roche, Sanofi, Servier, and Vantana. **Dr. Curigliano** reports personal fees from Bristol Myers Squibb, Eli Lilly, Ellipsis, Novartis, Pfizer, Roche, and Seagen. **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. Trigo** reports institutional grants from AstraZeneca and MSD; and personal fees from AstraZeneca, Boehringer, Bristol Myers Squibb, MSD, and Takeda. **Dr. Ellard** reports GlaxoSmithKline stock ownership. **Dr. Moreno** reports personal fees from Bayer, Bristol Myers Squibb, Janssen, and Pieris. **Drs. Abdeddaim, Antón,** and **Berton** have nothing to disclose. **Drs. Kumar, Guo,** and **Im** are former employees of GlaxoSmithKline. **Dr. Starling** reports institutional grants from AstraZeneca, Bristol Myers Squibb, and Pfizer; honoraria from Eli Lilly, Merck Serono, MSD Oncology, Pierre Fabre, and Servier; and travel support from AstraZeneca, Bristol Myers Squibb, Eli Lilly, Merck, MSD Oncology, and Roche.

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