Analysis of Antitumor Activity of Dostarlimab by Tumor Mutational Burden in Patients with Endometrial Cancer in the GARNET Trial

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**Employed by GlaxoSmithKline at the time this 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 EU, dostarlimab is approved as a monotherapy in adult patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability–high (MSI-H) endometrial cancer (EC) that has progressed on or after 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 after a platinum-containing regimen
- GARNET (NCT02715284) is a phase 1, single-arm study of dostarlimab monotherapy in multiple tumor types, including 2 EC cohorts
- Tumor mutational burden (TMB) has been studied as a predictor of response to anti–PD-1 therapy, although with limited data for EC[1]

Conclusions

- TMB-high (TMB-H) status and dMMR/MSI-H status show substantial overlap in the patient populations with EC
- TMB-H and dMMR/MSI-H EC have similar response rates
- Notably, the objective response rate (ORR) of patients with mismatch repair proficient (MMRp) and TMB-H EC was comparable to the ORR of patients with dMMR/MSI-H and TMB-H EC
  - TMB-H status in the patients with MMRp EC was not due to MSI-H (hypermutated) or POLε-mutated (ultramutated) status
- The study was not powered to assess antitumor activity by TMB status, and interpretation is limited by the small number of patients in each subgroup

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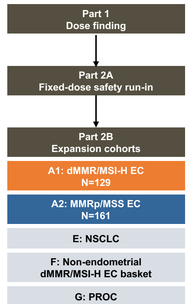
Objective

- To examine the antitumor activity of dostarlimab in patients with dMMR/MSI-H or MMRp/microsatellite stable (MSS) EC by TMB status

Methods

- GARNET (NCT02715284) is a phase 1, single-arm study of dostarlimab monotherapy in expansion cohorts in multiple tumor types (Figure 1)

Figure 1. Trial Design



Key inclusion/exclusion criteria for cohorts A1 and A2:

- Patients must have progression on or after platinum doublet therapy
- Patients must have received ≤2 prior lines of treatment for recurrent or advanced disease
- Patients must have measurable disease at baseline
- Patients must be anti–PD-(L)1 naive
- Patients could be screened based on local MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but patient cohort assignment was by MMR IHC results

dMMR, mismatch repair deficient; EC, endometrial cancer; IHC, immunohistochemistry; MMR, mismatch repair; MMRp, mismatch repair proficient; 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.

- Patients received 500 mg of dostarlimab IV every 3 weeks for 4 cycles, then 1000 mg IV every 6 weeks until disease progression
- The primary endpoints are ORR and duration of response by Response Evaluation Criteria in Solid Tumors version 1.1 per blinded independent central review
- This analysis of antitumor activity by TMB status is a post hoc analysis
- TMB status was an exploratory biomarker determined using the Foundation One test
- TMB-H status was defined as ≥10 mutations/megabase; TMB-L status was defined as <10 mutations/megabase
- Data reported are from a prespecified interim analysis with a data cutoff date of March 1, 2020

Results

- 129 patients with dMMR/MSI-H EC and 161 patients with MMRp/MSS EC had been enrolled and treated as of the data cutoff date of March 1, 2020; these patients constitute the safety populations of cohorts A1 and A2, respectively
- The primary efficacy population included those patients with ≥24 weeks of follow-up time in the study and with ≥1 measurable lesion at baseline per blinded independent central review
  - In total, 105 patients with dMMR/MSI-H EC and 156 patients with MMRp/MSS EC had data available and were included in this analysis (Table 1)

Table 1. Demographics and Baseline Characteristics

Characteristic	dMMR/MSI-H EC (n=105)	MMRp/MSS EC (n=156)
Age, median (range), years	63.5 (39–80)	64.5 (30–86)
Disease stage, n (%)[a]		
FIGO stage I or II at primary diagnosis	57 (54.3)	57 (36.5)
FIGO stage III or IV at primary diagnosis	48 (45.7)	98 (62.8)
Histology, n (%)[b]		
Endometrioid carcinoma grades 1 or 2	71 (67.6)	35 (22.4)
Serous	4 (3.8)	59 (37.8)
Clear cell	1 (1.0)	10 (6.4)
Squamous	1 (1.0)	3 (1.9)
Undifferentiated	4 (3.8)	3 (1.9)
Carcinosarcoma	0	2 (1.3)
Mixed carcinoma	4 (3.8)	11 (7.1)
Unspecified	14 (13.3)	24 (15.4)
Adenocarcinoma[c]	5 (4.8)	9 (5.8)
Prior lines of therapy, n (%)[d]		
1	66 (62.9)	72 (46.2)
2	27 (25.7)	67 (42.9)
≥3	12 (11.4)	17 (10.9)
Prior radiation	74 (70.5)	95 (60.9)

[a]One patient with MMRp EC had disease status/stage unknown; [b]Includes 1 patient with unknown histology; [c]Includes adenocarcinoma and adenocarcinoma with ambiguous differentiation; [d]Includes all prior lines of therapy, not just those in the recurrent setting.
dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; MSI-H, microsatellite instability high; MSS, microsatellite stable; FIGO, International Federation of Gynecology and Obstetrics.

Acknowledgments

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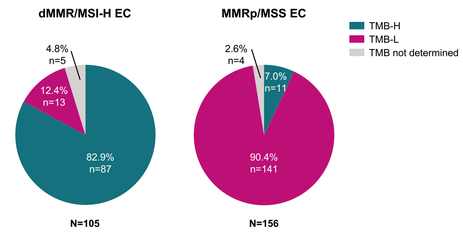
- TMB results by cohort are shown in Figure 2 and Table 2
  - TMB-H status was more common in the dMMR/MSI-H EC cohort than in the MMRp/MSS cohort

Figure 2. TMB Status by Cohort



dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; MSI-H, microsatellite instability high; MSS, microsatellite stable; TMB, tumor mutational burden; TMB-H, tumor mutational burden high; TMB-L, tumor mutational burden low.

Table 2. Mutations/Megabase by Cohort in Patients with a Known TMB Score Available

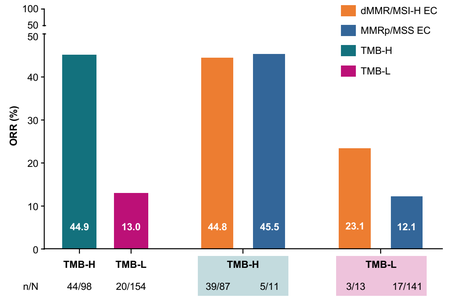
Parameter	dMMR/MSI-H EC (n=100)	MMRp/MSS EC (n=152)
Median (range)	20.17 (2.52–428.69)	3.78 (0–83.22)
Mean (StDev)	28.39 (45.39)	4.68 (7.28)

dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; MSI-H, microsatellite instability high; MSS, microsatellite stable; StDev, standard deviation; TMB, tumor mutational burden.

Objective Response Rate

- Patients with TMB-H status showed high response rates regardless of MMR or MSI status (Figure 3)
  - Although the sample size is limited, and few patients with MMRp EC were TMB-H, the ORR of patients with MMRp/MSS and TMB-H EC (45.5%) is comparable to patients with dMMR/MSI-H and TMB-H EC (44.8%) (Table 3)
- Of the 11 patients with MMRp/TMB-H EC, all had MSI and POLε test results available: 1 patient was MSI-H according to Foundation Medicine next-generation sequencing testing, and 1 patient had an intermediate MSI score; 9 were MSS. None of the 11 patients had a POLε exonuclease domain mutation identified

Figure 3. ORR by TMB Status (Pooled and by Cohort)



10 mutations/megabase (FDA-approved threshold) was used as the threshold for TMB-H status.
dMMR, mismatch repair deficient; EC, endometrial cancer; FDA, Food and Drug Administration; MMRp, mismatch repair proficient; MSI-H, microsatellite instability high; MSS, microsatellite stable; ORR, objective response rate; TMB, tumor mutational burden; TMB-H, tumor mutational burden high; TMB-L, tumor mutational burden low.

Table 3. ORR Breakdown by TMB Status and Cohort

n/N[a] (% [95% CI])	dMMR/MSI-H EC	MMRp/MSS EC	Overall
TMB-H	39/87 (44.8 [34.1–55.9])	5/11 (45.5 [16.7–76.6])	**44/98 (44.9 [34.8–55.3])**
TMB-L	3/13 (23.1 [5.0–53.8])	17/141 (12.1 [7.2–18.6])	**20/154 (13.0 [8.1–19.3])**
TMB not determined	5/5 (100 [47.8–100])	0/4 (0 [0–60.2])	**5/9 (55.6 [21.2–86.3])**
Overall	**47/105 (44.8 [35.0–54.8])**	**22/156 (14.1 [9.1–20.6])**	

[a]N (denominator) represents the number of patients in the group; n (numerator) represents the number of patients in the group with a response. 95% CIs were calculated using the Clopper-Pearson method.
dMMR, mismatch repair deficient; EC, endometrial cancer; FDA, Food and Drug Administration; MMRp, mismatch repair proficient; MSI-H, microsatellite instability high; MSS, microsatellite stable; ORR, objective response rate; TMB, tumor mutational burden; TMB-H, tumor mutational burden high; TMB-L, tumor mutational burden low.

Safety

- Safety on these patients has been previously reported[2]

Conflicts of Interest

Dr. Oaknin reports consulting fees from Deciphera Pharmaceuticals, Genmab, GlaxoSmithKline, Immunogen, and Mersana Therapeutics; institutional grants from Abbie Deutchland, Ability Pharmaceuticals, Advaxis Inc, Aeterna Zentaris, Amgen SA, Aprea Therapeutics AB, Bristol Myers Squibb, Clovis Oncology Inc, Eisai Ltd, F. Hoffmann–La Roche Ltd, GlaxoSmithKline, Immunogen Inc, Merck Sharp & Dohme de Espana SA, Millennium Pharmaceuticals Inc, PharmaMar, and Regeneron Pharmaceuticals; and travel support from AstraZeneca, Clovis Oncology, PharmaMar, and Roche.

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