Preliminary Safety, Efficacy, and PK/PD Characterization from GARNET, a Phase 1 Clinical Trial of the Anti-PD-1 Monoclonal Antibody, Dostarlimab, in Patients with Recurrent or Advanced MSI-H Endometrial Cancer

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GARNET TSR-042 CLINICAL TRIAL

BACKGROUND

- Dostarlimab (formerly TSR-042) is an investigational humanized anti-programmed death (PD)-1 monoclonal antibody that binds with high affinity to the PD-1 receptor and effectively blocks its interaction with the PD-1 ligands PD-L1 and PD-L2.
- Blocking PD-1 has been shown to increase antitumor immune responses (regression) and to increase survival of patients with multiple tumor types,[1] and PD-1 inhibitors are currently approved in the United States for recurrent advanced microsatellite instability-high (MSI-H) endometrial and nonendometrial MSI-H tumors.[2,3]
- Dostarlimab is the only anti-PD-1 therapy administered as a monotherapy every 3 weeks (Q3W) for 4 doses then every 6 weeks (Q6W) until disease progression.[2,3]
- In clinical trials, preliminary data show dostarlimab has activity and safety profiles that are similar to approved anti-PD-1 therapies.[4]
- The ongoing GARNET trial (NCT02715284) is evaluating dostarlimab as monotherapy in patients with advanced solid tumors.
  - GARNET included a weight-based dose escalation study (part 1) and a fixed-dose safety study (part 2A), both completed[5]; the results of these studies were used to determine the recommended phase 2 dose (RP2D; 500 mg Q3W for the first 4 cycles then 1000 mg Q6W).
- The study is now enrolling patients with specific tumor types into 4 expansion cohorts (part 2B; ongoing), including endometrial cancer (EC) and non-small cell lung cancer.
- Here, we present safety and efficacy data from the MSI-H EC cohort, as well as pharmacokinetic (PK) and receptor occupancy (RO) characterization at the RP2D.

OBJECTIVES

Primary

- To evaluate the clinical activity of dostarlimab at the RP2D in patients with previously treated recurrent or advanced MSI-H EC.
- To evaluate the safety and tolerability of dostarlimab at the RP2D in advanced solid tumors.

Secondary

- To further characterize the PK profile of dostarlimab.

Exploratory

- To further characterize the pharmacodynamic profile of dostarlimab.

METHODS

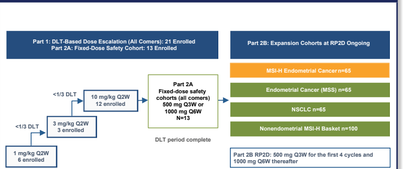
Patients

- Subjects with MSI-H EC who had progressed on or after at least 1, but received no more than 2 lines of anticancer therapy, were included.
- Key exclusion criteria included:
  - Prior therapy with agents targeting PD-1, PD-L1, or PD-L2.
  - Uncontrolled central nervous system metastases and/or carcinomatous meningitis or additional malignancy that progressed or required active treatment within the last 2 years.
  - Active autoimmune disease that required systemic treatment within the last 2 years.

Study Design

- GARNET is a multicenter, open-label, first-in-human phase 1 dose escalation study with expansion cohorts (approximately 65 patients per cohort) designed to assess the safety, PK, pharmacodynamics, and clinical activity of the PD-1 inhibitor dostarlimab in patients with advanced solid tumors (**Figure 1**).

Figure 1. GARNET Phase 1 Study



DLT=dose-limiting toxicity; MSI-H=microsatellite instability-high; MSS=microsatellite stable; NSCLC=non-small cell lung cancer; Q2W=every 2 weeks; Q3W=every 3 weeks; Q6W=every 6 weeks.
For more information on this trial: https://clinicaltrials.gov/ct2/show/NCT02715284 (accessed August 2, 2018; Sachdev JC, et al. Presented at ESMO; September 8-12, 2017; Madrid, Spain. Poster 1185P).

- The part 2B expansion cohort portion of GARNET is evaluating clinical activity, safety, and PK/pharmacodynamics of dostarlimab at the RP2D.
  - The primary efficacy endpoints include objective response rate (ORR), duration of response (DOR), and DOR per immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) assessed by investigators.
  - Safety parameters include treatment-emergent adverse events (TEAEs), immune-related AEs (irAEs) of interest, and clinical laboratory values.

Assessments

- Antitumor activity was assessed by investigators using irRECIST.
  - Radiographic evaluations and serum-based tumor marker testing were conducted 12 weeks after the first dose and every 6 weeks thereafter.
  - Confirmation of response was performed at 4 weeks or later after the first indication of response.
- Serum and peripheral blood mononuclear cells were collected for PK and RO analyses, respectively.
- RO was measured in patients with MSI-H EC using a CD3+ binding assay (direct RO).
- MSI status for patients with EC was confirmed centrally using a next-generation sequencing-based assay.
- Safety was evaluated by TEAEs, irAEs of interest, and clinical laboratory measures.

RESULTS

Patients

- At present, 35 patients in the MSI-H EC cohort received ≥1 treatment with dostarlimab at the RP2D.
- Patient demographics, prior lines of therapy, and International Federation of Gynecology and Obstetrics (FIGO) stage at diagnosis and histology at diagnosis are presented in **Table 1**. Patients in this cohort received a median of 1 prior line of therapy for advanced or metastatic disease.
- Histology data are presented in **Table 1**. The majority (26/35, 74%) of patients had endometrioid carcinoma.

Table 1. Demographic and Baseline Characteristics

Characteristics	MSI-H EC (n=35)
Age, mean (SD), years	63.1 (8.85)
Median	66.0
Q1, Q3	59.0, 69.0
Min, Max	39, 76
Age group, n (%), years	
<65	16 (45.7)
≥65	19 (54.3)
Median number of prior regimens (range)	2.0 (1–4)
Median number of prior regimens for metastatic disease[a] (range)	1.0 (0–3)
Prior platinum-based regimens, n (%)	
Paclitaxel with carboplatin	29 (82.9)
Carboplatin	8 (22.9)
Cisplatin	4 (11.4)
FIGO stage of disease at diagnosis, n (%)	
Stage 1	13 (37.1)
Stage 2	3 (8.6)
Stage 3	12 (34.3)
Stage 4	7 (20.0)
Histology at diagnosis	
Endometrioid carcinoma	26 (74.3)
Adenocarcinoma other	6 (17.1)
Undifferentiated carcinoma	3 (8.6)

[a]Hormonal therapy alone was not counted as prior regimen.
MSI-H EC=microsatellite instability-high endometrial cancer; SD=standard deviation.

Safety

- In the MSI-H EC cohort (n=35), all-grade TEAEs were reported in 32 patients (91.4%). Grade ≥3 AEs were reported in 16 patients (45.7%). Treatment-related TEAEs were reported in 23 patients (65.7%) (Table 2). Serious TEAEs were reported in 13 patients (37.1%) and were considered treatment-related in 2 patients (5.7%) (aspartate aminotransferase increased and pyrexia, 1 patient each). No treatment-related death was reported.

Table 2. All Grade Treatment-Related TEAEs Occurring in ≥5% of Patients in the MSI-H EC Cohort

Adverse Event Preferred Term	MSI-H EC (n=35)
Subjects with at least 1 treatment-related TEAE, n (%)	23 (65.7)
Diarrhea	7 (20.0)
Fatigue	5 (14.3)
Arthralgia	3 (8.6)
Hypothyroidism	3 (8.6)
Muscular weakness	3 (8.6)
Nausea	3 (8.6)
Aspartate aminotransferase increased	2 (5.7)
Dizziness	2 (5.7)
Dry eye	2 (5.7)
Hyperthyroidism	2 (5.7)
Pyrexia	2 (5.7)

MSI-H EC=microsatellite instability-high endometrial cancer; TEAE=treatment-emergent adverse event.

- irAEs related to anti-PD-1 therapies[5] were infrequent.
- Grade ≥3 treatment-related AEs were reported in 4 patients (11.4%), of which 3 patients experienced 1 AE each and 1 patient experienced 2 AEs (**Table 3**).
- The safety profile seen in this cohort was consistent with the safety profile seen in the overall GARNET study.

Table 3. Grade ≥3 Treatment-Related TEAEs in the MSI-H EC Cohort

Grade ≥ 3 Adverse Event Preferred Term	MSI-H EC (n=35)
Subjects with at least 1 treatment-related grade ≥3 TEAE, n (%)	4 (11.4)
Alanine aminotransferase increased	1 (2.9)
Anemia	1 (2.9)
Aspartate aminotransferase increased	1 (2.9)
Leukopenia	1 (2.9)
Neutropenia	1 (2.9)

MSI-H EC=microsatellite instability-high endometrial cancer; TEAE=treatment-emergent adverse event.

Clinical Activity

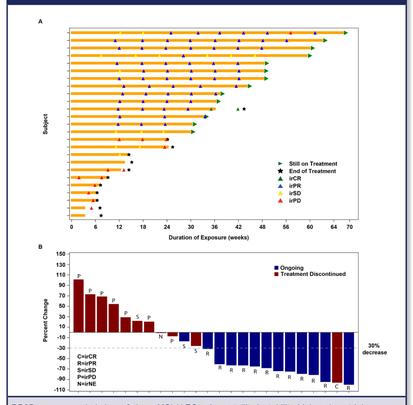
- At the data cutoff date of July 2, 2018, 25 patients with MSI-H EC had ≥1 tumor assessment or discontinued treatment prior to first postbaseline tumor assessment due to AEs or withdrawal of consent. Best overall tumor response by irRECIST is shown in **Table 4**.
  - The overall response rate was 52% (95% CI: 31.3, 72.2), including 1 patient with unconfirmed partial response who is ongoing in the study.
  - Twelve of the 13 responses (92.3%) are ongoing. Three patients with partial response have been receiving dostarlimab for >60 weeks (**Figure 2A**). Median DOR was not reached.
  - Percent change in the sum of all lesions is shown in **Figure 3**.

Table 4. Best Overall Tumor Response – irRECIST

Best Overall Response by irRECIST	MSI-H EC (n=25)
Complete response, n (%)	1 (4)
Partial response[a], n (%)	12 (48)
Stable disease, n (%)	3 (12)
Progressive disease, n (%)	7 (28)
Not evaluated/done, n (%)	2 (8)
Overall response rate, % (95% CI)	52 (31.3, 72.2)
Disease control rate[b], % (95% CI)	64 (42.5, 82.0)

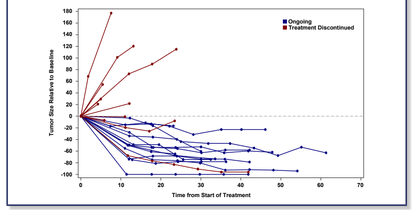
[a]11 confirmed and 1 unconfirmed PR.
[b]irCR+irPR+uirPR+irSD.
CI=confidence interval; irCR=immune-related complete response; irPR=immune-related partial response; irSD=immune-related stable disease; MSI-H EC=microsatellite instability-high endometrial cancer; uirPR=unconfirmed immune-related partial response.

Figure 2. Treatment Response to Dostarlimab at the RP2D in Patients with MSI-H EC. Duration of Exposure and Overall Response Based on irRECIST (A) and Best Percentage Change in Total Tumor Burden from Baseline Based on irRECIST (B)



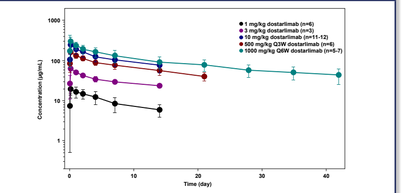
RP2D=recommended phase 2 dose; MSI-H EC=microsatellite instability-high endometrial cancer; irCR=immune-related complete response; irPR=immune-related partial response; irSD=immune-related stable disease; irPD=immune-related progressive disease; NE=not evaluable.

Figure 3. Relative Percent Change in Total Tumor Burden



- Dostarlimab exhibited linear and dose proportional PK (**Figure 4**).

Figure 4. PK Profiles After a Single Dose of Dostarlimab at Weight-based Doses (1, 3, and 10 mg/kg) as Well as Flat Doses (500 mg and 1000 mg)



- Dostarlimab had consistent and comparable exposure at the 500 mg (Q3W) and 1000 mg (Q6W) doses (**Table 5**).

Table 5. PK Summary of 500 mg Q3W and 1000 mg Q6W

Dose Regimen (mg)	C_{max} (µg/mL)	C_{last} (µg/mL)	T_{max} (h)	$AUC_{0\text{-}last}$ (h*µg/mL)
500 Q3W (n=6)	174 ± 35.2	40.2 ± 9.31	1.0 (0.5–3.0)	36424 ± 6674[a]
1000 Q6W (n=7)	322 ± 101	43.7 ± 18.2*	1.5 (0.5–3.0)	91376 ± 26808

Mean ± SD for all but T_{max} (median [range]).
*AUC following 500 mg (Q3W) should be multiplied by 2 to compare to that following 1000 mg (Q6W).
[a]n=5.
C_{max}=maximum plasma concentration; C_{last}=last measurable plasma concentration; T_{max}=time to maximum plasma concentration (C_{max}); $AUC_{0\text{-}last}$=area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration.

- Data as of August 17, 2018 show that dostarlimab maintained serum concentrations at least 8-fold higher than required for full RO (2.44 µg/mL, the lowest concentration observed for full RO)[4] throughout the course of treatment in the hybrid dose scheme of 4 x 500 mg Q3W and 1000 mg Q6W from part 2B patients.

CONCLUSIONS

- Preliminary efficacy data indicates robust activity of dostarlimab in MSI-H EC patients with previously platinum-treated advanced disease (52% ORR with 92.3% of responses ongoing).
- Preliminary safety findings indicate that dostarlimab is safe and well tolerated, with a profile characteristic of approved PD-1 inhibitors.[5]
- At RP2D, dostarlimab achieved serum concentrations at least 8-fold higher than required for full RO throughout the course of treatment.
- Safety and efficacy data for dostarlimab at the RP2D support the unique and convenient dosing schedule of 500 mg Q3W for the first 4 cycles and 1000 mg Q6W thereafter.

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