Efficacy and safety of dostarlimab in UK-specific patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) or DNA polymerase epsilon, catalytic subunit (POLƐ)-mutated solid tumours in the GARNET study

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Introduction

Dostarlimab is a PD-1 inhibitor with encouraging clinical activity in solid tumours.[1–6]

It is approved as monotherapy in Europe in adult patients with advanced/recurrent dMMR/MSI-H endometrial cancer (EC) that has progressed on or after platinum-based treatment.[7]

In the US, dostarlimab is approved for monotherapy use in adult patients with:

- Advanced/recurrent dMMR/MSI-H EC that has progressed on/after platinum-based treatment.
- Advanced/recurrent dMMR solid tumours that have progressed on/after prior therapy, with no satisfactory alternative treatment options.[8]

A UK-specific analysis of dostarlimab can provide clinicians with data representative of the UK population and treatment landscape.

Aim

Here we report the efficacy and safety of dostarlimab in a UK-specific population of cohort F of the GARNET trial (NCT02715284), with subgroup analysis in patients with colorectal cancer (CRC).

Methods

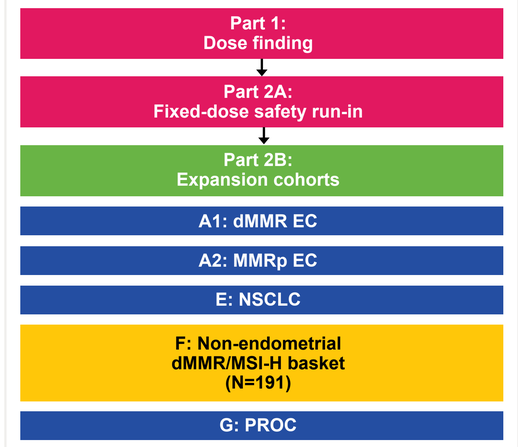
Study design

GARNET is a multi-centre, open-label, single-arm Phase I study.

Cohort F enrolled patients with advanced/recurrent dMMR/MSI-H or POLƐ-mutated, non-EC solid tumours (**Figure 1**).

Patients received dostarlimab 500 mg IV Q3W for 4 cycles, then 1000 mg Q6W until disease progression, discontinuation or withdrawal.

Figure 1. GARNET trial design



Key cohort F inclusion criteria:

- dMMR/MSI-H or POLƐ-mutated, measurable (by RECIST v1.1), advanced/recurrent non-EC solid tumours
- ECOG performance score 0–1
- Progression following prior systemic therapy, and no alternative treatment options
- Patients with CRC must have progressed after/been intolerant to, fluoropyrimidine, oxaliplatin and irinotecan

Key cohort F exclusion criteria:

- Prior anti–PD-(L)1 therapy
- Known uncontrolled central nervous system metastases
- Additional malignancy that progressed or required treatment within the last 2 years

Endpoints and analysis

Primary endpoints:

- ORR and DOR by BICR per RECIST v1.1
- Safety

Secondary endpoints:

- PFS, OS and DCR by BICR per RECIST v1.1

Data analysis:

- *Data are presented using summary statistics*
- *Two-sided 95% CIs are based on the Clopper-Pearson method*
- *Time-to-event analysis was performed using Kaplan-Meier methodology*
- *All patients who received ≥1 dose of dostarlimab were included in the safety analysis*
- *All patients in the safety population with measurable disease at baseline (defined as the existence of at least one target lesion) and ≥24 weeks of follow up were included in the efficacy analysis*

Results

Patient characteristics

Of 191 patients with dMMR solid tumours enrolled in Cohort F at the third prespecified interim analysis, 33 were UK patients (17%).

- Of the UK patients, 19 patients had CRC (58%).

Patient characteristics were similar between the overall UK-specific population and CRC subgroup (**Table 1**).

- There was no clear association between baseline characteristics evaluated and treatment response in UK CRC subgroup; however, most nonresponders had received ≥2 lines of prior therapy (77.8%).

Table 1. Patient characteristics

Characteristic	Overall UK population (n=33)	UK CRC subgroup		
		Total (n=19)	Responders (n=10)	Nonresponders (n=9)
Sex, n (%)				
Male	17 (51.5)	9 (47.4)	5 (50.0)	4 (44.4)
Female	16 (48.5)	10 (52.6)	5 (50.0)	5 (55.6)
Age, median (range)	58 (30–81)	57 (30–80)	56.5 (36–78)	59 (30–80)
Race, n (%)				
White	24 (72.7)	12 (63.2)	–	–
Non-White	5 (15.2)	4 (21.1)		
Unknown/not reported*	4 (12.1)	3 (15.8)		
ECOG PS, n (%)				
0	11 (33.3)	7 (36.8)	4 (40.0)	3 (33.3)
1	22 (66.7)	12 (63.2)	6 (60.0)	6 (66.7)
BMI, median (range)	24.2 (16.0–37.4)	25.2 (16.0–37.4)	26.8 (19.2–37.4)	23.6 (16.0–30.3)
Prior lines of therapy, n (%)				
<2	17 (51.5)	7 (36.8)	5 (50.0)	2 (22.2)
≥2	16 (48.5)	12 (63.2)	5 (50.0)	7 (77.8)

*In the overall UK population, race was unknown in 1 patient and not reported in 3 patients; in the UK CRC subgroup, race was not reported in 3 patients. Race was not reported in the responder and nonresponder groups due to low patient numbers.

Efficacy

In the overall UK efficacy population (n=31), ORR was 38.7%, with 4 CRs and 8 PRs (**Table 2**).

ORR was 52.6% (n=10) in the UK CRC subgroup, with 3 CRs and 7 PRs (**Table 2**).

- Median duration of follow-up was 16.5 (range: 0–39) months in the overall UK efficacy population, and 22.3 (range: 1–37) months in the UK CRC subgroup.

Median PFS was 5.4 months in the overall UK population, and not reached in the UK CRC subgroup (**Table 2**).

Median OS was 18.0 months in the overall UK population, and not reached in the UK CRC subgroup (**Table 2**).

Median DOR was not reached in either the overall UK population or the UK CRC subgroup.

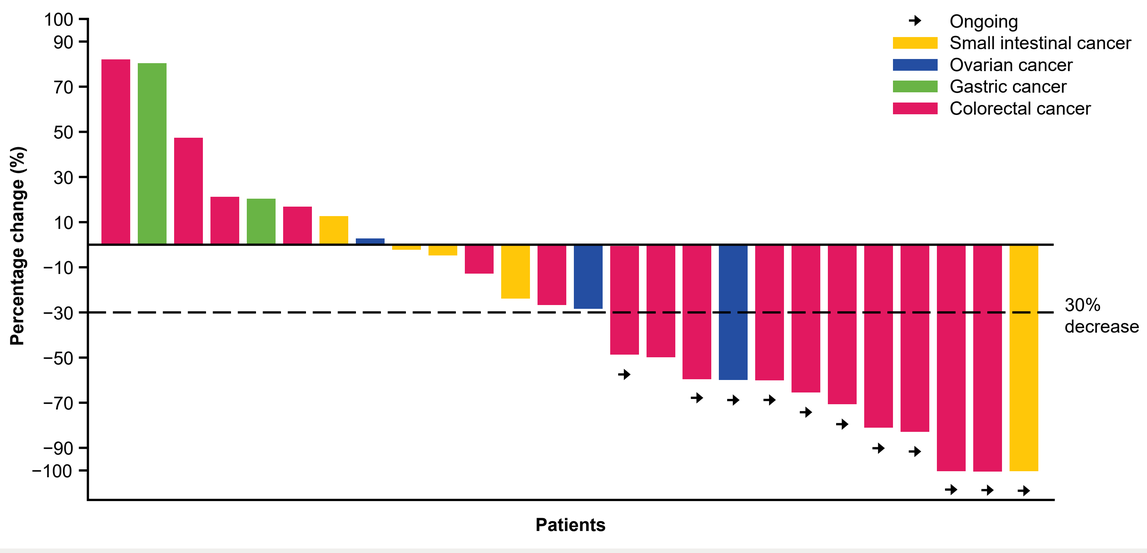
Target lesion size decreased in the majority of the UK CRC subgroup of patients (n=12/19, **Figure 2**).

Table 2. Clinical outcomes

Clinical outcome	Overall UK population (n=31)	UK CRC subgroup (n=19)
ORR,* n (%)	12 (38.7)	10 (52.6)
Best overall response, n (%)		
CR	4 (12.9)	3 (15.8)
PR	8 (25.8)	7 (36.8)
SD	5 (16.1)	2 (10.5)
PD	8 (25.8)	4 (21.1)
Not evaluable	4 (12.9)	1 (5.3)
Not done	2 (6.5)	2 (10.5)
DCR,† n (%)	17 (54.8)	12 (63.2)
Median PFS (95% CI), months	5.4 (2.1, NR)	NR (2.1, NR)
PFS rates, survival probability % (95% CI)		
12 months	39.7 (22.3, 56.6)	56.0 (30.6, 75.2)
24 months	39.7 (22.3, 56.6)	56.0 (30.6, 75.2)
36 months	39.7 (22.3, 56.6)	56.0 (30.6, 75.2)
Median OS (95% CI), months	18.0 (4.4, NR)	NR (6.5, NR)
OS rates, survival probability % (95% CI)		
12 months	54.1 (35.0, 69.7)	63.2 (37.9, 80.4)
24 months	47.3 (29.0, 63.6)	63.2 (37.9, 80.4)
36 months	47.3 (29.0, 63.6)	63.2 (37.9, 80.4)

*ORR is defined as CR plus PR; †DCR is defined as CR plus PR plus SD.

Figure 2: Percentage change in target lesion size (n=26)



At the time of data cut-off, n=26 patients (84%) were still on treatment. Best lesion size change is the maximum reduction or minimum increase (up to the first instance of PD) from baseline. Horizontal dotted line marks PR.

All of the UK CRC subgroup of patients who remained on study treatment for ≥96 weeks experienced at least a PR (**Figure 3**).

- Overall, 90.0% (n=9/10) of the UK CRC subgroup responders had a DOR ≥6 months.

Safety

AEs were reported in 93.9% (n=31/33) and 100% (n=19/19) of patients overall and in the UK CRC subgroup, respectively; TRAEs were reported in 72.7% (n=24/33) and 78.9% (n=15/19) of patients, respectively (**Table 3**).

Figure 3. Duration of treatment and response in overall UK population (n=31)

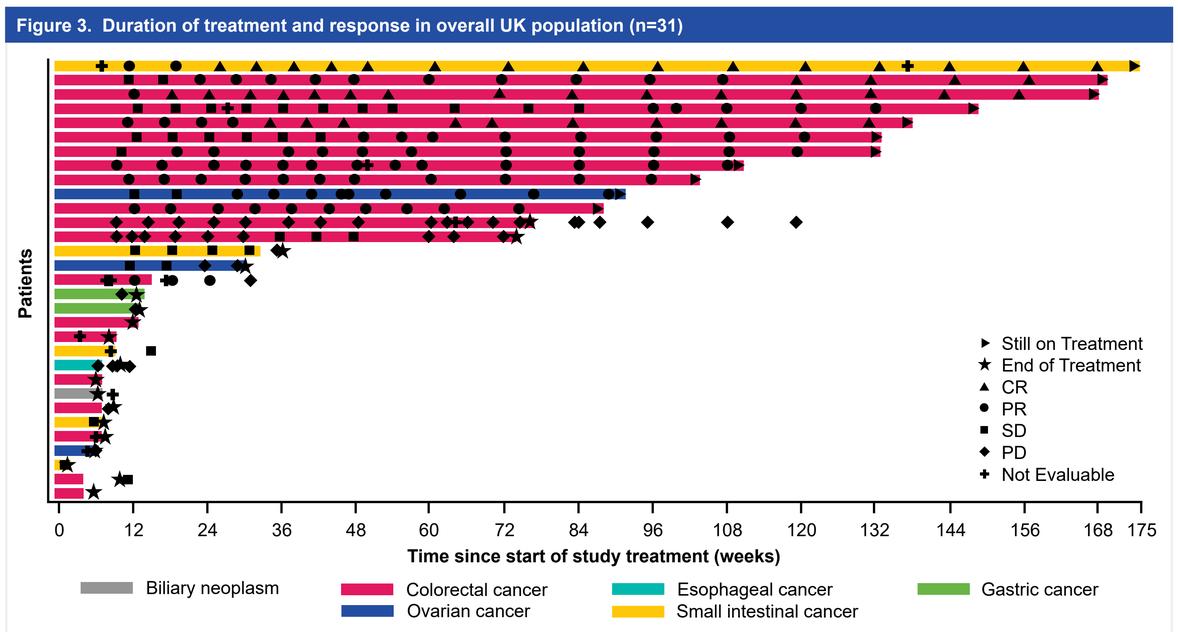


Table 3. Safety summary

Safety event category	Overall UK population, n (%) n=33	UK CRC subgroup, n (%) n=19
Any AE	31 (93.9)	19 (100)
≥Grade 3 AE	17 (51.5)	9 (47.4)
TRAE*	24 (72.7)	15 (78.9)
≥Grade 3 TRAE*	5 (15.2)	4 (21.1)
SAE	14 (42.4)	7 (36.8)
TR SAE*	5 (15.2)	4 (21.1)
AE leading to treatment withdrawal†	3 (9.1)	3 (15.8)
TRAE leading to treatment withdrawal*†	2 (6.1)	2 (10.5)
AE leading to drug treatment interruption†	14 (42.4)	8 (42.1)
Immune-related AE‡	12 (36.4)	8 (42.1)
TR immune-related AE*‡	11 (33.3)	7 (36.8)

*Related and possibly related AEs are considered as related AEs, missing relationship considered as 'drug-related'; †relating to study treatment; ‡immune-related AEs are defined as any ≥Grade 2 AEs based on pre-specified preferred terms. Patients are included once per category, even if they experience multiple events within that category.

Most TRAEs were generally consistent with those previously reported (**Table 4**).[5]

Table 4. Treatment-related adverse events

System organ class	Overall UK population, n=33 (≥5% cut-off), n (%)	CRC subgroup, n=19 (≥10% cut-off*), n (%)
Preferred term	n=33	n=19
Skin and subcutaneous tissue disorders	13 (39.4)	8 (42.1)
Rash	7 (21.2)	5 (26.3)
Pruritus	5 (15.2)	4 (21.1)
Dermatitis acneiform	2 (6.1)	1 (5.3)
Gastrointestinal disorders	10 (30.3)	6 (31.6)
Diarrhoea	7 (21.2)	4 (21.1)
Nausea	4 (12.1)	2 (10.5)
Abdominal pain	2 (6.1)	2 (10.5)
Musculoskeletal and connective tissue disorders	9 (27.3)	5 (26.3)
Arthralgia	6 (18.2)	4 (21.1)
Myalgia	2 (6.1)	1 (5.3)
Investigations	8 (24.2)	6 (31.6)
Alanine aminotransferase increased	4 (12.1)	2 (10.5)
Aspartate aminotransferase increased	3 (9.1)	1 (5.3)
General disorders and administration site conditions	7 (21.2)	5 (26.3)
Fatigue	7 (21.2)	5 (26.3)
Respiratory, thoracic and mediastinal disorders	6 (18.2)	2 (10.5)
Pneumonitis	3 (9.1)	2 (10.5)
Dyspnoea	3 (9.1)	0
Nervous system disorders	5 (15.2)	5 (26.3)
Blood and lymphatic system disorders	3 (9.1)	1 (5.3)
Anemia	2 (6.1)	0
Endocrine disorders	3 (9.1)	1 (5.3)
Hypothyroidism	2 (6.1)	1 (5.3)
Metabolism and nutrition disorders	3 (9.1)	1 (5.3)
Vascular disorders	2 (6.1)	2 (10.5)

*Preferred term included when reported by ≥5% of patients in the overall UK population. Patients are included ≤once per category, even if multiple events within that category were experienced.

Conclusions

Dostarlimab demonstrated durable, clinically meaningful anti-tumour activity in UK patients with dMMR/MSI-H or POLƐ-mutated solid tumours.

- Clinical activity was observed in CRC subgroup analysis.

Efficacy profiles were consistent with those reported in previous GARNET cohort F post-hoc analyses in patients with dMMR CRC.[5]

No new safety signals were observed.

Disclosures

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Abbreviations

AE, adverse event; BICR, blinded independent central review; BMI, body mass index; CI, confidence interval; CR, complete response; CRC, colorectal cancer; DCR, disease control rate; dMMR, mismatch repair deficient; DNA, deoxyribonucleic acid; DOR, duration of response; EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MMRp, mismatch repair proficient; MSI-H, microsatellite instability high; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; POLƐ, DNA polymerase epsilon, catalytic subunit; PR, partial response; PROC, platinum-resistant ovarian cancer; Q3/6W, every 3/6 weeks; RECIST, response evaluation criteria in solid tumors; SAE, serious adverse event; SD, stable disease; TR, treatment-related; TRAE, treatment-related adverse event; UK, United Kingdom; US, United States.

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