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Outcomes of dostarlimab versus chemotherapy in post-platinum patients with recurrent/advanced endometrial cancer: data from the GARNET trial and the National Cancer Registration Service in England

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ABSTRACT

Objectives Immune checkpoint inhibitors have emerged as novel treatment options in patients with endometrial cancer. In this study we aimed to compare the survival outcomes of patients with recurrent or advanced endometrial cancer. These patients had received dostarlimab after platinum-based chemotherapy in the single-arm, Phase I GARNET trial. We compared them with a matched indirect real-world cohort.

Methods The real-world cohort was established using National Cancer Registration and Analysis Service data, with five treatment-specific real-world sub-cohorts identified. To compare clinical outcomes between the GARNET trial and real-world cohorts, we performed matching-adjusted indirect comparisons. We used prognostic variables to create matching scenarios, including scenario 1 that incorporated grade, histology, and platinum-based chemotherapy number; scenario 2 that considered histology and platinum-based chemotherapy number; and scenario 3 that included race/ethnicity, stage at diagnosis, histology, and prior surgery. Overall survival was defined as the time between the first dostarlimab dose or second-line real-world treatment and death. Adjusted hazard ratios for matching-adjusted indirect comparisons were estimated via weighted Cox proportional-hazards models. Progression-free survival, using time-to-next treatment as a proxy for real-world cohorts, was summarized descriptively.

Results Distribution of baseline characteristics that were matched was similar between the GARNET cohort (n=153) and the real-world cohort (n=999). The most common International Federation of Gynecology and Obstetrics (FIGO) stage in both cohorts was stage III/IV (n=88; 57.5% and n=778; 77.9%, respectively), with endometroid histology predominating in the GARNET cohort (n=121; 79.1%) and non-endometrioid the predominant form in the real-world cohort (n=575; 57.6%). The median overall survival for dostarlimab was longer (range 27.1–40.5 months [95% confidence interval (CI) 6.4–non-estimable and 19.4–non-estimable]) both before and after matching for all scenarios compared with the real-world cohort (10.3 months). Across all matching scenarios, patients in the GARNET cohort had a decreased risk of death, with a HR for overall survival of 0.32 (p<0.0001) before matching, as compared with the overall real-world cohort and most treatment-specific real-world cohorts. For all three scenarios, progression-free survival rates at 12 and 18 months were higher for patients on dostarlimab compared with the real-world cohort (0.48 and 0.43 respectively before matching in the GARNET cohort vs 0.28 and 0.16 respectively in the real-world cohort; using time to next treatment as proxy). The effective sample size for scenario 1 was low when compared with the other scenarios (scenario 1: n=18; scenario 2: n=62; scenario 3: n=67).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is currently no established standard-of-care for patients with recurrent or advanced mismatch repair deficient/microsatellite instability-high endometrial cancer who have progressed on or after platinum-based chemotherapy. However, immune checkpoint inhibitors, such as dostarlimab, have shown promise as potential treatment options.

WHAT THIS STUDY ADDS

⇒ This study contributes to the growing body of evidence supporting the use of immune checkpoint inhibitors, specifically dostarlimab, as a treatment option for patients with recurrent/advanced mismatch repair deficient/microsatellite instability-high endometrial cancer following platinum-based chemotherapy. The findings suggest that patients in the GARNET trial (specifically, cohort A1) who received dostarlimab had significantly better survival outcomes compared with patients receiving current treatment regimens in real-world cohorts in the UK at the time of the study.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study offers additional evidence supporting the use of immune checkpoint inhibitors, such as dostarlimab, in the treatment of patients with recurrent/advanced endometrial cancer who have experienced progression on/after platinum-based chemotherapy.

Conclusion In this adjusted indirect dataset, patients with recurrent/advanced mismatch repair deficient/microsatellite instability-high endometrial cancer post-platinum-based chemotherapy who received dostarlimab in the GARNET trial had significantly improved overall survival compared with patients receiving current second-line treatment in England.

INTRODUCTION

The incidence of endometrial cancer has recently been increasing. It is the sixth most common cancer in females worldwide and the most common gynecological cancer in Europe (5 year prevalence: 34.1%).[1–3] While the prognosis is favorable for patients diagnosed at an early stage, those diagnosed with advanced disease have a 5 year survival estimate of 18%.[2 4] Additionally, 10–15% of patients with endometrial cancer experience recurrence after initial therapy, with a 5 year survival rate of approximately 20%.[5 6] Treatment guidelines recommend carboplatin and paclitaxel as standard-of-care for first-line recurrent/advanced endometrial cancer; however, no standard-of-care has been established for patients progressing after first-line treatment.[7 8] While chemotherapy is commonly used second-line, response rates are poor in this setting.[7–10]

Approximately 25–35% of endometrial cancers are mismatch repair deficient/microsatellite instability high.[11–14] Immune checkpoint inhibitors are a promising treatment option for these patients, with recent approvals by the European Medicines Agency. Dostarlimab was approved in April 2021 as monotherapy for patients with mismatch repair deficient/microsatellite instability-high recurrent/advanced endometrial cancer that has progressed on/after a platinum-containing regimen, based on data from the single-arm, Phase I GARNET (NCT02715284) trial.[15–17]

Real-world data are increasingly being used in treatment guideline development and regulatory decisions, and can contextualize data from single-arm, non-randomized clinical trials against clinically used treatment regimens.[18 19] This study compared clinical outcomes for dostarlimab in patients with recurrent/advanced endometrial cancer with those in a real-world cohort from the National Cancer Registration and Analysis Service in England,[10] including sub-cohorts of patients receiving the five most common post-platinum treatment regimens.

METHODS

Study Design

This study utilized a matching-adjusted indirect comparison technique to compare the clinical outcomes of patients with recurrent/advanced endometrial cancer who received dostarlimab following first-line platinum-based therapy versus a cohort of patients who received real-world treatment paradigms and progressed to second-line treatment, including five treatment-specific sub-cohorts. Patient-level longitudinal data were collected from the GARNET cohort, which received dostarlimab in the Phase I GARNET trial, while aggregated summary data were collected from a real-world cohort derived from patient data in England's National Cancer Registration and Analysis Service. This population-based cancer registry collects, quality assures, and analyzes data on all people living in England who are diagnosed with malignant and pre-malignant tumors[20] (Online supplemental methods). The GARNET trial was approved by the institutional ethics committee, institutional review board, and/or relevant competent authorities at each site.[17]

Study Populations

The GARNET cohort consisted of patients who received dostarlimab, regardless of follow-up time at the time of data cut-off (November 1, 2021) and was the safety population (intention-to-treat) for cohort A1 of part 2B (dose-expansion phase) of the GARNET trial (N=153). A real-world cohort of patients with a primary diagnosis of endometrial cancer between January 2013 and December 2018 was defined using data held by the National Cancer Registration and Analysis Service, and a subgroup of "GARNET-like" patients was selected from this cohort as the overall real-world cohort. GARNET-like patients were defined based on recurrent stage I/II endometrial cancer at diagnosis, probable recurrence captured as resumption of treatment following a gap >90 days between surgery, systemic anti-cancer therapy or radiation therapy, or advanced endometrial cancer (FIGO stages III or IV at diagnosis), who met all of the inclusion criteria and none of the exclusion criteria for the GARNET trial (Online supplemental figure 1). While mismatch repair deficient/microsatellite instability-high status was an eligibility criterion of cohort A1 of GARNET, these data were not routinely available within one of the National Cancer Registration and Analysis Service datasets (the National Cancer Registration Dataset) and hence, this characteristic was not used to define "GARNET-like" for these analyses.

Although the Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 was an eligibility criterion for GARNET, these data were not available for all patients in the real-world cohort. Patient characteristics and efficacy outcomes for the overall real-world cohort and a cohort excluding patients with unknown ECOG Performance Status were similar, and a sensitivity analysis excluding patients with unknown ECOG Performance Status showed no major impact on survival outcomes (Online supplemental table 1). Therefore, to avoid bias and small sample numbers, the overall real-world cohort used for these analyses included patients with unknown ECOG Performance Status.

To evaluate the efficacy of dostarlimab relative to the most common post-platinum treatment regimens in the real-world cohort, sub-cohorts of patients who received the five most common treatment regimens were constructed, including paclitaxel monotherapy, carboplatin and paclitaxel doublet, carboplatin and liposomal doxorubicin doublet, liposomal doxorubicin monotherapy, and carboplatin monotherapy.

Endpoints and Outcome Measures

The primary endpoint of the study was overall survival. An algorithm was employed to estimate the lines of therapy in the real-world cohort (see Online supplemental methods). The secondary endpoint was progression-free survival. In the real-world cohort, time-to-next treatment and time-to-treatment discontinuation were used as proxies for progression-free survival due to insufficient data on disease progression in one of the constituent datasets of the National Cancer Registration and Analysis Service (i.e., the National Cancer Registration Dataset). The definitions of the endpoints are detailed in Online supplemental methods.

Matching-adjusted Indirect Comparison and Matching Scenarios

A targeted literature review was conducted to select matching variables (Online supplemental methods).

Matching-adjusted indirect comparisons are specifically used where individual patient data are available for one treatment, but only aggregated summary information is available for the comparator. Three different scenarios were considered to assess the impact of matching variables on estimates and effective sample sizes (Online supplemental methods): scenario 1—based on grade, histology, number of platinum-based chemotherapies; scenario 2—based on histology, number of platinum-based chemotherapies; scenario 3—based on race/ethnicity, stage at diagnosis, histology, prior surgery. Individual patient data for the GARNET cohort were matched to the real-world cohorts using the selected matching variables for each of the three scenarios. After matching, re-weighted outcomes data from the GARNET trial were compared with observed outcomes data from the real-world cohorts.

Statistical analyses are described in Online supplemental methods. In brief, Cox proportional-hazards with weights obtained by the matching-adjusted indirect comparison method was used to re-estimate overall survival hazard ratios for the GARNET cohort vs the real-world cohorts. Overall survival and secondary endpoints were summarized descriptively using Kaplan–Meier methodology.

The commitment to provide data for independent analysis by the Editorial Team for the purposes of additional data analysis or reproducibility of the study in other centers is a commendable practice in ensuring transparency and replicability of research findings.

RESULTS

Baseline Characteristics

The GARNET cohort consisted of 153 patients before matching, while the overall real-world cohort included 999 patients who had received second-line chemotherapy, including the five most common treatment regimens (paclitaxel [n=116], carboplatin+paclitaxel [n=279], carboplatin+liposomal doxorubicin [n=141], liposomal doxorubicin [n=130], and carboplatin [n=93]), as well as other chemotherapy options (n=240) (Online supplemental figure 1). All characteristics were statistically different between the overall real-world and GARNET cohorts, except for age and surgery (Table 1). In the real-world cohort, 57.2% of patients (n=571) were 65 years or older, compared with 51.0% (n=78) in the GARNET cohort. Additionally, the GARNET cohort had a higher percentage of patients with endometrioid histology (79.1% [n=121] vs 42.4% [n=424]) and a lower percentage of patients with FIGO stage III/IV (57.5% [n=88] vs 77.9% [n=778]) and tumor grade 3/4 at diagnosis (30.1% [n=46] vs 38.9% [n=389]), compared with the real-world cohort. Furthermore, 83.7% (n=128) of patients in the GARNET cohort received only one prior platinum-based chemotherapy in the recurrent/advanced setting, whereas 100% of patients in the real-world cohort received only one prior platinum-based chemotherapy. Finally, in the real-world cohort ECOG Performance Status was unknown for 49.8% of patients (n=498).

After matching, the effective sample size for the GARNET cohort was 18, 62, and 67 for scenarios 1, 2, and 3, respectively. Following matching, the distributions of baseline characteristics that were matched were similar between the cohorts (Table 2).

Overall Survival

The results showed that patients in the GARNET cohort had better overall survival than patients in the overall real-world cohort and treatment-specific cohorts, both before and after matching, for all three scenarios (Figure 1 and Online supplemental figures 2–6). Median overall survival for dostarlimab was longer (overall range 27.1–40.5 months [95% confidence interval (CI) 6.4 non-estimable and 19.4 non-estimable]) than the overall real-world cohort (10.3 months [95% CI 9.2–11.1]) for all matching scenarios (Table 3), and overall survival rates were higher at 6, 12, and 18 months. The overall survival hazard ratios for the GARNET cohort versus the overall real-world cohort were statistically significant (P<0.05) before and after matching for all three scenarios (Table 3). Additionally, the overall survival hazard ratios (95% CI) for the GARNET cohort versus the five treatment-specific cohorts before matching (carboplatin and paclitaxel: 0.43 [0.32–0.58]; carboplatin and liposomal doxorubicin: 0.42 [0.30–0.59]; paclitaxel: 0.24 [0.17–0.34]; liposomal doxorubicin: 0.18 [0.12–0.26]; carboplatin: 0.32 [0.22–0.47]) were all statistically significant (P<0.05). The overall survival hazard ratios (95% CI) for the GARNET cohort versus the five treatment-specific cohorts were also statistically significant (P<0.05) under matching scenario 2 and scenario 3 (Online supplemental table 2).

Progression-free Survival

When using time-to-next treatment as a proxy for progression-free survival for the overall real-world cohort, the median progression-free survival (months [95% CI]) was longer for patients treated with dostarlimab for matching scenario 3 (13.8 [5.2–37.3]) compared with the overall real-world cohort (7.7 [7.1–8.2]), but shorter for scenario 1 (4.2 [2.7–16.6]) and similar for scenario 2 (8.1 [4.2–37.3]) (Table 4). Progression-free survival rates were higher for the GARNET cohort compared with the overall real-world cohort starting at month 12 for all three scenarios. Before matching, the median progression-free survival (months [95% CI]) was longer for the GARNET cohort (8.3 [4.2–18.0]) compared with the three monotherapy regimens only (paclitaxel: 5.8 [3.9–6.5]; liposomal doxorubicin: 4.1 [3.4–4.6]; carboplatin: 6.9 [5.8–8.3]; carboplatin and paclitaxel: 10.0 [9.0–11.3]; carboplatin and liposomal doxorubicin: 9.9 [8.3–11.2]) (Online supplemental table 3A).

When using time-to-treatment discontinuation as a proxy for progression-free survival for the overall real-world cohort, the median progression-free survival (months [95% CI]) was longer for patients treated with dostarlimab for all matching scenarios (scenario 1: 4.2 [2.7–16.6]; scenario 2: 8.1 [4.2–37.3]; scenario 3: 13.8 [5.2–37.3]) compared with the overall real-world cohort (3.4 [3.2–3.4]) (Table 4). The median progression-free survival was longer for dostarlimab-treated patients before matching than for all five treatment-specific cohorts (Online supplemental table 3B).

DISCUSSION

Summary of Main Results

Dostarlimab treatment was found to be associated with a significant improvement in survival outcomes when compared with real-world treatment paradigms. The overall survival hazard ratios indicated that the treatment effect of dostarlimab was significant for all comparisons under matching scenario 2 and scenario

Table 1 Baseline characteristics for GARNET cohort (before matching) and for overall and treatment-specific real-world cohorts

		Real-world cohort					
	GARNET (dostarlimab) cohort (n=153)	Overall (n=999)	Paclitaxel monotherapy (n=116)	Carboplatin +paclitaxel (n=279)	Carboplatin+ liposomal doxorubicin (n=141)	Liposomal doxorubicin monotherapy (n=130)	Carboplatin monotherapy (n=93)
Race, n (%)		*	*	*			
White	117 (76.5)	841 (84.2)	87 (75.0)	242 (86.7)	119 (84.4)	112 (86.2)	86 (92.5)
Black	5 (3.3)	57 (5.7)	10 (8.6)	18 (6.5)	6 (4.3)	4 (3.1)	3 (3.2)
Other	8 (5.2)	78 (7.8)	18 (15.5)	17 (6.1)	12 (8.5)	7 (5.4)	3 (3.2)
Unknown	23 (15.0)	23 (2.3)	1 (0.9)	2 (0.7)	4 (2.8)	7 (5.4)	1 (1.1)
Age (years)							
Median (range)	65 (39–85)	66 (36–85)	66 (36–82)	67 (37–84)	67 (42–84)	68 (37–85)	70 (37–83)
<65, n (%)	75 (49.0)	428 (42.8)	52 (44.8)	110 (39.4)	59 (41.8)	43 (33.1)	29 (31.2)
≥65, n (%)	78 (51.0)	571 (57.2)	64 (55.2)	169 (60.6)	82 (58.2)	87 (66.9)	64 (68.8)
ECOG PS†, n (%)		*	*	*	*	*	*
0	61 (39.9)	320 (32.0)	41 (35.3)	97 (34.8)	45 (31.9)	37 (28.5)	30 (32.3)
1	92 (60.1)	181 (18.1)	21 (18.1)	44 (15.8)	35 (24.8)	23 (17.7)	14 (15.1)
Unknown	0	498 (49.8)	54 (46.6)	138 (49.5)	61 (43.3)	70 (53.8)	49 (52.7)
Histology‡, n (%)		*	*	*	*	*	*
Endometrioid	121 (79.1)	424 (42.4)	47 (40.5)	117 (41.9)	55 (39.0)	58 (44.6)	35 (37.6)
Non-endometrioid	30 (19.6)	575 (57.6)	69 (59.5)	162 (58.1)	86 (61.0)	72 (55.4)	58 (62.4)
Unknown	2 (1.3)	0	0	0	0	0	0
FIGO stage‡, n (%)		*		*			
I/II	65 (42.5)	221 (22.1)	33 (28.4)	44 (15.8)	31 (22.0)	46 (35.4)	19 (20.4)
III/IV	88 (57.5)	778 (77.9)	83 (71.6)	235 (84.2)	110 (78.0)	84 (64.6)	74 (79.6)
Tumor grade‡, n (%)		*	*	*	*	*	*
1/2	102 (66.7)	274 (27.4)	26 (22.4)	79 (28.3)	32 (22.7)	34 (26.2)	27 (29.0)
3/4	46 (30.1)	389 (38.9)	48 (41.4)	112 (40.1)	54 (38.3)	54 (41.5)	30 (32.3)
Unknown	5 (3.3)	336 (33.6)	42 (36.2)	88 (31.5)	55 (39.0)	42 (32.3)	36 (38.7)
Number of prior platinum-based therapies§, n (%)		*	*	*	*	*	*
0	2 (1.3)¶	0	0	0	0	0	0
1	128 (83.7)	999 (100)	116 (100)	279 (100)	141 (100)	130 (100)	93 (100)
2+	23 (15.0)	0	0	0	0	0	0
Surgery, n (%)							
Yes	135 (88.2)	815 (81.6)	97 (83.6)	244 (87.5)	117 (83.0)	98 (75.4)	77 (82.8)
No	18 (11.8)	184 (18.4)	19 (16.4)	35 (12.5)	24 (17.0)	32 (24.6)	16 (17.2)

*$P<0.0001$: differences in baseline characteristics between cohorts were measured using the Chi-squared test; if at least one cell was ≤5, then Fisher's exact test was used.
†status at index.
‡at initial diagnosis.
§in the recurrent/advanced setting.
¶the prior therapies that these patients received were not counted as a line of therapy per trial protocol; these patients were excluded from this analysis.
ECOG PS, Eastern Cooperative Oncology Group Performance Status; FIGO, International Federation of Gynecology and Obstetrics.

Table 2 Baseline characteristics for the overall real-world cohort and the GARNET cohort (before and after matching)

	Overall real-world cohort (n=999)	GARNET (dostarlimab) cohort			
		Before matching (n=153)	Scenario 1 (ESS=18)	Scenario 2 (ESS=62)	Scenario 3 (ESS=67)
Race, n (%)					
White	841 (84.2)	117 (76.5)	82.6%	81.8%	**84.2%**
Black	57 (5.7)	5 (3.3)	1.1%	1.2%	**5.7%**
Other	78 (7.8)	8 (5.2)	3.3%	4.6%	**7.8%**
Unknown	23 (2.3)	23 (15.0)	13.0%	12.4%	**2.3%**
Age, n (%)					
<65 years	428 (42.8)	75 (49.0)	38.4%	50.2%	57.1%
≥65 years	571 (57.2)	78 (51.0)	61.6%	49.8%	42.9%
ECOG PS*, n (%)					
0	320 (32.0)	61 (39.9)	36.2%	39.4%	37.1%
1	181 (18.1)	92 (60.1)	63.8%	60.6%	62.9%
Unknown	498 (49.8)	0	0	0	0
Histology†, n (%)					
Endometrioid	424 (42.4)	121 (79.1)	**42.4%**	**42.4%**	**42.4%**
Non-endometrioid	575 (57.6)	30 (19.6)	**57.6%**	**57.6%**	**57.6%**
Unknown	0	2 (1.3)	**0**	**0**	**0**
FIGO stage†, n (%)					
I/II	221 (22.1)	65 (42.5)	28.2%	36.8%	**22.1%**
III/IV	778 (77.9)	88 (57.5)	71.8%	63.2%	**77.9%**
Tumor grade†, n (%)					
1/2	274 (27.4)	102 (66.7)	**27.5%**	45.9%	40.0%
3/4	389 (38.9)	46 (30.1)	**38.9%**	50.4%	56.2%
Unknown	336 (33.6)	5 (3.3)	**33.6%**	3.7%	3.8%
Number of prior platinum-based therapies‡, n (%)					
0	0	2 (1.3)§	**0**	**0**	0.7%
1	999 (100)	128 (83.7)	**100%**	**100%**	76.9%
2+	0	23 (15.0)	**0**	**0**	22.4%
Surgery, n (%)					
Yes	815 (81.6)	135 (88.2)	69.7%	89.6%	**81.6%**
No	184 (18.4)	18 (11.8)	30.3%	10.4%	**18.4%**

Scenario 1: Matching variables are histology, grade, and number of prior platinum-based therapies; scenario 2: Matching variables are histology and number of prior platinum-based therapies; scenario 3: Matching variables are race, histology, stage at initial diagnosis, and surgery (ECOG PS was not included as a matching variable due to patients with unknown status). Percentages for matching variables for each scenario are highlighted in bold. Differences in baseline characteristics between cohorts were measured using the Chi-squared test; if at least one cell was ≤5, then Fisher's exact test was used.
*Status at index.
†at initial diagnosis.
‡in the recurrent/advanced setting.
§the prior therapies that these patients received were not counted as a line of therapy per trial protocol; these patients were excluded from this analysis.
ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESS, effective sample size; FIGO, International Federation of Gynecology and Obstetrics.

3. Results for overall survival were considered less robust under matching scenario 1 due to the low effective sample size (n=18), and because about one-third of patients in the real-world cohort had unknown tumor grade status, which was a matching variable for this scenario.

Moreover, median progression-free survival was longer for dostarlimab for scenario 2 and scenario 3 when time-to-next treatment was used as a proxy, and longer for dostarlimab in all scenarios when time-to-treatment discontinuation was used as the proxy. Progression-free survival starting at month 12 was longer for dostarlimab vs the overall real-world cohort for all three scenarios and all available treatment comparisons (when using time-to-next treatment as a proxy), except for carboplatin and liposomal doxorubicin for scenario 1, where progression-free survival was longer

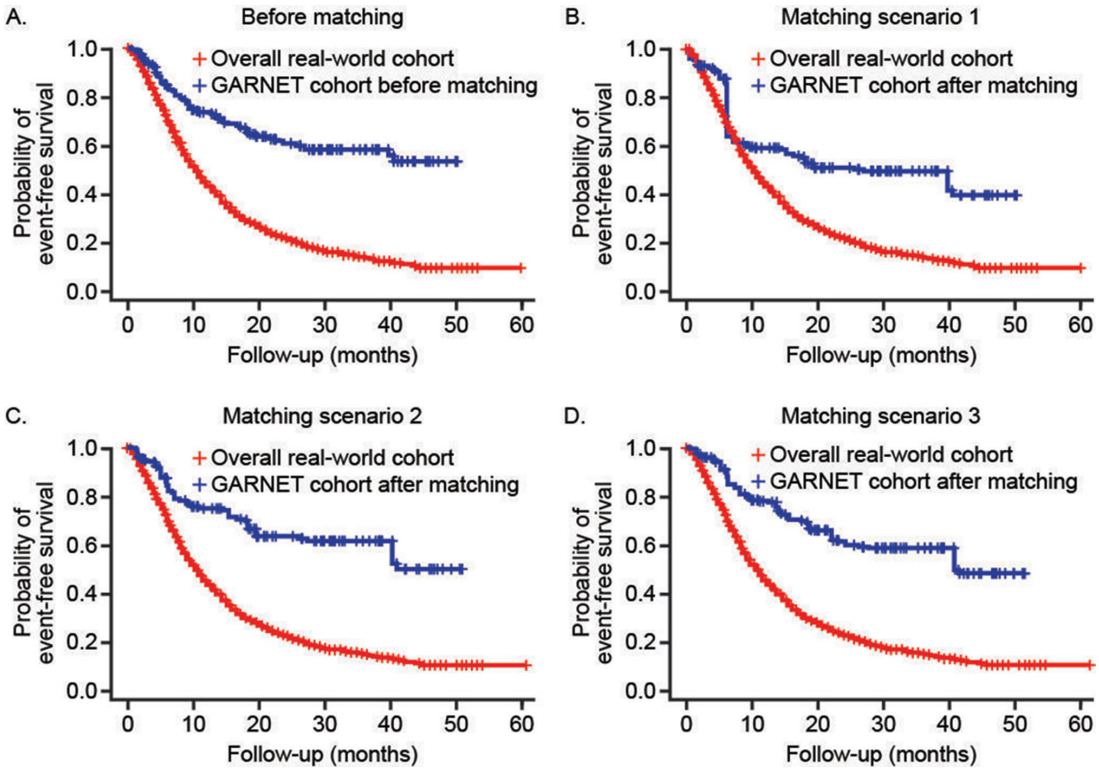

Figure 1 Kaplan-Meier curves for overall survival comparing the overall real-world cohort and the GARNET (dostarlimab, ITT) cohort A) before matching, (B) matching scenario 1*, (C) matching scenario 2†, (D) matching scenario 3‡. Tick marks represent censored data. *Matching variables: histology, grade, and number of prior platinum-based therapies; †matching variables: histology, and number of prior platinum-based therapies; ‡matching variables: race/ethnicity, histology, stage at initial diagnosis, and surgery. ITT, intention to treat.

starting at month 18. When time-to-next treatment was used as a proxy, progression-free survival was longer for real-world cohorts than when time-to-treatment discontinuation was used as a proxy. This could be due to time gaps before initiating the next treatment, the fixed duration of chemotherapy regimens for recurrent/advanced endometrial cancer (typically six cycles of platinum-based chemotherapy[7]), or reflect that treatment discontinuation without progression is frequent due to adverse events.

Results in the Context of Published Literature

Formal comparisons of response rates between the GARNET and real-world cohorts could not be performed in this study because the data were not captured in the National Cancer Registration and Analysis Service. However, the improved survival outcomes observed with dostarlimab may be due, in part, to the higher overall response rate reported in the GARNET trial for the mismatch repair deficient/microsatellite instability-high population (43.5% [95% CI:

Table 3 Overall survival for the overall real-world cohort and GARNET cohort (before and after matching)

		GARNET (dostarlimab) cohort			
	Overall real-world cohort (n=999)	Before matching (n=153)	Scenario 1 (ESS=18)	Scenario 2 (ESS=62)	Scenario 3 (ESS=67)
Median OS, months (95% CI)	10.3 (9.2 to 11.1)	NE (27.1 to NE)	27.1 (6.4 to NE)	40.5 (19.4 to NE)	39.9 (21.6 to NE)
OS rate (95% CI)					
6 months	0.70 (0.67 to 0.73)	0.85 (0.78 to 0.90)	0.88 (0.72 to 0.95)	0.88 (0.78 to 0.93)	0.91 (0.83 to 0.95)
12 months	0.44 (0.40 to 0.47)	0.73 (0.65 to 0.80)	0.59 (0.29 to 0.80)	0.75 (0.62 to 0.84)	0.78 (0.66 to 0.86)
18 months	0.29 (0.26 to 0.32)	0.67 (0.58 to 0.74)	0.56 (0.28 to 0.77)	0.70 (0.57 to 0.80)	0.69 (0.56 to 0.79)
HR for OS (95% CI)	–	0.32 (0.24 to 0.42)	0.47 (0.22 to 0.99)	0.30 (0.20 to 0.47)	0.31 (0.21 to 0.46)
P-value	–	<0.0001	0.0481	<0.0001	<0.0001

Scenario 1: Matching variables are histology, grade, and number of prior platinum-based therapies; scenario 2: Matching variables are histology and number of prior platinum-based therapies; scenario 3: Matching variables are race, histology, stage at initial diagnosis, and surgery (ECOG PS was not included as a matching variable due to patients with unknown status).
ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESS, effective sample size; NE, non-estimable; OS, overall survival.

34.0 to 53.4]),[21] compared with the response rates reported for commonly used chemotherapy regimens (10–27%).[7 22] Additionally, long-term follow-up data from GARNET showed an 83.7% probability of remaining in response at 2 years, indicating durable antitumor activity for dostarlimab.[23]

The PD-1 inhibitor pembrolizumab has also demonstrated robust and durable antitumor activity as monotherapy in the single-arm KEYNOTE-158 trial[24] in patients with advanced mismatch repair deficient/microsatellite instability-high endometrial cancer. Moreover, improved survival outcomes were reported in pembrolizumab combined with lenvatinib in the randomized KEYNOTE-775 trial in patients with mismatch repair proficient recurrent/advanced endometrial cancer (17.4 months vs 12.0 months with chemotherapy).[25] These findings support the use of PD-1 inhibitors as the treatment backbone for recurrent/advanced endometrial cancer.

It is important to consider that while all patients in the GARNET cohort had mismatch repair deficient/microsatellite instability-high endometrial cancer, the "GARNET-like" population was not selected for by biomarker status. These data were not routinely available within the National Cancer Registration and Analysis Service because biomarker testing had not been established in England.[26 27] As mismatch repair deficient/microsatellite instability-high status is predictive of response to PD-1 inhibitors in endometrial cancer,[21 25 28] this may partly explain the improved outcomes observed for dostarlimab compared with real-world regimens. However, outcomes in chemotherapy-treated patients are likely to be similar irrespective of the mismatch repair/microsatellite instability profile, as mismatch repair deficient/microsatellite instability-high status is neither predictive of response to chemotherapy[25] nor prognostic. Furthermore, statistically significant differences in baseline characteristics between the GARNET and overall real-world cohorts suggest that the former may be more likely to achieve favorable outcomes. For instance, a higher proportion of patients in GARNET had endometroid histology compared with the overall real-world cohort, which is associated with more favorable outcomes than non-endometrioid/serous histology.[29] However, the matching-adjusted indirect comparison technique used in this study reweights individual patient data to balance the summary baseline characteristics between cohorts under comparison, resulting in a form of pseudo-randomization that minimizes the impact of such differences on comparisons.[30]

Strengths and Weaknesses

Our analysis has several strengths, including its comparison of outcomes for dostarlimab with a real-world cohort of patients receiving multiple different treatment regimens, which may be more generalizable to outcomes for patients with recurrent/advanced endometrial cancer in England, where there is no established standard-of-care. Treatment-specific comparisons are also included, which could be insightful, particularly for countries with high use of a specific chemotherapy regimen. However, a key limitation is the quality of data recording or the lack of data points of interest, such as mismatch repair/microsatellite instability-high status and ECOG Performance status.[31] Algorithms or rules were used to determine lines of therapy, disease progression, and recurrence in the real-world setting, so there may be a degree of misclassification. The low effective sample size across matching scenarios means that caution should be applied when interpreting these data. Although improved median progression-free survival for dostarlimab was not seen in all treatment-specific comparisons, this endpoint may be less informative for immunotherapy than

Table 4 Progression-Free survival for the overall real-world cohort and GARNET cohort (before and after matching)

		GARNET (dostarlimab) cohort			
	Overall real-world cohort (n=999)	Before matching (n=153)	Scenario 1 (ESS=18)	Scenario 2 (ESS=62)	Scenario 3 (ESS=67)
			PFS (TTNT as proxy)		
Median PFS, months (95% CI)	7.7 (7.1 to 8.2)	8.3 (4.2 to 18.0)	4.2 (2.7 to 16.6)	8.1 (4.2 to 37.3)	13.8 (5.2 to 37.3)
PFS rate (95% CI)					
6 months	0.61 (0.58 to 0.64)	0.51 (0.43 to 0.59)	0.45 (0.23 to 0.64)	0.53 (0.39 to 0.64)	0.60 (0.47 to 0.70)
12 months	0.28 (0.25 to 0.31)	0.48 (0.40 to 0.56)	0.37 (0.19 to 0.56)	0.49 (0.36 to 0.61)	0.54 (0.42 to 0.66)
18 months	0.16 (0.14 to 0.19)	0.43 (0.34 to 0.51)	0.32 (0.16 to 0.50)	0.42 (0.29 to 0.54)	0.43 (0.30 to 0.56)
			PFS (TTD as proxy)		
Median PFS, months (95% CI)	3.4 (3.2 to 3.4)	8.3 (4.2 to 18.0)	4.2 (2.7 to 16.6)	8.1 (4.2 to 37.3)	13.8 (5.2 to 37.3)
PFS rate (95% CI)					
6 months	0.12 (0.10 to 0.15)	0.51 (0.43 to 0.59)	0.45 (0.23 to 0.64)	0.53 (0.39 to 0.64)	0.60 (0.47 to 0.70)
12 months	0.02 (0.01 to 0.03)	0.48 (0.40 to 0.56)	0.37 (0.19 to 0.56)	0.49 (0.36 to 0.61)	0.54 (0.42 to 0.66)
18 months	-†	0.43 (0.34 to 0.51)	0.32 (0.16 to 0.50)	0.42 (0.29 to 0.54)	0.43 (0.30 to 0.56)

Scenario 1: Matching variables are histology, grade, and number of prior platinum-based therapies; scenario 2: Matching variables are histology and number of prior platinum-based therapies; scenario 3: Matching variables are race, histology, stage at initial diagnosis, and surgery (ECOG PS was not included as a matching variable due to patients with unknown status).
*No more patients at risk.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESS, effective sample size; PFS, progression-free survival; TTD, time-to-discontinuation; TTNT, time-to-next treatment.

for chemotherapy, where a spectrum of responses is seen. Immunotherapy usually shows an 'all or nothing' response, where responders generally do well for a long time, and non-responders progress. Moreover, durable or delayed responses are expected in a small percentage of patients, and assessing efficacy purely on median survival values may be inappropriate, making comparisons of median progression-free survival between immunotherapy and chemotherapy regimens challenging.[32] Additionally, interpretation of time-to-treatment discontinuation is confounded by the fact that stopping treatment may reflect completion of the treatment cycles rather than signifying progression, since many treatments in this setting are for a set number of cycles. Finally, it should be noted that matching-adjusted indirect comparison covariate adjustments rely on assumptions that could be considered less reliable or robust than covariate adjustments analysis using pooled patient data from both arms, such as by regression or propensity score-based methods.

Implications for Practice and Future Research

This study adds to the growing body of evidence supporting the use of PD-1 inhibitors, including dostarlimab, as the primary treatment for pre-treated recurrent/advanced endometrial cancer with mismatch repair deficient/microsatellite instability-high status. The improved survival outcomes compared with real-world treatment paradigms observed in this study are consistent with previous reports of the clinical benefits of dostarlimab, such as a reduced dosing frequency (treatment every 6 weeks) and a manageable safety profile, similar to other PD-1 inhibitors.[21]

CONCLUSION

The results of this study suggest that patients with pre-treated mismatch repair deficient/microsatellite instability-high recurrent/advanced endometrial cancer who received dostarlimab in the GARNET cohort (cohort A1 of the GARNET trial) had more significantly improved survival outcomes than patients receiving current UK treatment paradigms at the time of the study. These findings were validated after adjusting for potential imbalances in baseline characteristics using the matching-adjusted indirect comparison approach, which further supports the evidence for the superior outcomes with dostarlimab in this patient population.

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