

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 GARNET³
- 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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Presenting author email: thierry.andre@aphp.fr

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Analysis of the Immune-Related Endpoints of the Mismatch Repair-Deficient Non-endometrial Solid Cancers Cohort from the GARNET Study

Thierry André,¹ Dominique Berton,² Giuseppe Curigliano,³ Hendrik-Tobias Arkenau,⁴ José Trigo,⁵ Susan Ellard,⁶ Victor Moreno,⁷ Cyril Abdeddaim,⁸ Antonio Antón,⁹ Sujatha Kumar,^{10*} Wei Guo,^{10*} Ellie Im,^{10*} Naureen Starling¹¹

¹Sorbonne University and Saint-Antoine Hospital, Paris, France; ²GINECO & Institut de Cancerologie de l'Ouest, Centre René Gauducheau, Saint-Herblain, France; ³Division of Early Drug Development for Innovative Therapies, IEO, European Institute of Oncology IRCCS, and University of Milano, Milan, Italy; ⁴Sarah Cannon Research Institute UK Limited, London, UK; ⁵Hospital Virgen de la Victoria y Regional IBIMA, Málaga, Spain; ⁶BC Cancer-Kelowna, British Columbia, Canada; ⁷START Madrid FJD, Fundación Jiménez Díaz Hospital, Madrid, Spain; ⁸Centre de Lutte Contre le Cancer Centre Oscar Lambret, Lille, France; ⁹Miguel Servet University Hospital, Zaragoza, Spain; ¹⁰GlaxoSmithKline, Waltham, MA, USA; ¹¹The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK. *Employed by GlaxoSmithKline when the study was conducted.

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

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

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

- MMR status was determined by immunohistochemistry
- 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

Part 1 Dose finding	Part 2A Fixed-dose safety run-in	Part 2B Expansion cohorts
A1: dMMR EC		
A2: MMRp EC		
E: NSCLC		
F: Non-endometrial dMMR/MSI-H basket		
G: PROC		

Key inclusion/exclusion criteria for cohort F:
•Patients with advanced dMMR or POLE-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)

^aAdrenal 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.

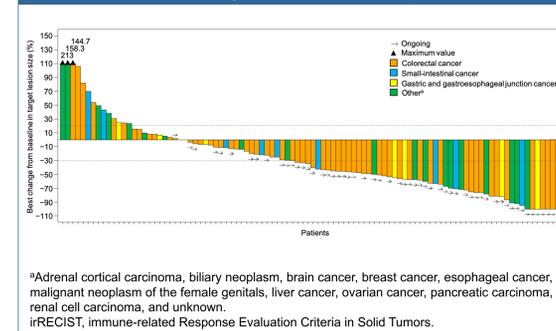
- The secondary efficacy population for the irRECIST analysis included 109 patients, with 3 patients assessed as having measurable disease at baseline per IA
- In patients with dMMR non-endometrial solid tumors, irORR was 45.0% based on IA using irRECIST, compared with a 38.7% ORR by blinded independent 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

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

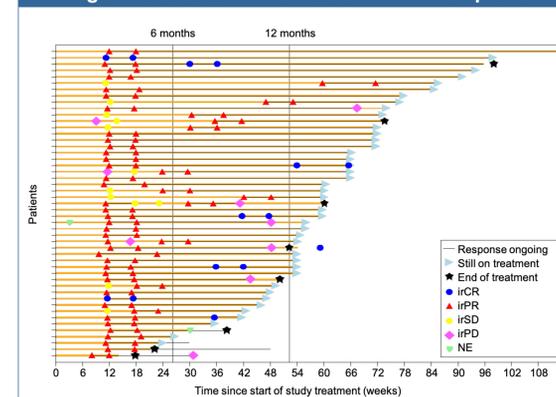
^aIncludes CR, PR, and SD ≥12 weeks; ^bOnly includes responders.
CR, complete response; DCR, disease control rate; DOR, duration of response; IA, investigator assessment; ir, immune-related; ORR, objective response rate; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial response;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

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



^aAdrenal 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



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

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- 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)

^aSafety population reflects a November 1, 2020, update; ^b1 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, Halodex, Kaledo Biosciences, MSD Oncology, Pierre Fabre, Roche, Sanofi, Servier, and Yantana. Dr. Curigliano reports personal fees from Bristol Myers Squibb, Eli Lilly, Eisai, Novartis, Pfizer, Roche, and Seagen. Dr. Arkenau reports consulting fees from Oncology; 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.