Safety and efficacy of anti–PD-1 antibody dostarlimab in patients (pts) with mismatch repair-deficient (dMMR) solid cancers: Results from GARNET study

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Disclosures

- Dr. André reports:
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Background

- Dostarlimab (TSR-042) is an investigational, humanized, PD-1 monoclonal antibody[1]
  - Binds the PD-1 receptor, blocking the interaction with ligands PD-L1 and PD-L2[1]
- The ongoing GARNET trial (NCT02715284) is evaluating dostarlimab in patients with advanced solid tumors
- Presented here is antitumor activity and safety data from patients with mismatch mutation repair-deficient (dMMR) non-endometrial cancers, including mainly GI tumors
- Primary Objective
  - To measure antitumor activity by ORR and DOR as assessed by BICR per RECIST v1.1

1. Laken H, et al. *Eur J Cancer*. 2016;69(Suppl 1):S102.

BICR, blinded independent central review; dMMR, mismatch mutation repair-deficient; DOR, duration of response; GI, gastrointestinal; ORR, objective response rate; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; RECIST, Response Evaluation Criteria in Solid Tumors.

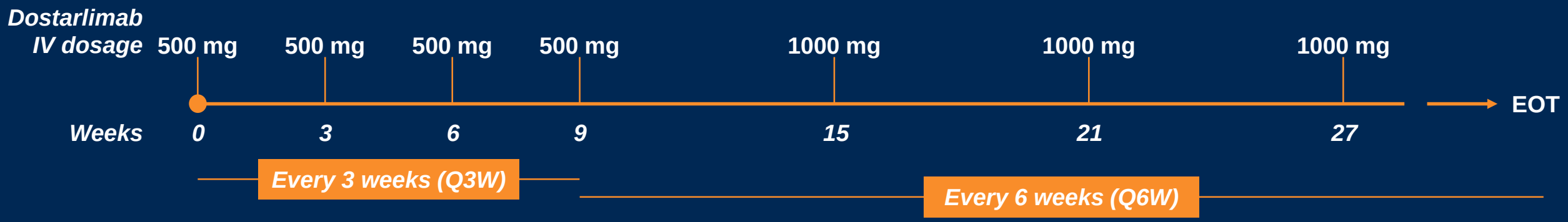
Key Inclusion Criteria

- Patients with advanced dMMR/MSI-H or POLE-mut solid tumors
- Patients must have progressive disease (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
- Patient with colorectal cancer (CRC) must have PD after or been intolerant to fluoropyrimidine, oxaliplatin, and irinotecan
- Screening was based on local testing results using immunohistochemistry (IHC), polymerase chain reaction (PCR), or next generation sequencing (NGS) performed in a certified local laboratory, but patient eligibility needed to be determined by MMR IHC results for this analysis

BICR, blinded independent central review; dMMR, mismatch mutation repair-deficient; MSI-H, microsatellite instability high; POLE-mut, polymerase ε-mutation; RECIST, Response Evaluation Criteria in Solid Tumors.

GARNET Dosing Schedule

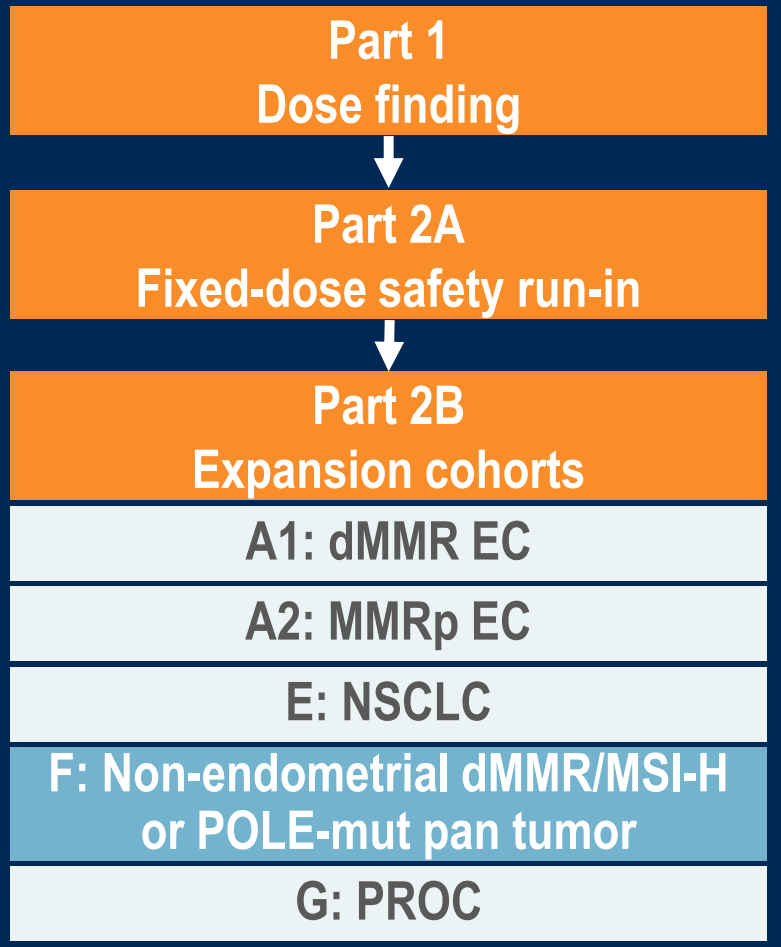
- Patients received 500 mg of dostarlimab Q3W for 4 cycles and 1000 mg of dostarlimab Q6W thereafter for up to 2 years or until disease progression or discontinuation



EOT, end of treatment; IV, intravenous; Q3W, every 3 weeks; Q6W, every 6 weeks.

Methods

- Cohort F: Non-endometrial dMMR/MSI-H or POLE-mut pan tumor
- Patients were included in the efficacy analysis if
  - Had locally determined dMMR by IHC
  - Received ≥1 dose of dostarlimab
  - Had measureable disease at baseline
  - Had ≥6 months of follow-up by the data cutoff date, March 1, 2020



dMMR, mismatch mutation repair-deficient; EC, endometrial cancer; MMRp, mismatch mutation repair-proficient; NSCLC, non-small cell lung cancer; POLE-mut, polymerase ε-mutation; PROC, platinum-resistant ovarian cancer.

Patient Demographics and Baseline Characteristics: Efficacy Population

Characteristic	Cohort F N=106
Median age, years (range)	61.5 (24–85)
Sex, n (%)	
Male	58 (55)
Female	48 (45)
ECOG performance status, n (%)	
0	42 (40)
1	64 (60)
Histology, n (%)	
Colorectal	69 (65)
Small intestine	12 (11)
Gastric and gastroesophageal junction	8 (8)
Pancreatic carcinoma	4 (4)
Ovarian	2 (2)
Hepatocellular carcinoma	2 (2)
Other[a]	9 (8)

[a]Biliary neoplasm, breast, esophageal, genital neoplasm malignant female, and unknown.
ECOG, Eastern Cooperative Oncology Group

- Of the efficacy population, 99 (93.4%) had GI tumors, including 69 (65%) with CRC

Characteristic	Cohort F N=106
Disease stage at restaging, n (%)	
Locally advanced	3 (3)
Metastatic	103 (97)
Number of prior lines of systemic therapy, n (%)	
1	25 (24)
2	48 (45)
3	25 (24)
≥4	8 (8)
Prior therapy, n (%)	
Surgery	92 (87)
Radiotherapy	21 (20)
Chemotherapy	106 (100)

Antitumor Activity

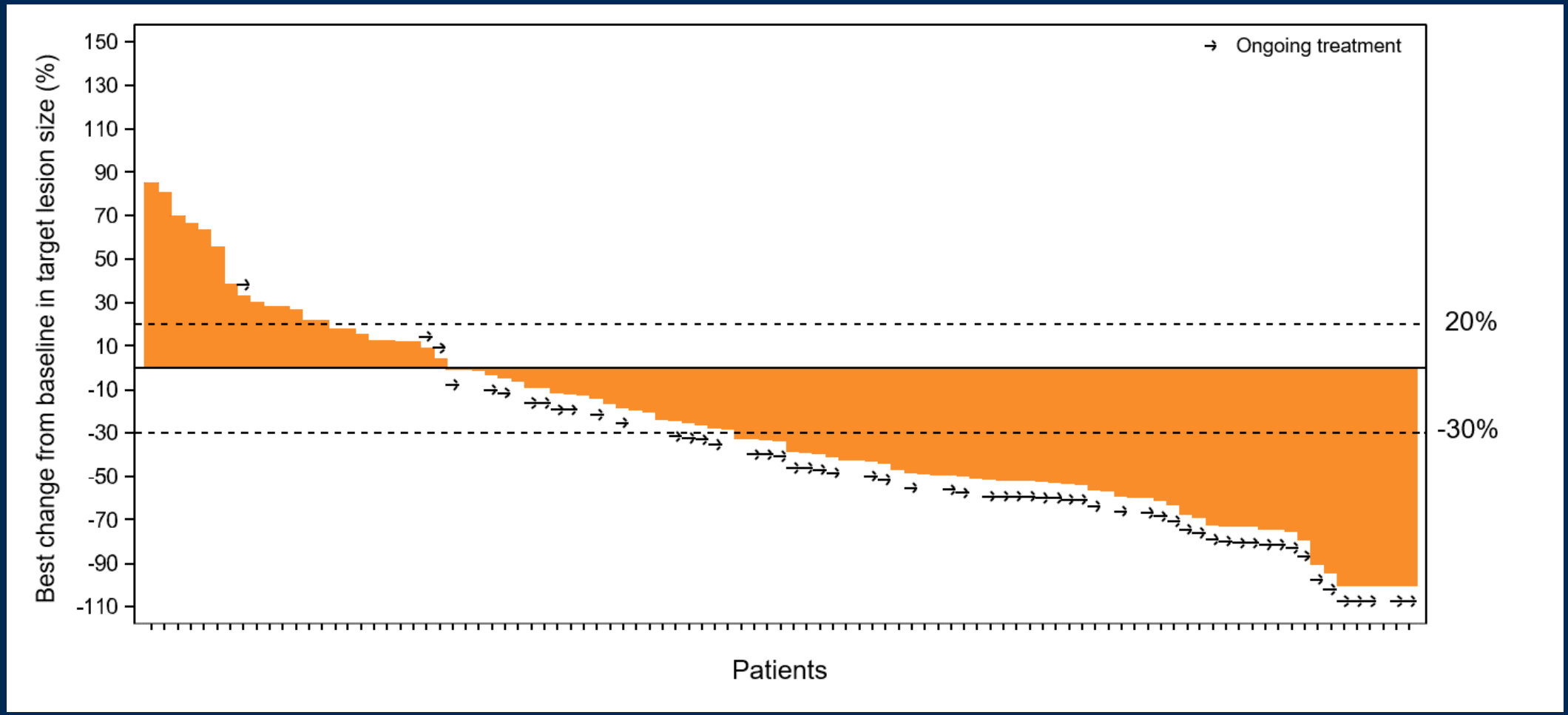
- Confirmed ORR by BICR per RECIST v1.1 in patients with dMMR was 38.7% (95% CI, 29.4–48.6)
  - CR rate of 8%
- ORR was consistent across both CRC and non-CRC tumor types

Tumor type	Patients, N	Confirmed ORR (RECIST v1.1)	
		n	95% CI[a]
Overall	**106**	**41 (38.7%)**	**(29.4%–48.6%)**
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	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	1	CR	
Breast cancer	1	CR	
Gallbladder	1	CR	
Adrenal cortical	1	PR	
Genital neoplasm malignant female	1	PR	
Pleural	1	PR	
Unknown origin	1	PR	
Renal cell carcinoma	1	SD	
Esophageal cancer	1	PD	

[a]Exact, 2-sided 95% CI for binomial proportion.

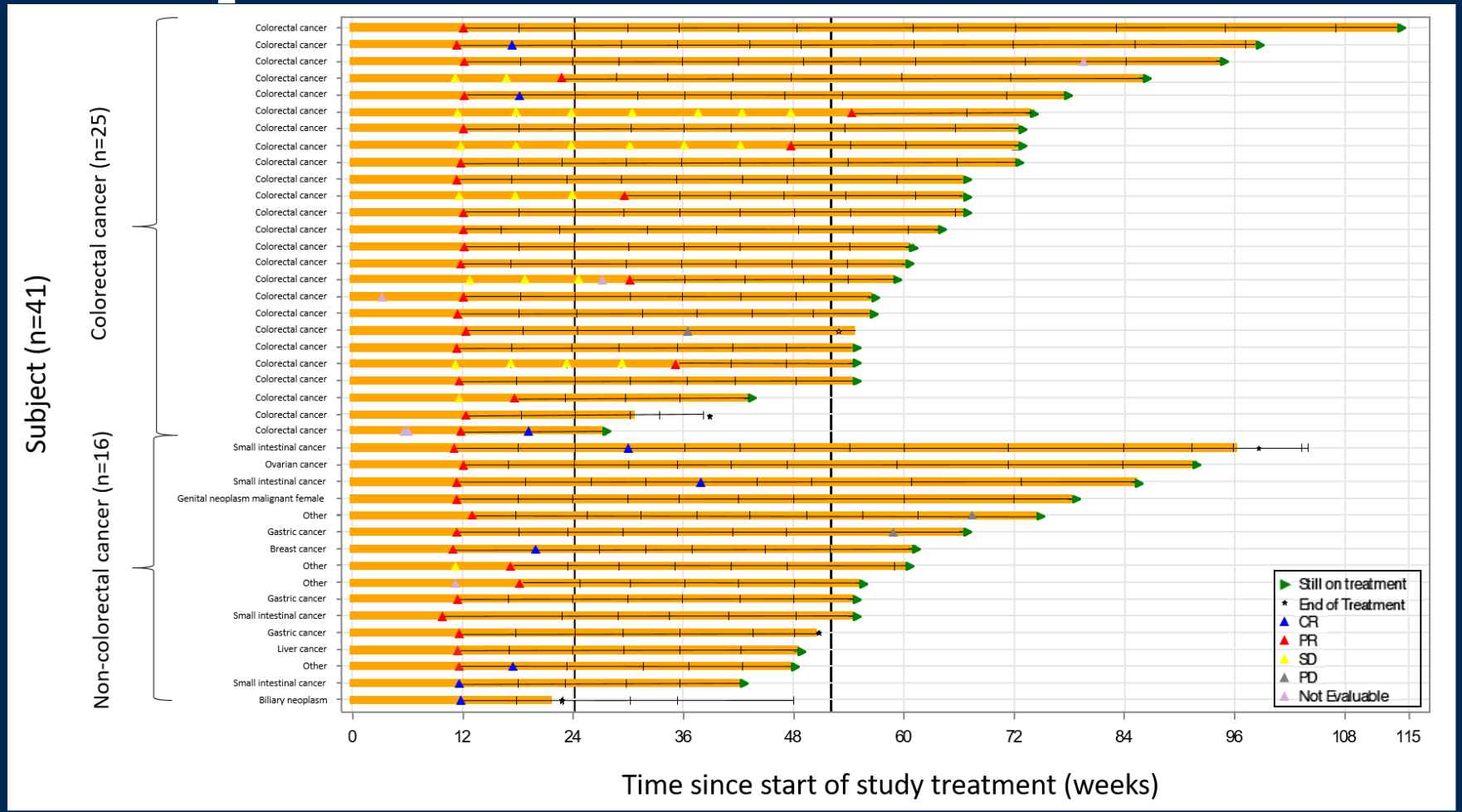
CRC, colorectal cancer; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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



Duration of Response

- For the 41 patients with a response, the median follow-up was 12.4 months
- Median DOR was not reached (range: 1.74–21.88 months)
- The probability of maintaining a response at 12 and 18 months was 91.0% and 80.9%, respectively[a]
- Responses were durable across tumor types



[a]Kaplan-Meier estimated probability

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Safety

- Safety population included 144 patients who received ≥1 dose of dostarlimab
- Most treatment-emergent adverse events were low grade and manageable
- Grade ≥3 treatment-related adverse events occurred in 12 (8%) patients
- 5 (3.5%) patients discontinued treatment due to treatment-related adverse events
- No deaths associated with dostarlimab were reported

Safety Summary, n (%)	Cohort F (N=144[a])
Any TEAE	140 (97)
Grade ≥3 TEAE	61 (42)
Any grade TRAE	99 (69)
Grade ≥3 TRAE	12 (8)
Treatment-related SAE	9 (6)
Any TRAE leading to discontinuation	5 (4)
TRAE leading to death	0

[a]Includes 2 patients with POLE mutation plus dMMR, 3 patients with POLE mutation plus MMRp, and 139 patients dMMR only.
dMMR, mismatch mutation repair-deficient; MMRp, mismatch mutation repair-proficient; POLE, polymerase ε; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Safety

Preferred term, n (%)	Cohort F (N=144[a])
Any grade TRAEs occurring in ≥5% of pts	
Asthenia	19 (13)
Diarrhea	18 (13)
Pruritis	18 (13)
Arthralgia	13 (9)
Fatigue	13 (9)
Hypothyroidism	12 (8)
Rash	12 (8)
AST increased	11 (8)
ALT increased	9 (6)
Nausea	8 (6)

Preferred term, n (%)	Cohort F (N=144[a])
Grade ≥3 TRAEs occurring in ≥1% of pts	
Lipase increased[b]	2 (1)
Hyperlipasemia[c]	2 (1)
Grade ≥3 irTRAEs	
Lipase increased	2 (1)
Adrenal insufficiency	1 (<1)
ALT increased	1 (<1)
AST increased	1 (<1)
Diarrhea	1 (<1)
Hyperthyroidism	1 (<1)
Rash	1 (<1)

[a]Includes 2 patients with POLE mutation plus dMMR, 3 patients with POLE mutation plus MMRp, and 139 patients dMMR only. [b]Includes 1 patient with both lipase increased and hyperlipasemia and 1 patient with only lipase increased. [c]Includes 1 patient with both lipase increased and hyperlipasemia and 1 patient with only hyperlipasemia.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; dMMR, mismatch mutation repair-deficient; irTRAE, immune-related treatment-related adverse event; MMRp, mismatch mutation repair-proficient; pt, patient; TRAE, treatment-related adverse event.

Conclusions

- Majority of patients were enrolled with advanced disease that had progressed on prior therapy with limited treatment options
  - These represent patients with a high unmet need
- Convenient schedule of administration (Q3W for 4 cycles then Q6W)
- Dostarlimab demonstrated durable antitumor activity in a cohort of patients with locally determined dMMR CRC and non-CRC solid tumors
  - Majority of this cohort were GI tumors (93.4% were GI tumors, 65% were CRC tumors)
  - Responses were seen across all tumor types
- No new safety signals were detected and most TRAEs were low grade
  - Only 3.5% of patients discontinued dostarlimab due to a TRAE
  - Grade ≥3 TRAEs occurred in 12 (8%) of patients
  - No deaths were attributed to dostarlimab
- Cohort is open for further enrollment
    - Follow-up is ongoing and will be reported at future data cuts
    - Data for the whole cohort with dMMR and MSI determination centrally will be reported in the future

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GARNET Cohort F Investigators

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