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Safety and Efficacy of the Anti–PD-1 Monoclonal Antibody Dostarlimab in Patients With Recurrent or Advanced dMMR Endometrial Cancer

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Dr. Sabatier Disclosures

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Background

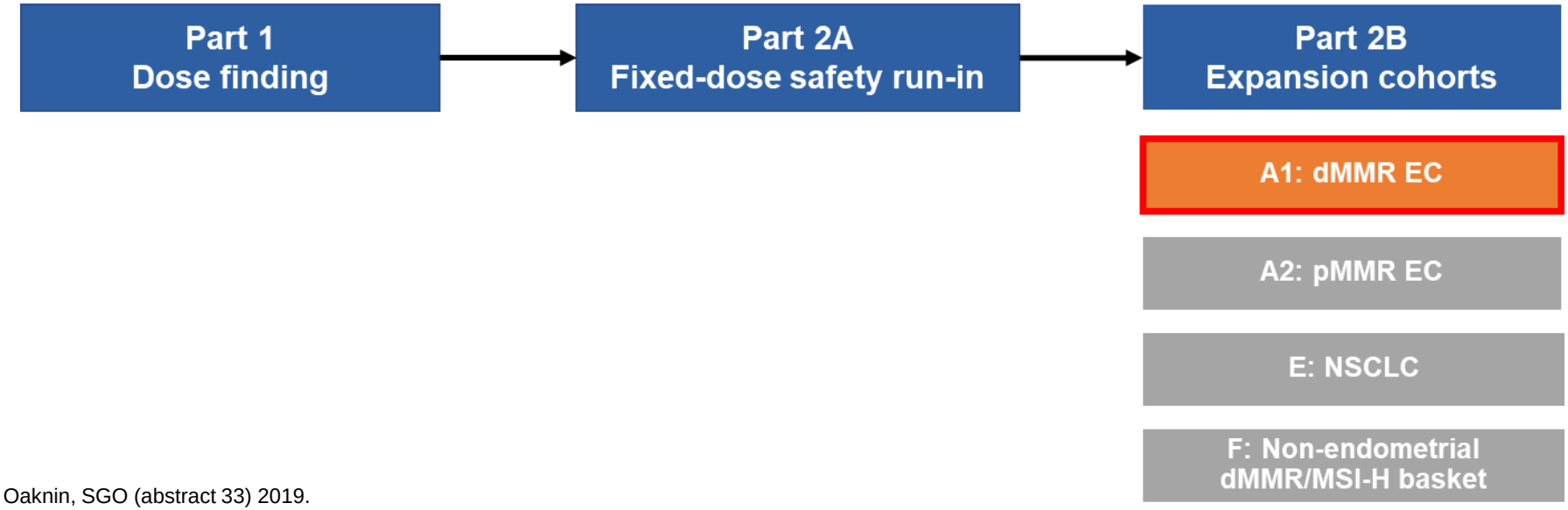
- EC is the most common gynecologic malignancy in the US and EU[1]
  - EC has the highest rates of dMMR and MSI-H of all tumors (≈30%)[2]
- Treatment options are limited for patients who progress on or after first-line therapy, and overall survival is typically <1 year
  - Most patients receive single-agent chemotherapy with response rates of <15%[3–5]
  - Pembrolizumab has an accelerated approval in the US for MSI-H/dMMR solid tumors, including EC[6]
  - Pembrolizumab + lenvatinib has an accelerated approval in the US, Canada, and Australia for patients with advanced EC that progressed following a platinum-based chemotherapy
- Dostarlimab (TSR-042) is an investigational humanized anti–PD-1 monoclonal antibody that competitively inhibits the PD-1 receptor and blocks ligand binding (PD-L1 and PD-L2)
- Dostarlimab has demonstrated clinical activity in various tumor types, including second-line, PD-1–naïve patients with NSCLC[7,8]

1. Siegel, *CA Cancer J Clin* 2016; 2. Cancer Genome Atlas Research Network, *Nature* 2013; 3. Muggia, *J Clin Oncol* 2002; 4. Fracasso, *Gynecol Oncol* 2006; 5. Dizon, *J Clin Oncol* 2009. 6. FDA News Release, https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm, March 2018; 7. Oaknin, *Ann Oncol* 2018; 8. Perez, SITC (abstract P326) 2018.

dMMR, mismatch repair deficiency; EC, endometrial cancer; EU, European Union; MSI-H, microsatellite instability-high; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2; US, United States.

GARNET Trial Design

- GARNET (NCT02715284) 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
- In Part 2B, dostarlimab was dosed at the RTD determined from Part 1 and 2A
  - 500 mg Q3W for 4 doses, then 1000 mg Q6W until disease progression
- At SGO 2019 we presented the EC cohorts based on MSI-H/MSS by NGS/PCR[1]
- Today we present the dMMR EC by IHC



1. Oaknin, SGO (abstract 33) 2019.

dMMR, mismatch repair deficient; EC, endometrial cancer; IHC, immunohistochemistry; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NGS, next-generation sequencing; PCR, polymerase chain reaction; pMMR, mismatch repair proficient; NSCLC, non-small cell lung cancer; RTD, recommended therapeutic dose.

Clinical Trials.gov, https://clinicaltrials.gov/ct2/show/NCT02715284, January 2020.

GARNET Expansion Cohorts

Part 2B
Expansion cohorts

- **A1: dMMR EC**
- **A2: pMMR EC**
- **E: NSCLC**
- **F: Non-endometrial dMMR/MSI-H basket**

Key inclusion criteria for cohort A1

- Patients with recurrent or advanced EC that progressed on or after treatment with a platinum-containing regimen
- dMMR status by IHC testing
- Patients must have received ≤2 prior lines of treatment for recurrent or advanced disease

Primary objectives for Part 2B

ORR and DOR per RECIST v1.1

Safety and tolerability

Secondary/exploratory objectives

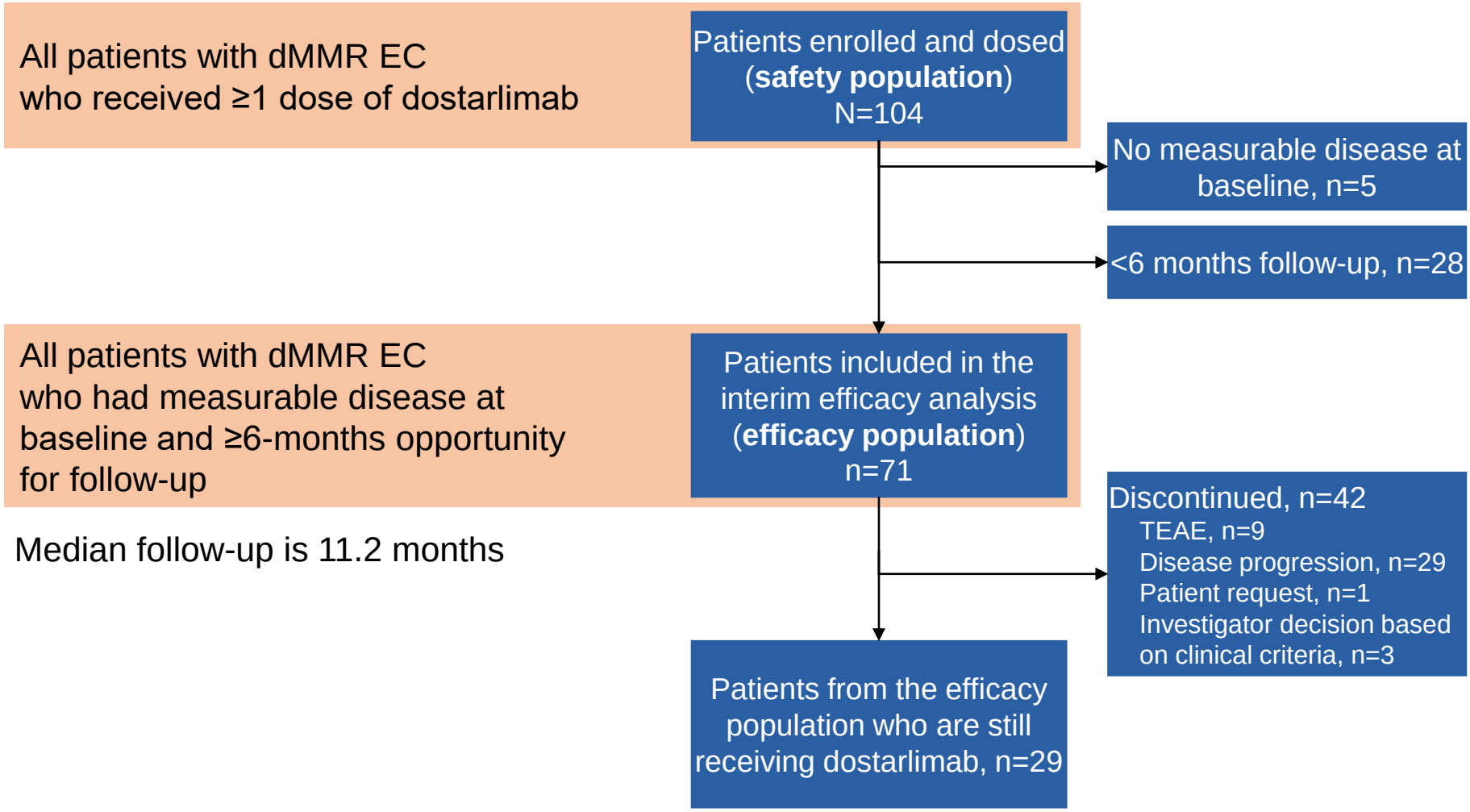
Further characterize the PK and PDy profile

Data cutoff for this interim analysis

July 8, 2019

dMMR, mismatch repair deficient; DOR, duration of response; EC, endometrial cancer; IHC, immunohistochemistry; MSI-H, microsatellite instability-high; NSCLC, non-small cell lung cancer; ORR, objective response rate; PDy, pharmacodynamic; PK, pharmacokinetic; pMMR, mismatch repair proficient; RECIST, Response Evaluation Criteria in Solid Tumors.

Disposition of Patients With dMMR EC



dMMR, mismatch repair deficient; EC, endometrial cancer; TEAE, treatment-emergent adverse event.

Demographics and Baseline Characteristics

Characteristic	Safety population n=104	Efficacy population n=71
Age, median (range)	64.5 (39–80)	64.0 (39–80)
Ethnicity, n (%)		
White	83 (80)	58 (82)
Black	2 (2)	1 (1)
Other/not reported	19 (18)	12 (17)
ECOG performance status, n (%)		
0	40 (38)	23 (32)
1	64 (62)	48 (68)
Disease stage at diagnosis, n (%)		
I/II	47 (45)	36 (51)
III	37 (36)	25 (35)
IV	18 (17)	10 (14)
Unknown	2 (2)	0
Histology, n (%)		
Endometrioid carcinoma (grade 1 and 2)	70 (67)	50 (70)
Endometrial carcinoma type II	25 (24)	15 (21)
Other*	9 (9)	6 (8)
Prior platinum-based doublet chemotherapy, n (%)	104 (100)	71 (100)
Number of prior lines of therapy, n (%)†		
1	67 (64)	42 (59)
2	25 (24)	18 (25)
3+	12 (12)	11 (16)

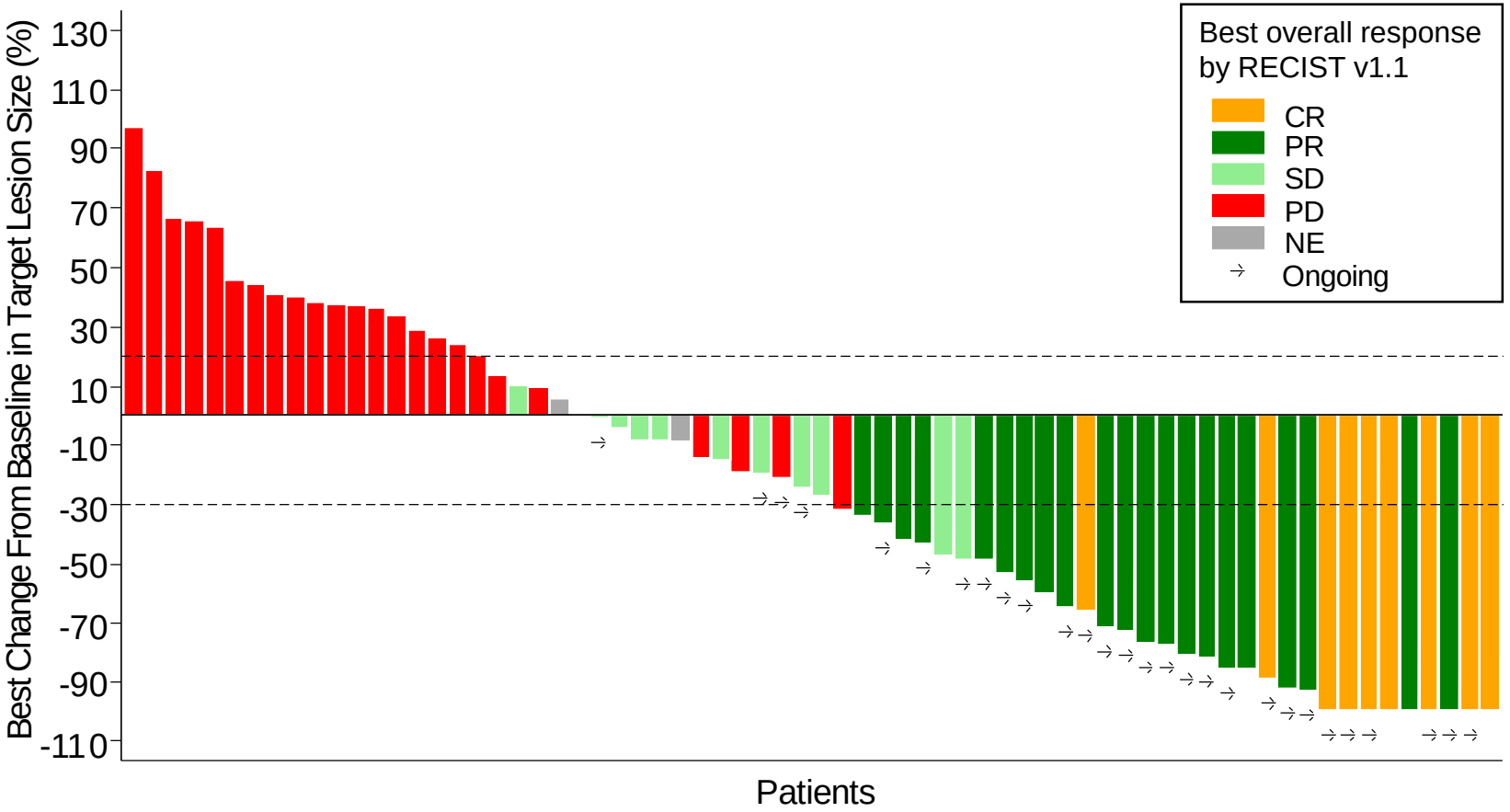
*Includes patients with squamous carcinoma, undifferentiated carcinoma, mixed carcinoma, and unknown.
†Includes lines of therapy prior to the advanced/recurrent setting.
ECOG, Eastern Cooperative Oncology Group.

Objective Response Rate – Primary Endpoint

Variable	dMMR EC n=71, n (%)
Objective response rate	30 (42) [95% CI 31–55]*
Complete response	9 (13)
Partial response	21 (30)
Stable disease	11 (16)
Progressive disease	27 (38)
Not evaluable†	3 (4)
Response ongoing‡	25 of 30 (83)
Disease control rate	41 (58) [95% CI 45–69]*

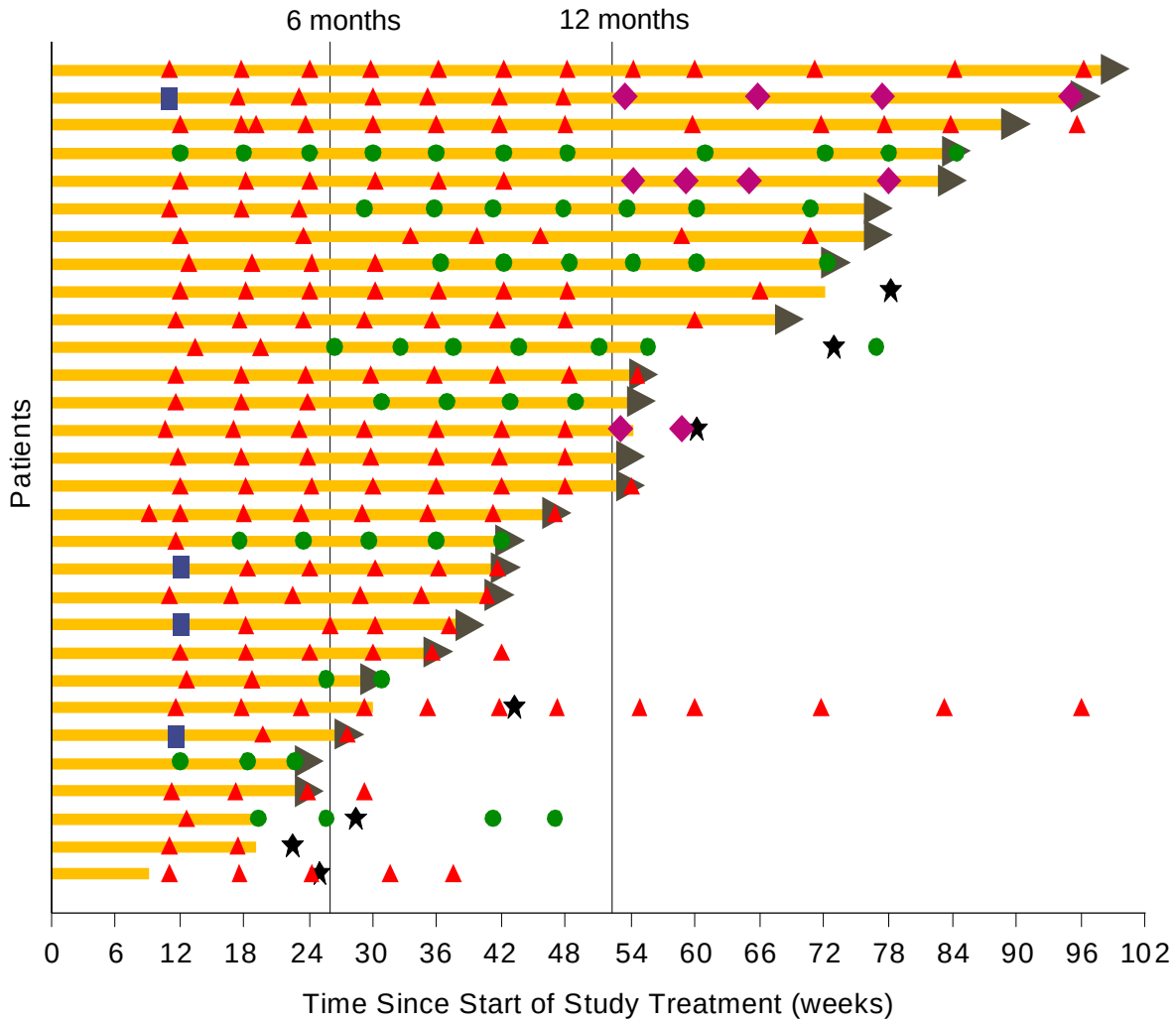
*Exact 2-sided 95% CI for the binomial proportion.
†Not evaluable based on RECIST v1.1.
‡All responders who have not yet died or progressed (including clinical progression), denominator for percentage is number of responders.
dMMR, mismatch repair deficient; EC, endometrial cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

Best Overall Response (Colors) and Change in Target Lesion Size From Baseline (Bar Length)



Maximum percentage change in target lesions from baseline is indicated by bar length. Best overall response is indicated by color coding of bars and includes assessment of target, non-target, and new lesions.
CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Treatment Duration of Responders



- Median follow-up is 11.2 mos
- Median DOR not reached (1.87+ to 19.61+ mos)
- 25 of 30 (83%) responders remain in response as of the data cutoff
- Deepening of responses:
  - **SD → PR**: 4 patients
  - **PR → CR:** 7 patients

Patients were permitted to remain on treatment after progression if they were considered to be benefiting from treatment.
CT scans after treatment discontinuation were used to monitor disease for follow-up.
CR, complete response; DOR, duration of response; mos, months; PD, progressive disease; PR, partial response; SD, stable disease.

Safety – Primary Endpoint

- Most TEAEs were grade 1–2
- 2 patients (2%) discontinued the study due to TRAEs: increased transaminases in both cases
- 24 patients (23%) had treatment interruptions due to TEAEs
- No deaths due to TRAEs were reported

Any-grade TRAEs in ≥5% of patients, n (%)	N=104
Asthenia	16 (15)
Diarrhea	16 (15)
Fatigue	15 (14)
Nausea	13 (13)
Pruritus	10 (10)
Hypothyroidism	9 (9)
Arthralgia	8 (8)
Anemia	7 (7)

Grade ≥3 immune-related TRAEs in any patient, n (%)	N=104
Diarrhea	3 (3)
Colitis	2 (2)
Lipase increased	2 (2)
Transaminases increased*	2 (2)
Amylase increased	1 (1)
Alanine aminotransferase increased	1 (1)
Pancreatitis, acute	1 (1)

*One patient had AST/ALT increased, and one patient had solely ALT increased.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Conclusions

- This dataset is the largest to date for patients with dMMR EC: 104 safety / 71 efficacy
  - All patients had progressed on or following platinum-based therapy (SOC)
  - These patients have limited treatment options and are a high unmet need
- Dostarlimab monotherapy resulted in a robust ORR of 42% in patients with recurrent or advanced dMMR EC that had progressed on or following platinum treatment
  - Responses were durable, and the median DOR was not reached (1.87+ to 19.61+ months)
  - Median follow-up was 11.2 months
  - 25 of 30 (83%) responders remain in response
- The safety profile was acceptable and consistent with that of other anti–PD-1 antibodies
  - <2% of the patients discontinued treatment due to TRAEs, and no treatment-related deaths were reported
- The GARNET trial is ongoing and currently enrolling
- The RUBY trial (NCT03981796), a randomized, placebo-controlled, phase 3 trial of dostarlimab + carboplatin-paclitaxel in first-line advanced or recurrent EC (including carcinosarcomas), is currently enrolling

dMMR, mismatch repair deficiency; DOR, duration of response; EC, endometrial cancer; ORR, objective response rate; PD-1, programmed death-1; SOC, standard of care; TRAE, treatment-related adverse event.

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