Time Course of Treatment-Related Adverse Events During Dostarlimab Therapy in the GARNET Trial

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Background

Dostarlimab is a humanized programmed death 1 (PD-1) receptor monoclonal antibody that blocks interaction with the ligands PD-L1 and PD-L2

In the US, dostarlimab is approved as a monotherapy in adult patients with the following:

- Recurrent or advanced mismatch repair deficient (dMMR) endometrial cancer (EC) that has progressed on or after a platinum-containing regimen[1]
- A dMMR solid tumor that has progressed on or after prior treatment and who have no satisfactory alternative treatment options[2]

In the EU, dostarlimab is approved as a monotherapy in adult patients with recurrent or advanced dMMR/microsatellite instability–high (MSI-H) EC that has progressed on or after treatment with a platinum-containing regimen[3]

GARNET (NCT02715284) is a phase 1 study assessing the antitumor activity and safety of dostarlimab monotherapy in patients with solid tumors[4]

Objective

To evaluate the time of onset of TRAEs and irTRAEs during dostarlimab treatment across the part 2B cohorts of the GARNET trial: cohort A1 (dMMR EC), cohort A2 (mismatch repair proficient [MMRp] EC), cohort E (non–small cell lung cancer [NSCLC]), and cohort F (dMMR non-EC)

Methods

GARNET is a phase 1, multicenter, open-label, single-arm study of dostarlimab in multiple tumor types

In part 2B, dostarlimab was dosed at the recommended therapeutic dose determined from parts 1 and 2A

- 500 mg intravenously every 3 weeks for 4 cycles, then 1000 mg every 6 weeks until disease progression or discontinuation (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 local immunohistochemistry

Primary endpoints were evaluation of antitumor activity (in terms of objective response rate and duration of response), safety, and tolerability

The data cutoff date was March 1, 2020

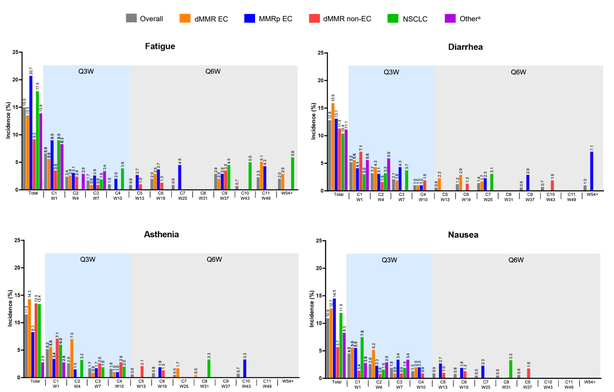
Results

Table 1. Safety Summary

Event, n (%)	Overall (N=515)	Cohort A1 dMMR EC (N=126)	Cohort A2 MMRp EC (N=145)	Cohort F dMMR non-EC (N=141)	Cohort E NSCLC (N=67)	Other[a] (N=36)
Any TEAE	504 (97.9)	120 (95.2)	145 (100.0)	137 (97.2)	67 (100.0)	35 (97.2)
Grade ≥3 TEAE	259 (50.3)	61 (48.4)	81 (55.9)	61 (43.3)	37 (55.2)	19 (52.8)
Any-grade TRAE	346 (67.2)	80 (63.5)	104 (71.7)	96 (68.1)	46 (68.7)	20 (55.6)
Grade ≥3 TRAE	70 (13.6)	17 (13.5)	28 (19.3)	12 (8.5)	9 (13.4)	4 (11.1)
Treatment-related SAE	40 (7.8)	12 (9.5)	13 (9.0)	9 (6.4)	5 (7.5)	1 (2.8)
Any TRAE leading to discontinuation	25 (4.9)	5 (4.0)	10 (6.9)	5 (3.5)	4 (6.0)	1 (2.8)
TRAE leading to death	0	0	0	0	0	0

[a]Other includes 19 patients with MMR status unknown EC, 13 patients with MMR status unknown non-EC, and 4 patients with MMRp non-EC. dMMR, mismatch repair deficient; EC, endometrial cancer; MMR, mismatch repair; MMRp, mismatch repair proficient; NSCLC, non–small cell lung cancer; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

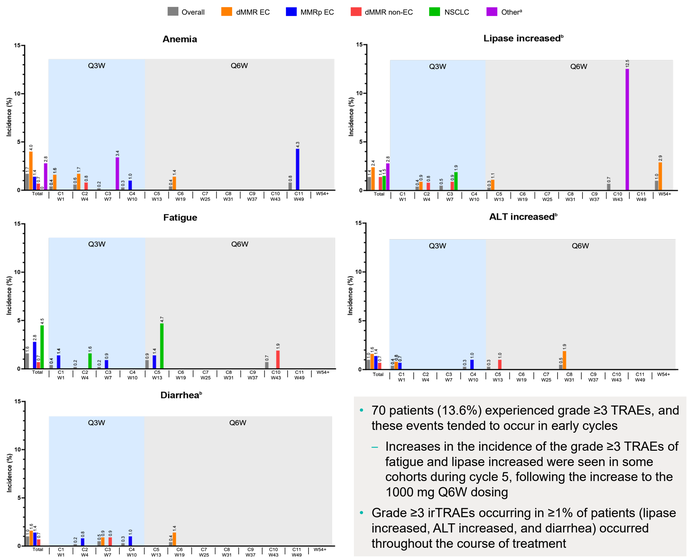
Figure 2. TRAEs Occurring in ≥10% of Patients, by Cycle



- Few TRAEs were seen in ≥10% of patients overall
- More than 72% of TRAEs, including fatigue, diarrhea, asthenia, and nausea, occurred during cycles 1–4

[a]Other includes 19 patients with MMR status unknown EC, 13 patients with MMR status unknown non-EC, and 4 patients with MMRp non-EC. C, cycle; dMMR, mismatch repair deficient; EC, endometrial cancer; MMR, mismatch repair; MMRp, mismatch repair proficient; NSCLC, non–small cell lung cancer; Q3W, every 3 weeks; Q6W, every 6 weeks; TRAE,treatment-related adverse event; W, week.

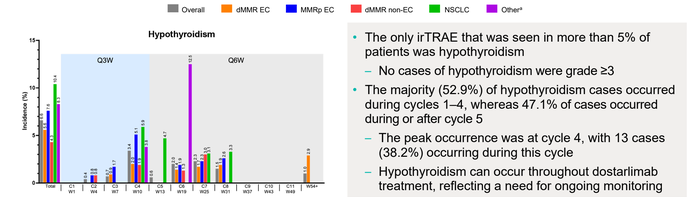
Figure 3. Grade ≥3 TRAEs Occurring in ≥1% of Patients, by Cycle



- 70 patients (13.6%) experienced grade ≥3 TRAEs, and these events tended to occur in early cycles
  - Increases in the incidence of the grade ≥3 TRAEs of fatigue and lipase increased were seen in some cohorts during cycle 5, following the increase to the 1000 mg Q6W dosing
- Grade ≥3 irTRAEs occurring in ≥1% of patients (lipase increased, ALT increased, and diarrhea) occurred throughout the course of treatment

[a]Other includes 19 patients with MMR status unknown EC, 13 patients with MMR status unknown non-EC, and 4 patients with MMRp non-EC;
[b]Lipase increased, ALT increased, and diarrhea were the only grade ≥3 irTRAEs occurring in ≥1% of patients.
ALT, alanine aminotransferase; C, cycle; dMMR, mismatch repair deficient; EC, endometrial cancer; MMR, mismatch repair; MMRp, mismatch repair proficient; NSCLC, non–small cell lung cancer; Q3W, every 3 weeks; Q6W, every 6 weeks; TRAE, treatment-related adverse event; W, week.

Figure 4. Most Common irTRAE: Hypothyroidism, by Cycle



- The only irTRAE that was seen in more than 5% of patients was hypothyroidism
  - No cases of hypothyroidism were grade ≥3
- The majority (52.9%) of hypothyroidism cases occurred during cycles 1–4, whereas 47.1% of cases occurred during or after cycle 5
  - The peak occurrence was at cycle 4, with 13 cases (38.2%) occurring during this cycle
  - Hypothyroidism can occur throughout dostarlimab treatment, reflecting a need for ongoing monitoring

[a]Other includes 19 patients with MMR status unknown EC, 13 patients with MMR status unknown non-EC, and 4 patients with MMRp non-EC. C, cycle; dMMR, mismatch repair deficient; EC, endometrial cancer; ir, immune-related; MMR, mismatch repair; MMRp, mismatch repair proficient; NSCLC, non–small cell lung cancer; Q3W, every 3 weeks; Q6W, every 6 weeks; TRAE, treatment-related adverse event; W, week.

Table 2. Patients on Treatment at the Start of Each Dostarlimab Cycle

	Overall	C1 W1	C2 W4	C3 W7	C4 W10	C5 W13	C6 W19	C7 W25	C8 W31	C9 W37	C10 W43	C11 W49	W54+
Monotherapy overall	515	515	468	421	382	322	250	214	195	174	153	132	101
dMMR EC	126	126	115	107	99	87	69	60	54	50	43	39	34
MMRp EC	145	145	130	116	99	73	54	44	39	34	30	23	14
dMMR non-EC	141	141	127	115	107	97	77	66	60	57	52	47	33
NSCLC	67	67	62	54	51	43	34	32	30	22	20	19	17
Other[a]	36	36	34	29	26	22	16	12	12	11	8	4	3

[a]Other includes 19 patients with MMR status unknown EC, 13 patients with MMR status unknown non-EC, and 4 patients with MMRp non-EC. C, cycle; dMMR, mismatch repair deficient; EC, endometrial cancer; MMR, mismatch repair; MMRp, mismatch repair proficient; NSCLC, non–small cell lung cancer; W, week.

Table 3. Resolution of Grade ≥3 TRAEs

Category	Patients with TRAE, N[a,b]	Resolved, n (%)	Median time to resolution, (range), days
Investigations	23	18 (78.3)	15.5 (1–107)
Gastrointestinal disorders	16	12 (75.0)	19.5 (2–69)
Blood and lymphatic system disorders	12	12 (100)	8.0 (2–64)
General disorders and administration site conditions	11	7 (63.6)	11.0 (2–22)
Metabolism and nutrition disorders	7	6 (85.7)	17.0 (1–45)
Skin and subcutaneous tissue disorders	5	5 (100)	14.0 (3–30)
Endocrine disorders	4	3 (75.0)	15.0 (6–16)
Respiratory, thoracic, and mediastinal disorders	4	2 (50.0)	9.5 (3–16)
Vascular disorders	4	4 (100)	3.0 (1–27)
Infections and infestations	3	2 (66.7)	5.0 (5–5)
Hepatobiliary disorders	2	2 (100)	14.5 (11–18)
Nervous system disorders	2	2 (100)	9.0 (1–17)
Injury, poisoning, and procedural complications	1	1 (100)	1.0 (1–1)
Musculoskeletal and connective tissue disorders	1	1 (100)	30.0 (30–30)

[a]Individual patients may have experienced more than one category of grade ≥3 TRAE; [b]If a patient experienced the same event multiple times the highest grade was taken. If a patient experienced the same event with the same grade more than once, the longest time to recovery was taken. If a patient experienced the same event multiple times within the highest grade within the same time to recovery, all events must have resolved to be counted.
TRAE, treatment-related adverse event.

Conclusions

- No new safety signals were detected with dostarlimab compared to other anti–PD-1 inhibitors
- Most treatment-related adverse events (TRAEs) were low grade and occurred in the first 4 cycles (the first 12 weeks of treatment)
  - Some cases occurred later, suggesting a need for ongoing monitoring
  - The irTRAE hypothyroidism peaked during cycle 4 and occurred throughout the study period
- Few increases in the incidence of TRAEs were seen during cycle 5, following the transition to the 1000 mg every 6 weeks (Q6W) dosing schedule
  - The TRAEs with increased incidence after transition were fatigue and lipase increased
- Across the categories of grade ≥3 TRAEs observed, the majority resolved with a median time to resolution ranging from 1 to 30 days

Disclosures

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