
SGO 50TH ANNUAL MEETING
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Preliminary Safety, Efficacy, and Pharmacokinetic/ Pharmacodynamic Characterization from GARNET, a Phase 1/2 Clinical Trial of the Anti-PD-1 Monoclonal Antibody, Dostarlimab, in Patients with Recurrent or Advanced MSI-H and MSS Endometrial Cancer (EC)

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- **Personal financial interests:**
  - **Advisory boards:** Roche, AstraZeneca, Pharma Mar SA, Clovis Oncology, Tesaro, Immunogen and Genmab
  - **Support for travel and/or accommodation**: Roche, AstraZeneca, Clovis Oncology, Tesaro, and Pharma Mar SA
- **Institutional financial interests:** AbbVie Deutschland, Ability Pharmaceuticals, Advaxis Inc., Aeterna Zentaris, Amgen SA, Aprea Therapeutics AB, Clovis Oncology Inc., EISAI Ltd, F. Hoffmann - La Roche Ltd, Regeneron Pharmaceuticals, Immunogen Inc., Merck, Sharp & Dohme de España SA, Millennium Pharmaceuticals Inc., Pharma Mar SA, Tesaro Inc.
- **Leadership roles:**
  - GEICO Executive Board member as a Co-Chair.
  - GCIG Phase II Committee and Cervix Cancer Committee Representative on behalf of GEICO
  - ESMO Faculty Member Gynaecological Track for ESMO 2018 and Chair of Gynaecological Track for ESMO 2019
- **Membership**: ESMO, ASCO, GCIG, SEOM, GOG

Background

- EC is the most common gynecologic malignancy in the US[1]
  - EC can be classified as microsatellite stable (MSS/75%) or microsatellite instability-high (MSI-H/25%)[2]
- There are limited treatment options for patients who progress on or after 1st line therapy
  - Patients typically receive single agent chemotherapy with response rates of 7-13%[3-5]
  - The only approved therapy in the recurrent EC setting is pembrolizumab for **MSI-H tumors** (ORR of 36% in n=14)[6]
- Dostarlimab (TSR-042) is an investigational humanized anti-PD-1 monoclonal antibody that competitively inhibits the PD-1 receptor by blocking ligand binding (PD-L1 and PD-L2)
- Dostarlimab has demonstrated significant clinical activity in various tumor types, including 2nd line PD-1 naïve NSCLC patients[7,8]

1. Siegel RL, et al. *CA Cancer J Clin*. 2016;66:7–30; 2. Levine DA, The Cancer Genome Atlas Research Network. *Nature*. 2013;497:67–73. 3. Thigpen JT, et al. *J Clin Oncol.* 2004;22:3902–3908.
4. Fleming GF, et al. *J Clin Oncol.* 2004;22:2159–2266. 5. Humber CE, et al. *Ann Oncol.* 2007;18:409–420. 6. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm.
7. Oaknin A, et al. *Ann Oncol.* 2018;29(Suppl 8):mdy285.144. 8. Perez DR, et al. SITC 2018 (abstract P326), https://www.sitcancer.org/2018/abstracts/titles.

EC: endometrial cancer; MSS: microsatellite stable; MSI-H: microsatellite instability-high; ORR: objective response rate; PD-1: programmed death-1; NSCLC: Non-small cell lung cancer

GARNET Trial

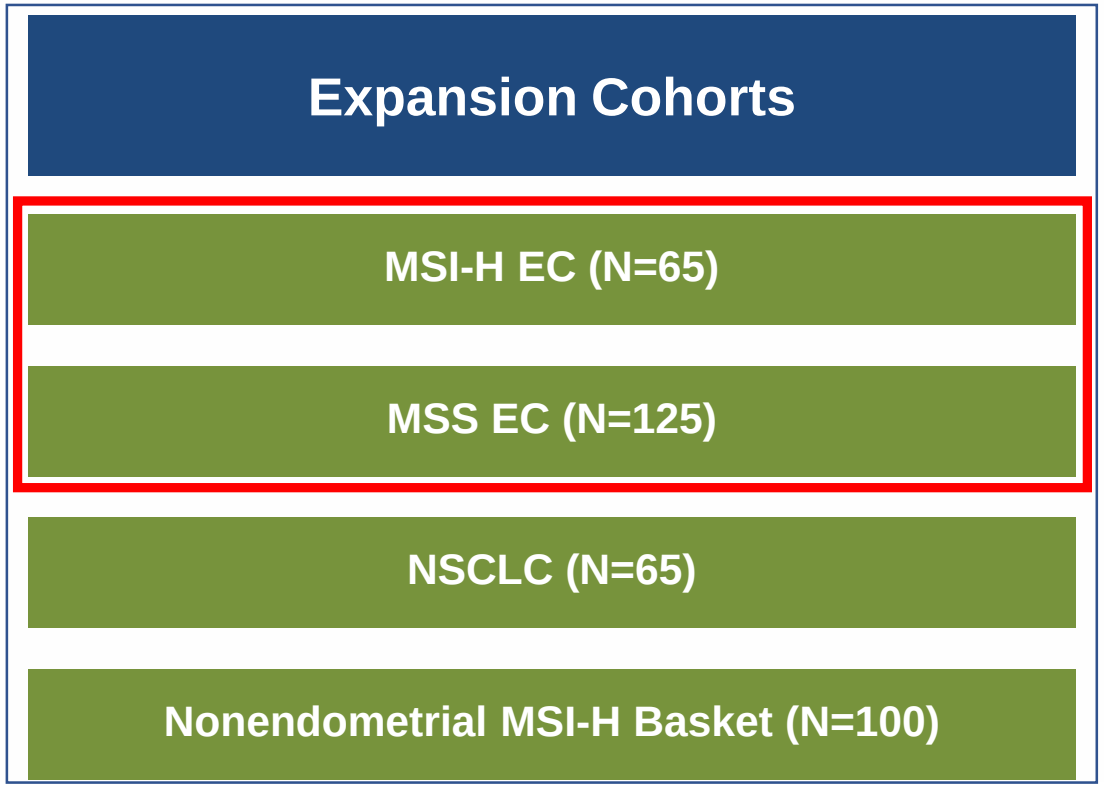
- GARNET is a multicenter, open-label, first-in-human phase 1 dose escalation study with expansion cohorts designed to assess the clinical activity and safety of dostarlimab in patients with advanced solid tumors
- Dostarlimab was dosed at 500 mg Q3W for 4 doses, then 1000 mg Q6W until disease progression, which achieves serum concentrations sufficient for full receptor occupancy for all patients throughout both dosing cycles
- We present results of the two EC expansion cohorts, MSI-H and MSS based on next generation sequencing[1]

Primary Objectives of EC Expansion Cohorts

- ORR and DOR in MSI-H and MSS patients
- Safety and tolerability

Secondary / Exploratory Objectives

- Further characterize the PK and PDy profile



1. MSI-H and MSS status were confirmed centrally using next generation sequencing (NGS): FoundationOne (Foundation Medicine)

Q3W: every 3 weeks; Q6W: every 6 weeks; ORR: Overall response rate; DOR: Duration of response; PK: pharmacokinetic; PDy: pharmacodynamic.

MSI-H: microsatellite instability-high; MSS: microsatellite stable; NSCLC: non-small cell lung cancer.
For more information on this trial: https://clinicaltrials.gov/ct2/show/NCT02715284.

Inclusion and Exclusion Criteria

Key inclusion criteria

- MSI-H or MSS recurrent or advanced EC patients who progressed on or after treatment with a platinum-containing regimen
- Patients must have received ≤2 prior lines of treatment for recurrent or advanced disease[1]

Key exclusion criteria

- Prior therapy with agents targeting PD-1, PD-L1, or PD-L2
- Active autoimmune disease that required systemic treatment within the last 2 years
- Uncontrolled central nervous system metastases and/or carcinomatous meningitis or additional malignancy that progressed or required active treatment within the last 2 years

1. Treatment given for stage <IIIb was not counted towards the number of lines of treatment for recurrent or advanced disease.

Patient Demographics & Baseline Characteristics

Approximately half of the patients had received 2 or more prior lines of therapy

Characteristics	MSI-H EC (n=41)	MSS EC (n=79)	MSI status unknown[a] (n=5)	Total (N=125)
Age, median (min, max), years	64 (39, 76)	66 (32, 86)	67 (60, 77)	65 (32, 86)
Total number of prior regimens, n (%)				
1	23 (56.1%)	42 (53.2%)	3 (60.0%)	68 (54.4%)
2	12 (29.3%)	28 (35.4%)	2 (40.0%)	42 (33.6%)
≥3	6 (14.6%)	9 (11.4%)	0	15 (12.0%)
Prior paclitaxel with carboplatin, n (%)	34 (82.9%)	67 (84.8%)	4 (80.0%)	105 (84.0%)
FIGO stage of disease at diagnosis[b], n (%)				
Stage I or II	9 (22.0%)	14 (17.7%)	0 (0%)	23 (18.4%)
Stage III	8 (19.5%)	12 (15.2%)	0 (0%)	20 (16.0%)
Stage IV	21 (51.2%)	46 (58.2%)	5 (100.0%)	72 (57.6%)
Histology at diagnosis, n (%)				
Endometrioid	32 (78.0%)	31 (39.2%)	1 (20.0%)	64 (51.2%)
Serous carcinoma	0 (0%)	21 (26.6%)	3 (60.0%)	24 (19.2%)
Clear cell carcinoma	0 (0%)	4 (5.1%)	0 (0%)	4 (3.2%)
Others	9 (22.0%)	23 (29.1%)	1 (20.0%)	33 (26.4%)

[a]Based on central testing, MSI status could not be determined.
[b]FIGO stage unknown for 3 patients with MSI-H EC and 7 patients with MSS EC. FIGO: International Federation of Gynecology and Obstetrics.

Treatment–Emergent Adverse Events (TEAEs)

- Dostarlimab was well tolerated
  - 5.6% of all patients experienced a grade ≥3 immune related, treatment-related TEAE
  - No deaths occurred due to a treatment-related TEAE

Adverse Event	Total (N=125)
Patients with all grade treatment-related TEAE, n (%)	**88 (70.4%)**
All grade treatment-related TEAEs occurring in ≥10% of total patients	
Fatigue	18 (14.4%)
Diarrhea	16 (12.8%)
Nausea	15 (12.0%)

TEAE: treatment-emergent adverse event.

Immune-related Adverse Event	Total (N=125)
Patients with grade ≥3 immune-related, treatment-related TEAE, n (%)	**7 (5.6%)**
Alanine aminotransferase increased	2 (1.6%)
Aspartate aminotransferase increased	2 (1.6%)
Hyperglycemia	2 (1.6%)
Autoimmune haemolytic anaemia	1 (0.8%)
Colitis	1 (0.8%)
Infusion related reaction	1 (0.8%)

TEAE: treatment-emergent adverse event.

Best Overall Tumor Response

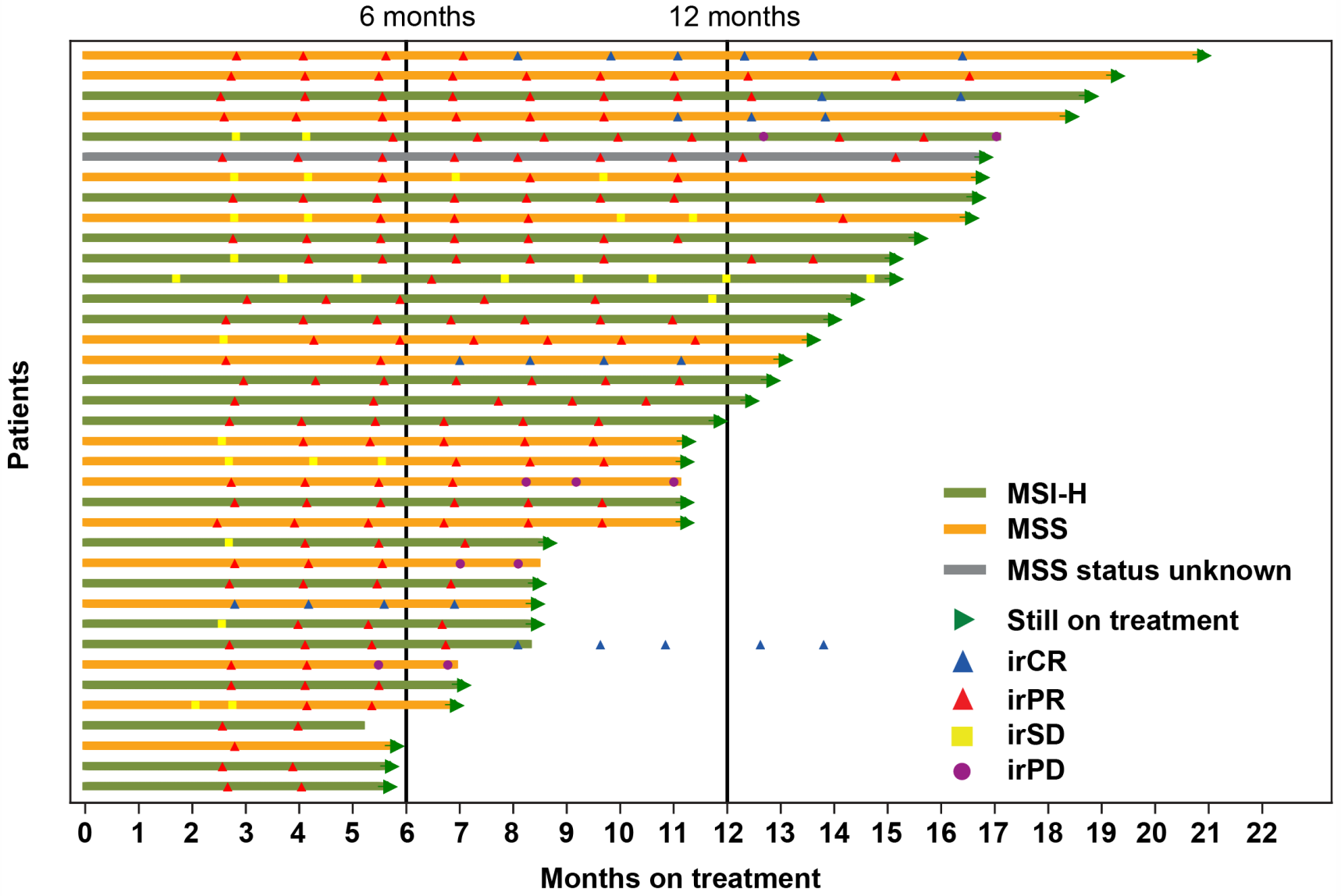
Dostarlimab demonstrated clinically meaningful response rates regardless of MSI status, with an ORR of 30% (49% in the MSI-H cohort and 20% in the MSS cohort)

Best Overall Response		MSI-H EC (n=41)	MSS EC (n=79)	MSI status unknown[a] (n=5)	Total (N=125)
Overall response rate	**n (%)** (95% CI)	**20 (48.8%)** (32.9, 64.9)	**16 (20.3%)** (12.0, 30.8)	**1 (20.0%)** (0.5, 71.6)	**37 (29.6%)** (21.8, 38.4)
Complete response	n (%)	2 (4.9%)	4 (5.1%)	0 (0%)	6 (4.8%)
Partial response	n (%)	18[b] (43.9%)	12[c] (15.2%)	1 (20.0%)	31 (24.8%)
Disease control rate[d]	% (95% CI)	63.4% (46.9, 77.9)	46.8% (35.5, 58.4)	60.0% (14.7, 94.7)	52.8% (43.7, 61.8)
Response ongoing	%	85.0%	81.3%	100%	83.8%

[a]Based on central testing, MSI status could not be determined; [b]17 confirmed and 1 still on treatment and yet to be confirmed; [c]11 confirmed and 1 still on treatment and yet to be confirmed; [d]irCR+irPR+uirPR+irSD.
irCR: immune-related complete response; irPR: immune-related partial response; irSD: immune-related stable disease; uirPR: unconfirmed immune-related partial response. CI: confidence interval.

Data extract date: January 21, 2019.

Duration of Treatment – Responding Patients

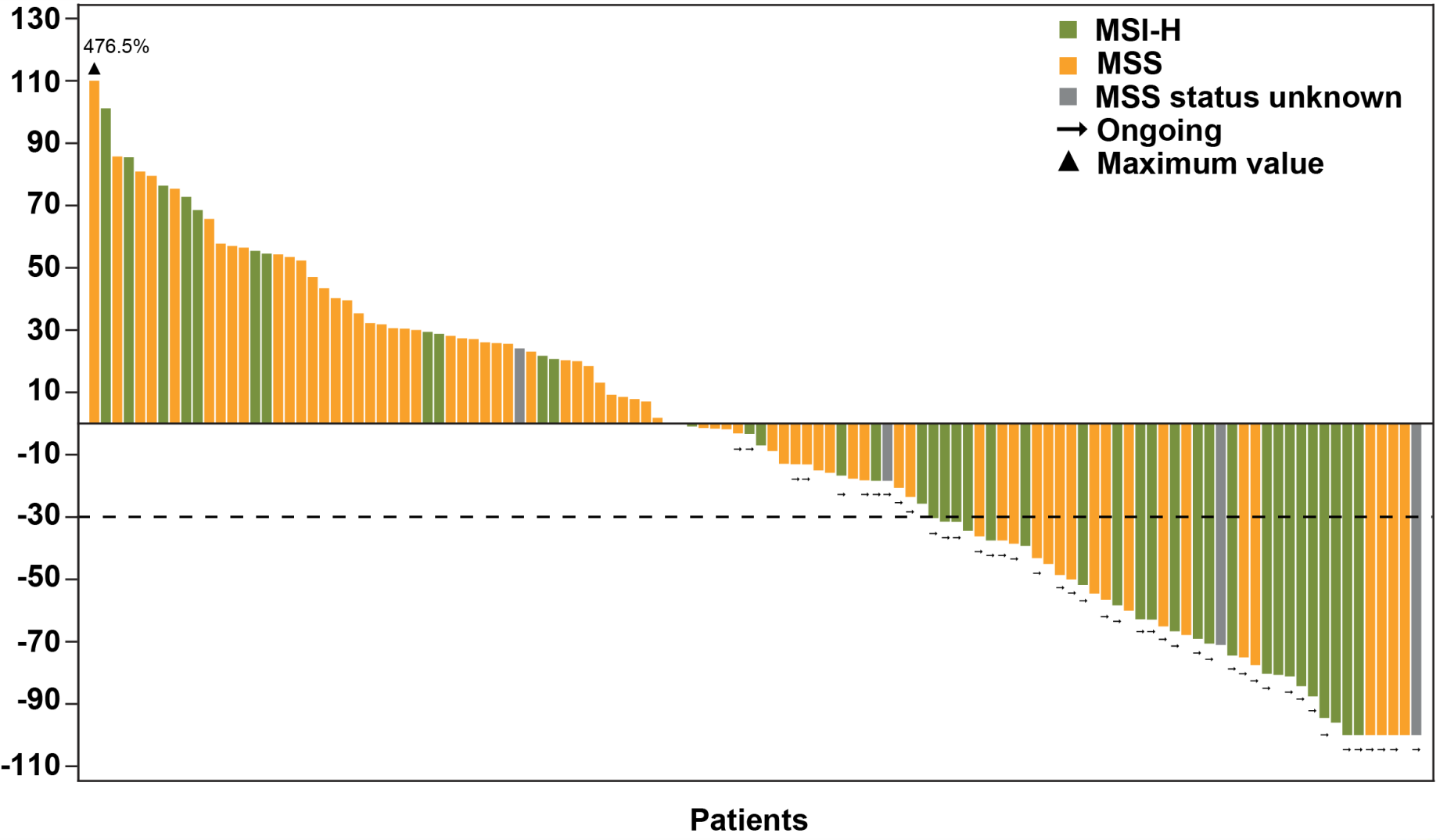


- Responses were durable in both the MSI-H and MSS cohorts
- 84% of the responders (31 of 37) are still on treatment
- Median DOR has not been reached; Of responders:
  - 89% remained on treatment for >6 months
  - 49% remained on treatment for >1 year
- Median follow-up is 10 months

irCR: immune-related complete response; irPR: immune-related partial response; irSD: immune-related stable disease; irPD: immune-related progressive disease.

SD is defined as at least one SD or Non-CR/Non-PD assessment (or better) ≥ 12 weeks - 10 days (≥74 days) after baseline and before progression (and not qualifying for a CR or PR).

Change in Tumor Size



>50% reduction in total tumor burden in 85% of MSI-H and 69% of MSS responders

Conclusions

- GARNET is the single largest study of anti-PD-1 monotherapy in patients with advanced/recurrent EC
- Dostarlimab was administered at a unique and convenient dosing schedule of 500 mg Q3W for 4 doses, followed by 1000 mg Q6W thereafter
- Dostarlimab maintained serum concentrations ensuring full receptor occupancy throughout the dosing cycle for all patients
- Dostarlimab demonstrated clinically meaningful response rates:
  - ORR of 30%
  - ORR of 49% in patients with MSI-H tumors
  - ORR of 20% in patients with MSS tumors
- Responses were durable in both MSI-H and MSS cohorts:
  - Median DOR has not been reached; ~ 50% of all responders remained on treatment for >1 year
- Dostarlimab was well tolerated; TRAEs were generally low grade; grade ≥3 irAEs were uncommon (<6%)
- Further investigation of dostarlimab in combination with chemotherapy in 1st line EC in a phase 3 trial will be initiated in 2H 2019

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