Survival Outcomes for Dostarlimab and Real-World Treatment Paradigms in Post-Platinum Patients With Advanced/Recurrent Endometrial Cancer: The GARNET Trial Vs an External Control Arm From the Flatiron Health Database

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Background

Endometrial cancer (EC) is the fourth most common cancer among women in developed countries.[1]

- The prognosis for patients with advanced/recurrent EC is poor, with a 5-year survival rate of just 18% for advanced disease[2] and limited treatment options following platinum-based chemotherapy (PBCT).[3]

The anti-programmed death (PD)-1 antibody dostarlimab was recently approved for the treatment of mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) EC (European Union)[4] or dMMR EC (United States [US]) that has progressed on or after treatment with a platinum-containing regimen.[5]

- Approval was based on results from the single-arm Phase I GARNET trial, which assessed dostarlimab efficacy and safety in patients with dMMR/MSI-H EC.[4,6]

The aim of this study was to compare overall survival (OS) of patients with dMMR/MSI-H advanced/recurrent EC treated with dostarlimab in the GARNET trial with an external control arm of patients from the Flatiron Health database with advanced/recurrent EC receiving real-world non-anti-PD-ligand (L)1/2 therapies.

Methods

Study Design

This was a comparative external control arm study, which compared survival outcomes of patients with advanced/recurrent EC who have progressed after 1–2 lines of PBCT treated with dostarlimab in the GARNET trial with those from a real-world cohort receiving current, non-anti-PD-(L)1/2 treatments.

The dostarlimab treatment arm was a subset of patients from the safety analysis data set (N=129) of Cohort A1 of part 2B of the GARNET trial (patients with advanced/recurrent dMMR/MSI-H EC), with a data cut-off of March 1, 2020.[6]

- Patients who had received additional anti-PD-(L)1/2 therapy following dostarlimab (n=5) were excluded from the current study, giving a final data set of 124 patients.

The external control arm was constructed by applying GARNET eligibility criteria to the Flatiron Health database. This is a longitudinal database, comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction. During the study period, the de-identified data originated from approximately 280 cancer clinics (~800 sites of care).

- The study included 185 patients diagnosed with advanced/recurrent EC from January 1, 2013 to August 31, 2020 with Eastern Cooperative Group (ECOG) performance status (PS) 0–1 at index, who had received 1–2 lines of prior chemotherapy (including at least 1 line of PBCT), and had not received anti-PD-(L)1/2 therapy; hormone monotherapy was allowed but did not count as index therapy.
- Index date was defined as the date of index treatment (i.e., post-platinum therapy received in second- or third-line [2L/3L]) initiation and must have occurred January 1, 2013–August 31, 2018.
  - If patients had received two lines of PBCT, the 2L or 3L regimen was randomly assigned to be the index therapy, to align with patient treatment histories observed in GARNET.
- MMR/MSI status was not fully available in the Flatiron Health database, and so was not used as an inclusion criterion for the real-world cohort or included as a factor in the analysis.

The primary endpoint of the analysis was OS, defined as the interval between the start of dostarlimab (GARNET cohort) or index treatment (real-world cohort) and the date of death.

Inverse Probability of Treatment Weighting (IPTW)

To address confounding bias, a propensity score model was constructed with the following prognostic factors: histology, grade of disease at initial EC diagnosis, ECOG PS, and the number of prior PBCTs.

- Prioritized prognostic factors associated with survival in patients with advanced/recurrent EC were identified by targeted literature review, followed by consultation with a panel of oncologists.
- IPTW was performed using stabilized weights based on propensity scores for each patient derived from the model (stabilized-IPTW adjustment).

Survival Analysis

Kaplan–Meier (KM) analysis was used to describe the distribution of OS by cohort. Weighted KM curves were created following stabilized-IPTW adjustment.

Adjusted hazard ratio (HR) was obtained for OS in patients treated with dostarlimab and patients in the real-world cohort using a weighted Cox regression model following stabilized-IPTW adjustment.

Results

Baseline Characteristics

Patient baseline characteristics for the GARNET cohort (N=124) and the real-world cohort (N=185) before stabilized-IPTW are summarized in **Table 1** and are summarized after stabilized-IPTW adjustment in **Table 2**.

The three most common index treatments in the real-world cohort were carboplatin + paclitaxel (23/185; 12.4%), pegylated liposomal doxorubicin (19/185; 10.3%), and bevacizumab (16/185; 8.6%).

Table 1. Baseline characteristics before stabilized-IPTW for the GARNET cohort versus external control arm

Baseline characteristic	GARNET cohort (N=124), n (%)	Real-world cohort (N=185), n (%)
Age group		
<65 years	63 (50.8)	83 (44.9)
≥65 years	61 (49.2)	102 (55.1)
Race		
Black	3 (2.4)	41 (22.2)
Other race	8 (6.5)	26 (14.1)
White	93 (75.0)	113 (61.1)
Unknown	20 (16.1)	5 (2.7)
ECOG PS		
0	54 (43.5)	86 (46.5)
1	70 (56.5)	99 (53.5)
Histology		
Endometrioid	82 (66.1)	106 (57.3)
Non-endometrioid	41 (33.1)	79 (42.7)
Unknown	1 (0.8)	0 (0.0)
FIGO stage at diagnosis		
Stage I/II	54 (43.5)	66 (35.7)
Stage III/IV	70 (56.5)	105 (56.8)
Unknown	0 (0.0)	14 (7.6)
Grade at diagnosis		
Grade 1/2	83 (67.0)	70 (37.8)
Grade 3	35 (28.2)	44 (23.8)
Unknown/not assessable	6 (4.8)	71 (38.4)
# prior PBCTs in A/R setting		
0	2 (1.6)	0 (0.0)
1	105 (84.7)	166 (89.7)
2+	17 (13.7)	19 (10.3)

A/R, advanced/recurrent; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; IPTW, inverse probability of treatment weighting; PBCT, platinum-based chemotherapy

Table 2. Baseline and prognostic factors considered for analyses after stabilized-IPTW – GARNET cohort versus real-world cohort

Category/statistic	GARNET cohort (N=121)*, %	Real-world cohort (N=185), %	Standardized difference	P-value
Age group				
<65 years	47.7	44.4	0.07	0.575
≥65 years	52.3	55.6	-0.07	
Race				
Black	1.8	22.3	-0.66	<0.001
Other race	5.2	13.2	-0.28	
White	70.5	62.0	0.18	
Unknown	22.5	2.5	0.64	
ECOG PS				
0	51.2	47.3	0.08	0.513
1	48.8	52.7	-0.08	
Histology				
Endometrioid	69.1	61.9	0.15	0.202
Non-endometrioid	30.9	38.1	-0.15	
FIGO stage at diagnosis				
Stage I/II	39.1	39.1	0.00	0.011
Stage III/IV	60.9	53.8	0.14	
Unknown	0.0	7.2	-	
Grade at diagnosis				
Grade 1/2	50.9	50.1	0.02	0.957
Grade 3	22.9	24.4	-0.03	
Unknown/not assessable	26.2	25.5	0.01	
# prior PBCTs in A/R setting				
1	89.5	86.7	0.09	0.466
2+	10.5	13.3	-0.09	

A/R, advanced/recurrent; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; IPTW, inverse probability of treatment weighting; PBCT, platinum-based chemotherapy
*Patients with 0 prior PBCTs in A/R setting (n=2) and patients with unknown histology (n=1) were removed from the GARNET cohort as equivalent patients were not observed in the real-world cohort

Survival Outcomes

Before adjustment, median OS was higher for patients in the GARNET cohort compared with the real-world cohort (not estimable [NE; 95% confidence interval (CI): 18.4 months–NE] vs 11.1 months [95% CI: 8.1–15.2], respectively; HR 0.48 [95% CI: 0.31–0.65]).

After adjustment using stabilized-IPTW, median OS remained higher for patients treated with dostarlimab compared with patients receiving current, non-anti-PD-(L)1/2 treatments in the real-world cohort (**Figure 1**).

- A greater proportion of patients treated with dostarlimab remained alive at 6, 12, 18, and 24 months compared with patients in the real-world cohort (**Table 3**).

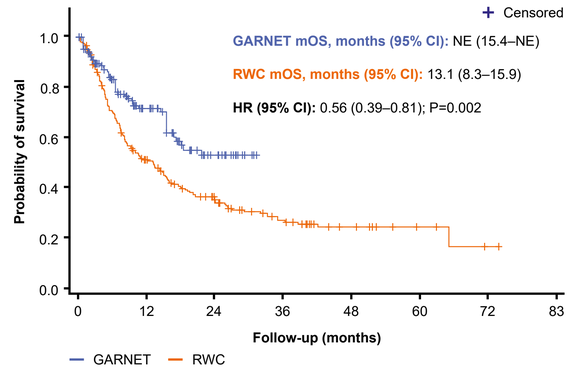
Accordingly, patients treated with dostarlimab had a 44% lower hazard of death after stabilized-IPTW compared with patients receiving real-world non-anti-PD-(L)1/2 treatments (**Figure 1**).

Table 3. OS rates following stabilized-IPTW adjustment for patients in the GARNET cohort versus the real-world cohort

Follow-up time	GARNET cohort (N=121), % survival (95% CI)	Real-world cohort (N=185), % survival (95% CI)
6 months	83.1 (70.3–90.7)	69.5 (61.8–76.0)
12 months	71.5 (56.9–81.9)	51.0 (43.0–58.5)
18 months	56.9 (40.5–70.3)	39.9 (32.1–47.6)
24 months	52.9 (36.7–66.7)	33.8 (26.2–41.5)

CI, confidence interval; IPTW, inverse probability of treatment weighting; OS, overall survival

Figure 1. OS after adjustment with stabilized-IPTW in the GARNET cohort versus the real-world cohort



CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; mOS, median overall survival; NE, not estimable; OS, overall survival; RWC, real-world cohort

Limitations

All patients in the GARNET cohort were dMMR/MSI-H; MMR/MSI status was not fully available in the real-world cohort.

- A recent systematic literature review showed that MMR/MSI status is not a significant prognostic factor for non-anti-PD-(L)1/2 treatments in the advanced/recurrent setting.[7]

Comparison of certain variables, such as prior surgery and radiation, was also limited by under-reporting and was therefore not used in propensity score models for this analysis.

While the analysis adjusted for endometrioid versus non-endometrioid histology, potential discrepancies between different non-endometrioid histological subtypes (e.g., serous) could not be adjusted for due to the small sample size for each subtype.

Conclusions

These results indicate that patients with dMMR/MSI-H advanced/recurrent EC receiving dostarlimab in the GARNET trial had significantly longer survival compared with patients receiving current non-anti-PD-(L)1/2 treatments in the real-world setting.

- This is consistent with previous analyses showing that dostarlimab-treated patients with advanced/recurrent EC had improved OS when compared with doxorubicin-treated patients.[8]

Disclosures

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QS is an employee of GSK and owns stock in GSK.
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