The Time Course of Adverse Events During Dostarlimab Treatment in Patients with Recurrent or Advanced Endometrial Cancer in the GARNET Trial

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

Background

- Endometrial cancer (EC) is the most common gynaecological malignancy in the US and EU
  - EC has demonstrated an approximately 30% rate of mismatch repair deficient (dMMR) and microsatellite instability–high (MSI-H) tumours, the highest among all tumours
- Dostarlimab (TSR-042) is a programmed death 1 (PD-1) receptor monoclonal antibody that blocks interaction with ligands PD-L1 and PD-L2
  - Dostarlimab has demonstrated clinical activity in advanced solid tumours, including dMMR EC, colorectal cancer, and non–small cell lung cancer
- In the EU, dostarlimab is approved as a monotherapy in adult patients with dMMR/MSI-H recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen
- In the US, dostarlimab is approved as a monotherapy in adult patients with dMMR recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen and in adult patients with dMMR recurrent or advanced solid tumours that have progressed on or following prior treatment and who have no satisfactory alternative treatment options
- The ongoing GARNET trial (NCT02715284) is evaluating dostarlimab in patients with advanced solid tumours

Conclusions

- Dostarlimab has an acceptable safety profile with manageable adverse events when analysed over the dMMR and mismatch repair proficient (MMRp) EC safety population of the GARNET trial
- Only 5.5% of patients discontinued treatment because of treatment-related adverse events (TRAEs)
- TRAEs and immune-related TRAEs (irTRAEs) were seen in a low percentage of patients
- TRAEs and irTRAEs were seen more frequently earlier in the time course of dostarlimab treatment
  - irTRAEs were infrequent but could be seen throughout the course of treatment, so careful monitoring is necessary
- No increase in the rate of TRAEs or irTRAEs was seen when changing to the 1000-mg Q6W dosage of dostarlimab

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References

1. Oaknin A, et al. Poster presentation at the European Society for Gynecological Oncology (ESGO) State of the Art Conference; December 14–16, 2020; virtual meeting. Abstract 385.
2. Oaknin A, et al. Oral presentation at European Society for Medical Oncology (ESMO) 45th Congress; September 19–21, 2020; virtual meeting. LBA36.

Acknowledgments

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Conflicts of Interest

Dr. Oaknin reports consulting fees from AstraZeneca, Deciphera Pharmaceutical, Genmab, GlaxoSmithKline, Immunogen, Mersana Therapeutics, MSD, Roche, and Sutro; institutional grants from Abbvie Deutchland, Ability Pharmaceuticals, Advaxis Inc, Aeterna Zentaris, Amgen SA, Aprea Therapeutics AB, Bristol Meyers Squibb, Clovis Oncology Inc, Eisai Ltd, F. Hoffmann–La Roche Ltd, GlaxoSmithKline, Immunogen Inc, Merck Sharp & Dohme de Espana SA, Millennium Pharmaceuticals Inc, PharmaMar, Regeneron Pharmaceuticals; and travel support from AstraZeneca, Clovis Oncology, PharmaMar, and Roche. **Dr. Gilbert** reports honoraria from AstraZeneca, Merck, and Pfizer. **Dr. Tinker** reports institutional grants from AstraZeneca; and personal fees from AstraZeneca and Eisai. **Dr. Pothuri** reports institutional grant support from AstraZeneca, Celsion, Clovis Oncology, Genentech/Roche, GlaxoSmithKline, Merck, and Mersana; and advisory board fees from Arquer, AstraZeneca, Clovis Oncology, GlaxoSmithKline, Elevar, Eisai, Merck, Mersana, and Toray. **Drs. Guo and Im** are former employees of GlaxoSmithKline.

Objective

- Presented here is the evaluation of the time of onset of TRAEs and irTRAEs during dostarlimab treatment in patients with dMMR (cohort A1) and MMRp (cohort A2) EC in the GARNET trial

Methods

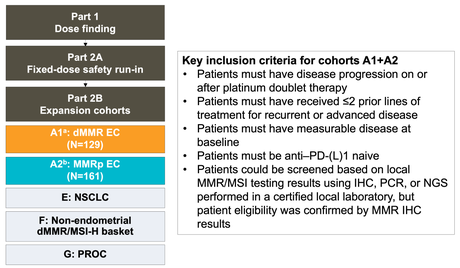
- GARNET is a phase 1, single-arm study of dostarlimab monotherapy in multiple tumour types
- In part 2B, dostarlimab was dosed at the recommended therapeutic dose determined from parts 1 and 2A
  - 500 mg intravenously every 3 weeks for 4 cycles, then 1000 mg every 6 weeks until disease progression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

Figure 1. GARNET Study Dosing Schedule

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

- Mismatch repair status was determined by immunohistochemistry (Figure 2)
- Primary endpoints were objective response rate (ORR) and duration of response (DOR)
- Data cutoff date was March 1, 2020

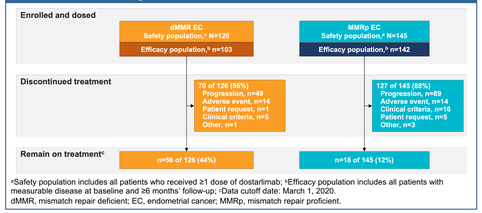
Figure 2. GARNET Trial Design



[a]Cohort enrollment includes 3 patients with MMRunk/MSI-H disease; [b]Cohort enrollment includes 16 patients with MMRunk/MSS disease. dMMR, mismatch repair deficient; IHC, immunohistochemistry; MMR, mismatch mutation repair; MMRp, mismatch repair proficient; MMRunk, mismatch repair status unknown; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSS, microsatellite stable; NGS, next–generation sequencing; NSCLC, non–small cell lung cancer; PCR, polymerase chain reaction; PD-(L)1, programmed death (ligand) 1; PROC, platinum-resistant ovarian cancer.

Results

Figure 3. Enrollment and Outcomes



[a]Safety population includes all patients who received ≥1 dose of dostarlimab; [b]Efficacy population includes all patients with measurable disease at baseline and ≥6 months' follow-up; [c]Data cutoff date: March 1, 2020.
dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient.

Results *(cont'd)*

Table 1. Demographics and Baseline Characteristics

Characteristic	dMMR EC (n=103)	MMRp EC (n=142)
Age, median (range), years	**65 (39–80)**	**66 (30–86)**
Disease stage,[a] n (%)		
Stage III or IV at primary diagnosis	56 (54.4)	88 (62.0)
Stage I or II at primary diagnosis	47 (45.6)	53 (37.3)
Histology,[b] n (%)		
Endometrioid carcinoma type I (grades 1 and 2)	**70 (68.0)**	**33 (23.2)**
Endometrial carcinoma type II	**32 (31.1)**	**109 (76.8)**
Serous	4 (3.9)	54 (38.0)
Clear cell	1 (<1)	9 (6.3)
Squamous	1 (<1)	3 (2.1)
Undifferentiated	4 (3.9)	3 (2.1)
Carcinosarcoma	0	2 (1.4)
Mixed carcinoma	4 (3.9)	9 (6.3)
Unspecified	14 (13.6)	22 (15.5)
Adenocarcinoma[c]	4 (3.9)	7 (4.9)
Prior lines of therapy, n (%)		
1	65 (63.1)	65 (45.8)
2	27 (26.2)	62 (43.7)
≥3	11 (10.7)	15 (10.6)
Prior radiation, n (%)	**73 (70.9)**	**88 (62.0)**

[a]One patient with MMRp EC had disease status/stage unknown; [b]Includes one patient with unknown histology; [c]Includes adenocarcinoma and adenocarcinoma with ambiguous differentiation.
dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient.

- The ORR was 44.7% in patients with dMMR EC and 13.4% in patients with MMRp EC (Table 2)
  - There were 11 complete responses and 35 partial responses in patients with dMMR EC and 3 complete responses and 16 partial responses in patients with MMRp EC

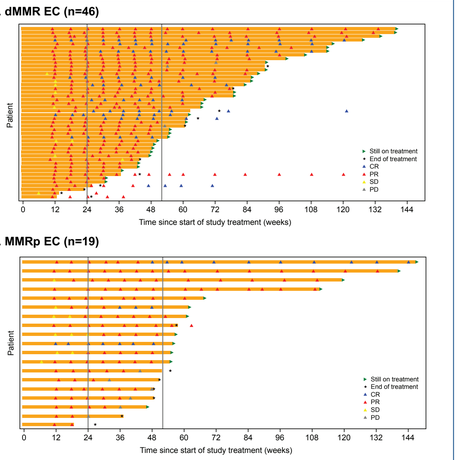
Table 2. Primary Endpoint Analysis: ORR[1]

Variable	dMMR EC (n=103)	MMRp EC (n=142)
Median follow-up time, months	**16.3**	**11.5**
ORR,[a] n (%, 95% CI)	**46 (44.7%, 34.9%–54.8%)**	**19 (13.4%, 8.3%–20.1%)**
CR, n (%)	11 (10.7)	3 (2.1)
PR, n (%)	35 (34.0)	16 (11.3)
SD, n (%)	13 (12.6)	31 (21.8)
PD, n (%)	39 (37.9)	77 (54.2)
NE, n (%)	5 (4.8)	15 (10.6)
Disease control rate,[b] n (%, 95% CI)	**59 (57.3%, 47.2%–67.0%)**	**50 (35.2%, 27.4%–43.7%)**
Response ongoing, n (%)	**41 (89.1)**	**12 (63.2)**
Median DOR (range), months	**NR (2.63 to 28.09+)**	**NR (1.54+ to 30.36+)**
Kaplan–Meier estimated probability of remaining in response		
at 6 months, %	97.8	83.0
at 12 months, %	90.6	61.3
at 18 months, %	79.2	61.3

[a]Responses required confirmation at a subsequent scan; SD had to be observed at ≥12 weeks on study to qualify as SD; [b]Includes confirmed CR, PR, or SD at ≥12 weeks.
CR, complete response; dMMR, mismatch repair deficient; DOR, duration of response; EC, endometrial cancer; MMRp, mismatch repair proficient; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

- Responses were durable among responders (Figure 4)
  - Median DOR was not reached in either the dMMR EC population (2.63 to 28.09+ months) or the MMRp EC population (1.54+ to 30.36+ months)
- At data cutoff (March 1, 2020), 41 responders with dMMR EC, or 89.1%, remained in response, and 12 responders with MMRp EC, or 63.2%, remained in response
- The safety population included 126 patients with dMMR EC and 145 patients with MMRp EC who had received ≥1 dose of dostarlimab (Table 3)
- Most treatment-emergent adverse events (TEAEs) were low grade and manageable
- Grade ≥3 TEAEs occurred in 52.4% of patients, and grade ≥3 TRAEs occurred in 16.6% of patients
- Only 15 (5.5%) patients discontinued treatment because of TRAEs
- No deaths associated with dostarlimab were reported

Figure 4. Primary Endpoint Analysis: DOR[1]



CR, complete response; dMMR, mismatch repair deficient; DOR, duration of response; EC, endometrial cancer; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease.

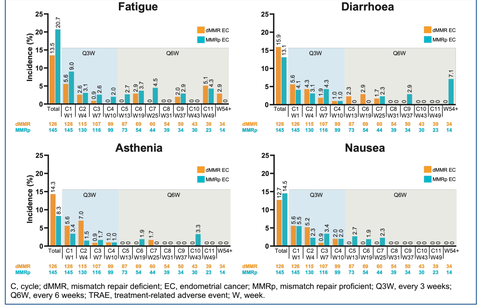
Table 3. Safety Summary[2]

Event, n (%)	dMMR EC (N=126)	MMRp EC (N=145)
Any TEAE	120 (95.2)	145 (100)
Grade ≥3 TEAE	61 (48.4)	81 (55.9)
Any-grade TRAE	80 (63.5)	104 (71.7)
Grade ≥3 TRAE	17 (13.5)	28 (19.3)
Treatment-related SAE	12 (9.5)	13 (9.0)
Any TRAE leading to discontinuation	5 (4.0)	10 (6.9)
TRAE leading to death	0	0

dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

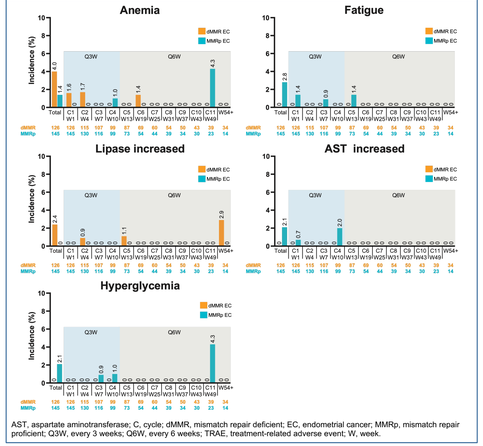
- Few TRAEs were seen in ≥10% of patients (Figure 5)
- 75% of the total cases of fatigue, diarrhoea, asthenia, and nausea occurred during cycles 1–3
- Grade ≥3 TRAEs were infrequent and tended to occur in early cycles (Figure 6)

Figure 5. TRAEs in ≥10% of Patients



C, cycle; dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; Q3W, every 3 weeks; Q6W, every 6 weeks; TRAE, treatment-related adverse event; W, week.

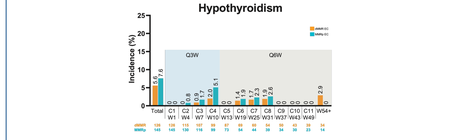
Figure 6. Grade ≥3 TRAEs Occurring in ≥2% of Patients, by Cycle



AST, aspartate aminotransferase; C, cycle; dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; Q3W, every 3 weeks; Q6W, every 6 weeks; TRAE, treatment-related adverse event; W, week.

- The only irTRAE seen in more than 5% of patients was hypothyroidism (Figure 7)
- 94% of hypothyroidism cases occurred between cycles 2 and 8, with a peak at cycle 4
  - Hypothyroidism can occur in later cycles, reflecting a need for ongoing monitoring

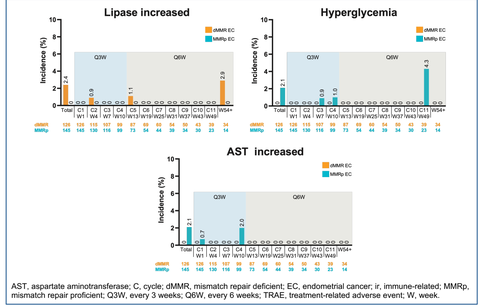
Figure 7. Most Common irTRAE: Hypothyroidism



C, cycle; dMMR, mismatch repair deficient; EC, endometrial cancer; ir, immune-related; MMRp, mismatch repair proficient; TRAE, treatment-related adverse event; W, week.

- irTRAEs were infrequent and occurred throughout the course of treatment (Figure 8)

Figure 8. Grade ≥3 irTRAEs Occurring in ≥2% of Patients, by Cycle



AST, aspartate aminotransferase; C, cycle; dMMR, mismatch repair deficient; EC, endometrial cancer; ir, immune-related; MMRp, mismatch repair proficient; Q3W, every 3 weeks; Q6W, every 6 weeks; TRAE, treatment-related adverse event; W, week.