

LINNET: A Phase 2 Study to Evaluate Lorigerlimab in Participants With Advanced Gynecologic Cancers

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INTRODUCTION

- Gynecologic malignancies represent a substantial global health burden, with ovarian, endometrial, and cervical cancers contributing significantly to cancer-related morbidity and mortality worldwide^{1,2}
- Despite advances in treatment and meaningful clinical benefits observed with current therapies, treatment resistance remains a major challenge, highlighting the need for novel targeted therapeutic strategies^{3,4}
- Lorigerlimab, an investigational, tetravalent, bispecific, Fc-bearing (IgG4) DART[®] molecule designed to bind to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), demonstrated manageable safety and preliminary signs of clinical activity in a phase 1 study (NCT03761017/CP-MGD019-01)^{5,6}
- Here, we report preliminary data from an ongoing phase 2 study of lorigerlimab in participants with platinum-resistant ovarian cancer (PROC) or clear cell gynecologic cancer (CCGC)

METHODS

Study Design and Population

- This open-label, multicohort, noncomparative phase 2 study (NCT06730347/CP-MGD019-03) allowed the inclusion of adult participants with histologically confirmed high-grade serous epithelial PROC, primary peritoneal, or fallopian tube cancer (cohort A) or CCGC (cohorts B and C), including ovarian (primary peritoneal and fallopian tube), endometrial, vaginal, vulvar, or cervical cancer (Figure 1)

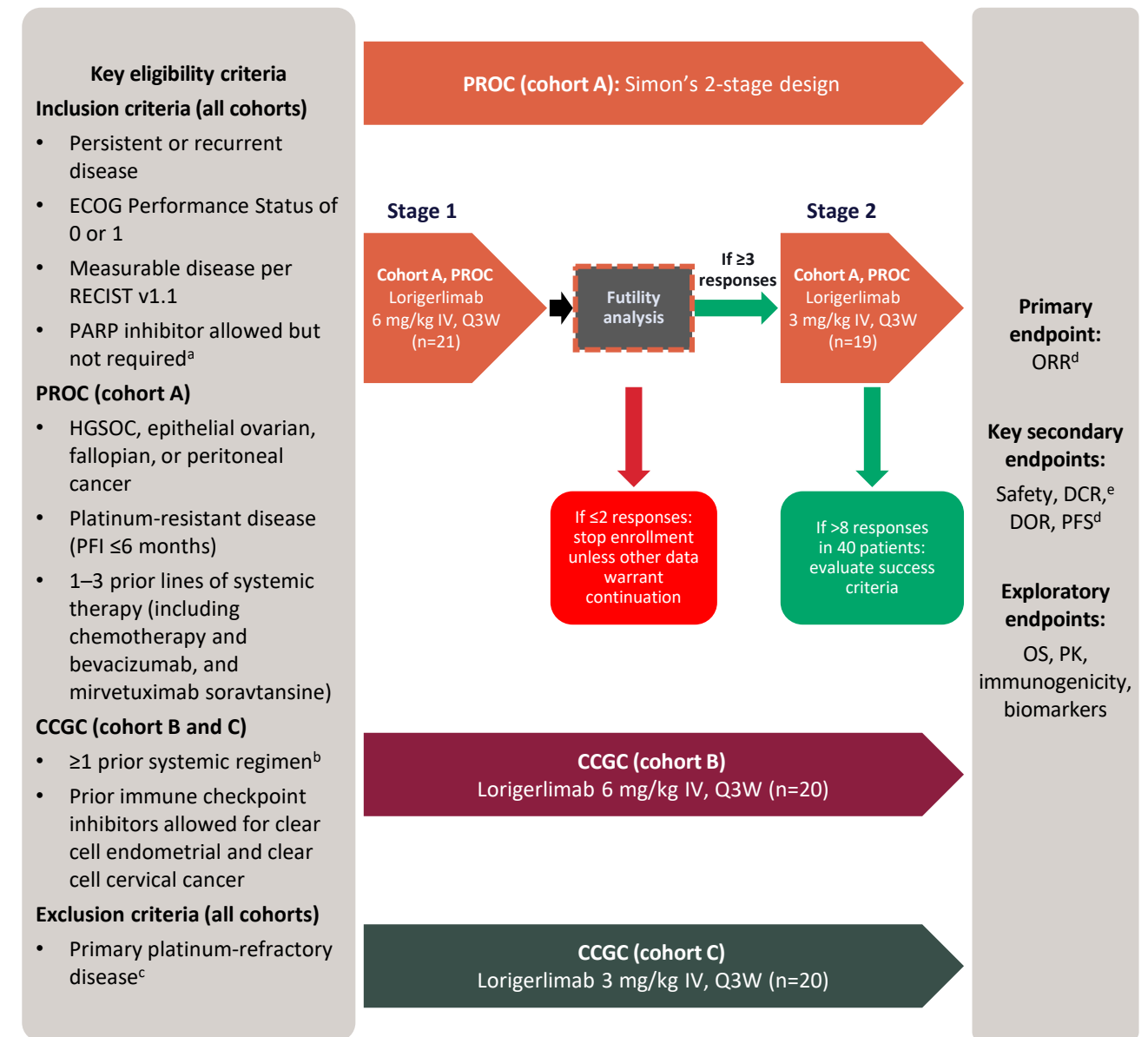
Treatment

- Lorigerlimab was administered intravenously (IV) every 3 weeks (Q3W) at 6 mg/kg in cohorts A and B and 3 mg/kg in cohort C (Figure 1)
- Cohort A used a Simon's 2-stage design with a prespecified interim futility assessment after stage 1 to guide stage 2 enrollment. Enrollment in cohort A stage 2 did not commence due to futility
- As of Amendment 4, cohort C was opened (CCGC; 3 mg/kg) and cohort B (CCGC; 6 mg/kg) was closed before reaching the target sample size. Cohort A did not progress to stage 2 enrollment

Assessments

- Tumor assessments were performed every 9 weeks for the initial 54 weeks on study treatment and every 12 weeks thereafter
- Objective response rate (ORR) and disease control rate (DCR) were summarized using 2-sided 95% exact binomial confidence intervals (CIs)
- The Kaplan-Meier method was used to estimate duration of response (DOR), progression-free survival (PFS), and overall survival (OS)

Figure 1. Trial Design



*Participants with a known history of documented BRCA mutation (germline or somatic) must have received a PARP inhibitor if one is locally approved and available. Participants must have experienced disease progression or recurrence to the PARP inhibitor prior to enrollment. Radiation therapy, including chemotherapy as a radiosensitizer, was not counted as prior systemic therapy. Primary platinum-refractory disease was defined as disease that did not respond to (ie, complete response or partial response) or had progressed within 3 months of the last dose of first-line platinum-containing chemotherapy. By investigator, per RECIST v1.1, DCR was defined as participants with a CR, PR, or SD for ≥3 months. BRCA, breast cancer gene; CCGC, clear cell gynecologic cancer; CR, complete response; DCR, disease control rate; DOR, duration of response; HDOS, high-grade serous ovarian cancer; IV, intravenous; ORR, objective response rate; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PR, partial response; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; PROC, platinum-resistant ovarian cancer; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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RESULTS

Participant Disposition

- As of the September 1, 2026 data cutoff, 42 participants were treated
 - 24 participants with PROC in cohort A stage 1
 - 17 participants with CCGC in cohort B
 - 1 participant with CCGC in cohort C; data were excluded from the presented safety/efficacy summaries due to limited data at the cutoff
- Median treatment exposure was 2.2 months (range, 0.7–9.2) in cohort A and 2.9 months (range, 1.3–12.0) in cohort B
- A total of 39/42 (92.8%) participants discontinued treatment
 - All 24 (100.0%) participants in cohort A discontinued treatment, including 14 due to progressive disease (PD), 7 due to adverse events (AEs), 2 due to physician decision, and 1 due to participant decision
 - A total of 15/17 (88.2%) participants in cohort B discontinued treatment, including 10 due to PD, 3 due to AEs, and 2 due to participant decision

Participant Baseline Characteristics

- The median age was 62 years in cohort A and 55 years in cohort B, and most participants had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 in each cohort (54.2% and 70.6%, respectively) (Table 1)
- The primary site of disease was the ovary in both cohort A (87.5%) and cohort B (100%), and the median number of prior lines of therapy was 2 and 1 in cohorts A and B, respectively. All participants had received a platinum-containing regimen and a taxane; 66.7% of participants in cohort A had also received a poly (ADP-ribose) polymerase inhibitor (Table 1)
- No participants in cohort A had microsatellite instability (MSI)-high or mismatch repair (MMR) deficiency (Table 1). In cohort B, MMR deficiency was observed in 3 (17.6%) participants; 1 (5.9%) of these participants had MSI-high

Table 1. Baseline Demographics and Disease Characteristics in Cohorts A and B

Parameters	PROC (cohort A) n=24	CCGC (cohort B) n=17
Age, median (range), years	62 (38–73)	55 (37–78)
Race, n (%)		
White	10 (41.7)	9 (52.9)
Black or African American	0	1 (5.9)
Asian	14 (58.3)	7 (41.2)
ECOG performance status, n (%)		
0	13 (54.2)	12 (70.6)
1	11 (45.8)	5 (29.4)
Primary disease site, n (%)		
Ovary	21 (87.5)	17 (100)
Fallopian tube	2 (8.3)	0
Primary peritoneal	1 (4.2)	0
Tumor metastasis, n (%)		
Lymph node	15 (62.5)	8 (47.1)
Liver	4 (16.7)	6 (35.3)
Lung	3 (12.5)	4 (23.5)
Other	23 (95.8)	14 (82.4)
Prior lines of therapy, median (range)	2 (1–3)	1 (1–3)
Number of prior lines, n (%)		
1	4 (16.7)	9 (52.9)
2	9 (37.5)	6 (35.3)
3	11 (45.8)	2 (11.8)
Prior therapy, n (%)		
Platinum-containing regimen	24 (100)	17 (100)
Taxane	24 (100)	17 (100)
Bevacizumab	19 (79.2)	9 (52.9)
PARP inhibitor	16 (66.7)	3 (17.6)
PD-L1 expression, n (%)		
CPS <1	3 (12.5)	6 (35.3)
CPS ≥1	18 (75.0)	8 (47.1)
Unknown	3 (12.5)	3 (17.6)
MSI, n (%)		
MSS	17 (70.8)	7 (41.2)
MSI-H	0	1 (5.9)
Unknown	7 (29.2)	5 (29.4)
Other ^a	0	4 (23.5)

^aOther includes low probability of MSI-H and MSS/MSI-L. CCGC, clear cell gynecologic cancer; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; MSI, microsatellite instability; MSS, microsatellite stable; MSI-H, microsatellite instability-high; MSS-L, microsatellite instability-low; NA, not available; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; PROC, platinum-resistant ovarian cancer.

DISCLOSURES

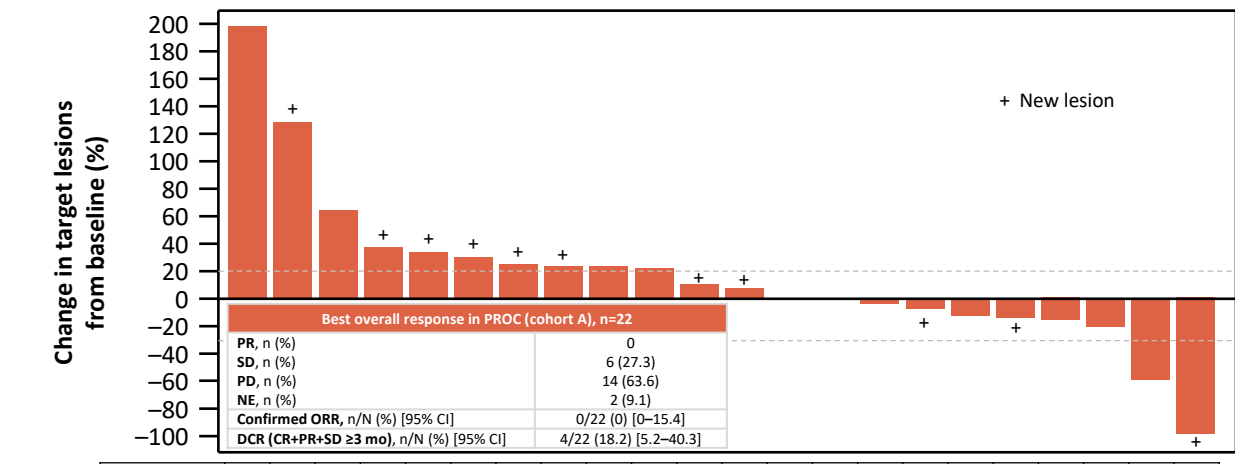
A. A. Jazaeri reports clinical trial funding to his institution from MacroGenics Inc., Merck, Thelystics, Immun, Iovance, Immatics, Outpace Bio, GSK, and Lixte; personal consulting fees from Gerson Lehrman Group, Guidepoint, Thelystics, Emxex, IQVIA, Rice Biotech Launchpad, Sentinel Bio, and Duracyste.

Efficacy

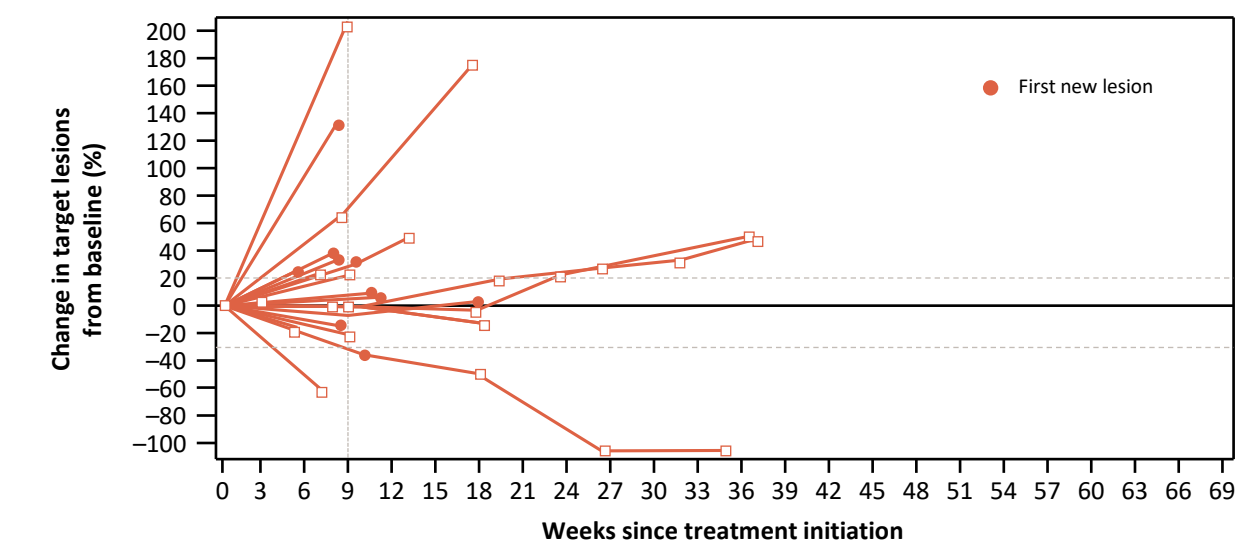
- In cohort A, among the 22 evaluable participants with PROC, 6 had a best response of stable disease (SD) and 14 had PD (Figures 2A and 2B)
- In cohort B, among the 16 evaluable participants with CCGC, 4 (25.0%) had a confirmed partial response (PR), and 3 had SD (Figures 2C and 2D; Figure 3)
 - All responses remained ongoing at data cutoff, including responses in 2 participants who had discontinued study treatment

Figure 2. Best Percent Change in Target Lesions Among Treated Participants With Measurable Disease at Baseline and ≥1 Postbaseline Assessment in Cohort A (A, B) and Cohort B (C, D)

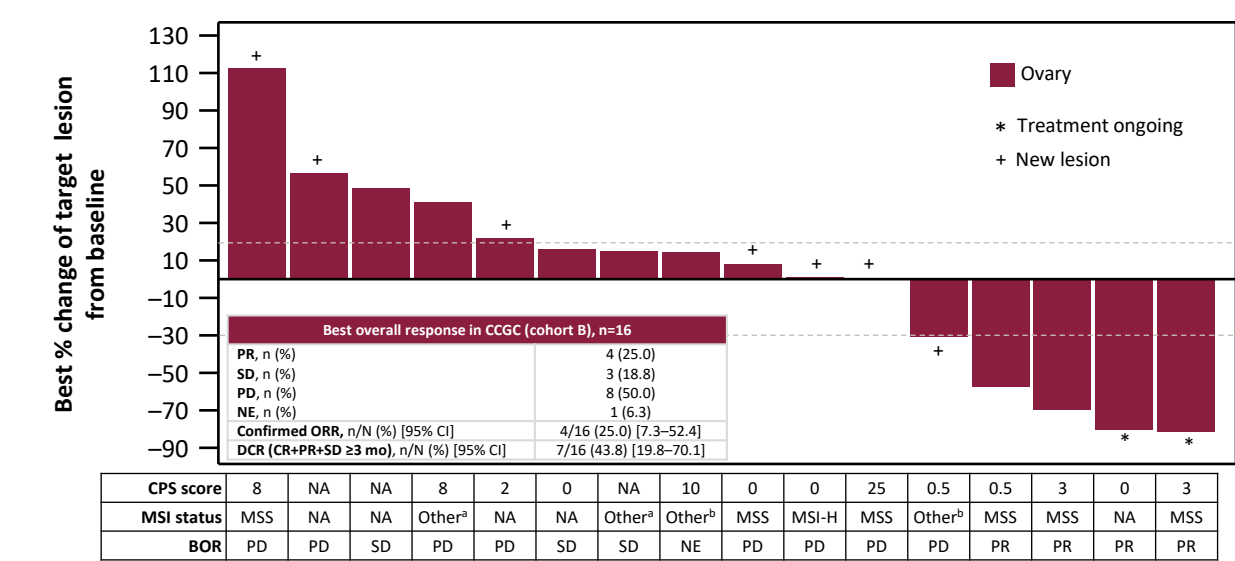
(A) PROC (Cohort A)



(B) PROC (Cohort A)



(C) CCGC (Cohort B)



(D) CCGC (Cohort B)

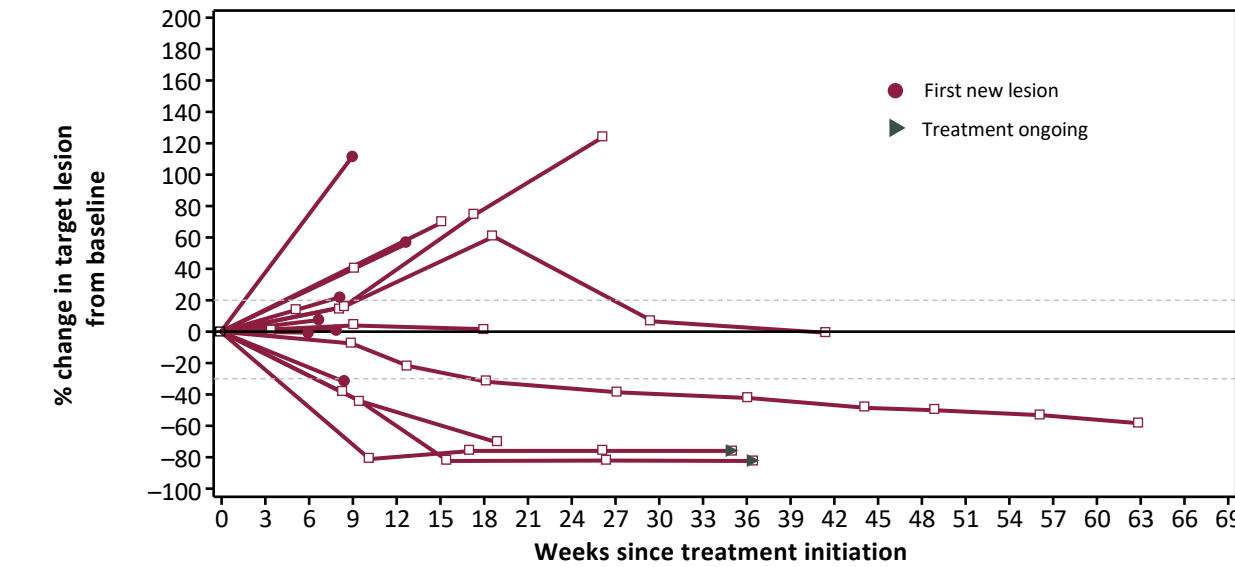
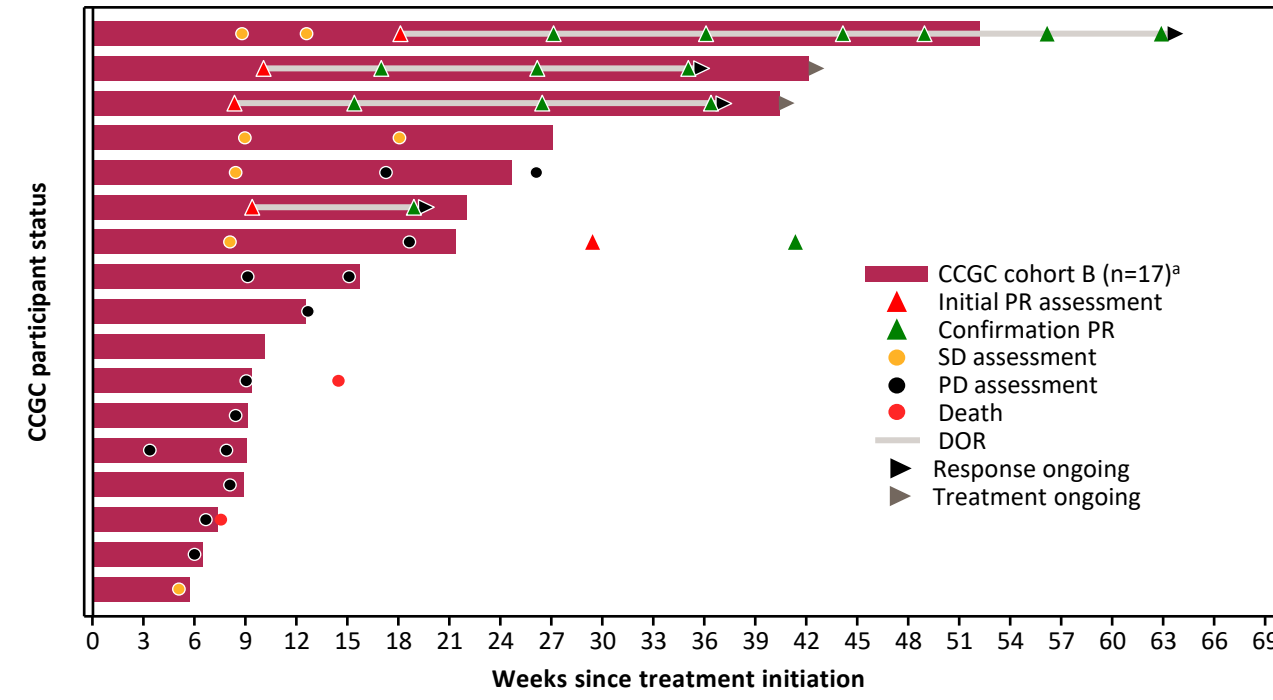


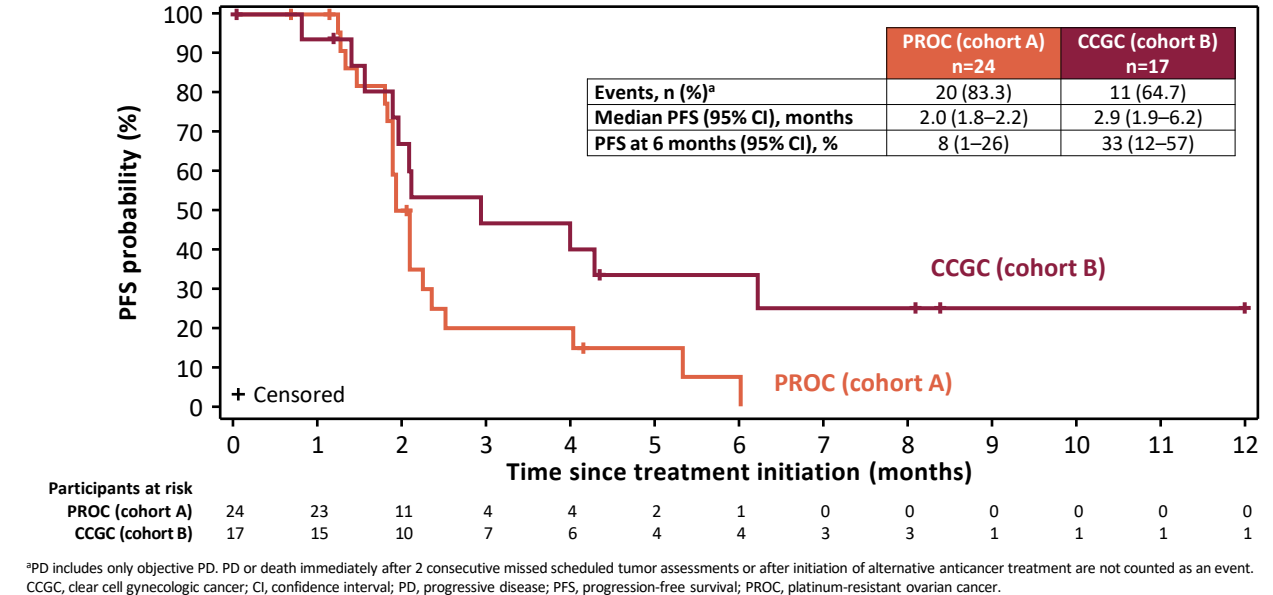
Figure 3. Assessment of Duration of Treatment and Tumor Response Over Time in Participants With CCGC (Cohort B)



*Participants who received ≥1 dose of lorigerlimab and had measurable disease at baseline. CCGC, clear cell gynecologic cancer; DOR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease.

- Median PFS in the safety population was 2 months (95% CI, 1.8–2.2) for cohort A (n=24) and 2.9 months (95% CI, 1.9–6.2) for cohort B (n=17); the PFS rates at 6 months were 8% (95% CI, 1–26) and 33% (95% CI, 12–57), respectively (Figure 4)

Figure 4. Progression-Free Survival in Cohort A and Cohort B Participants



*PD includes only objective PD, PD or death immediately after 2 consecutive missed scheduled tumor assessments or after initiation of alternative anticancer treatment are not counted as an event. CCGC, clear cell gynecologic cancer; CI, confidence interval; PD, progressive disease; PFS, progression-free survival; PROC, platinum-resistant ovarian cancer.

Safety

- All 41 (100%) participants in cohort A and cohort B experienced treatment-emergent adverse events (Table 2)
- Treatment-related adverse events (TRAEs) occurred in 40 of 41 (97.6%) participants (Table 2)
 - Overall, the most common TRAEs were fatigue (39.0%); nausea and pruritus (31.7% each); alanine aminotransferase increased (29.3%), and aspartate aminotransferase increased, pyrexia, and rash maculopapular (26.8% each) (Figure 5)
 - Grade ≥3 TRAEs occurred in 20 of 41 (48.8%) participants
 - Fatal TRAE (septic shock) occurred in 1 of 41 (2.4%) participants in cohort A (Table 2)
- TRAEs led to lorigerlimab discontinuation in 10 of 41 (24.4%) participants (Table 2)
- Safety monitoring and management guidance and close surveillance were implemented to support the early identification and mitigation of potential risks

Table 2. Summary of Adverse Events in Cohorts A, B, and Overall

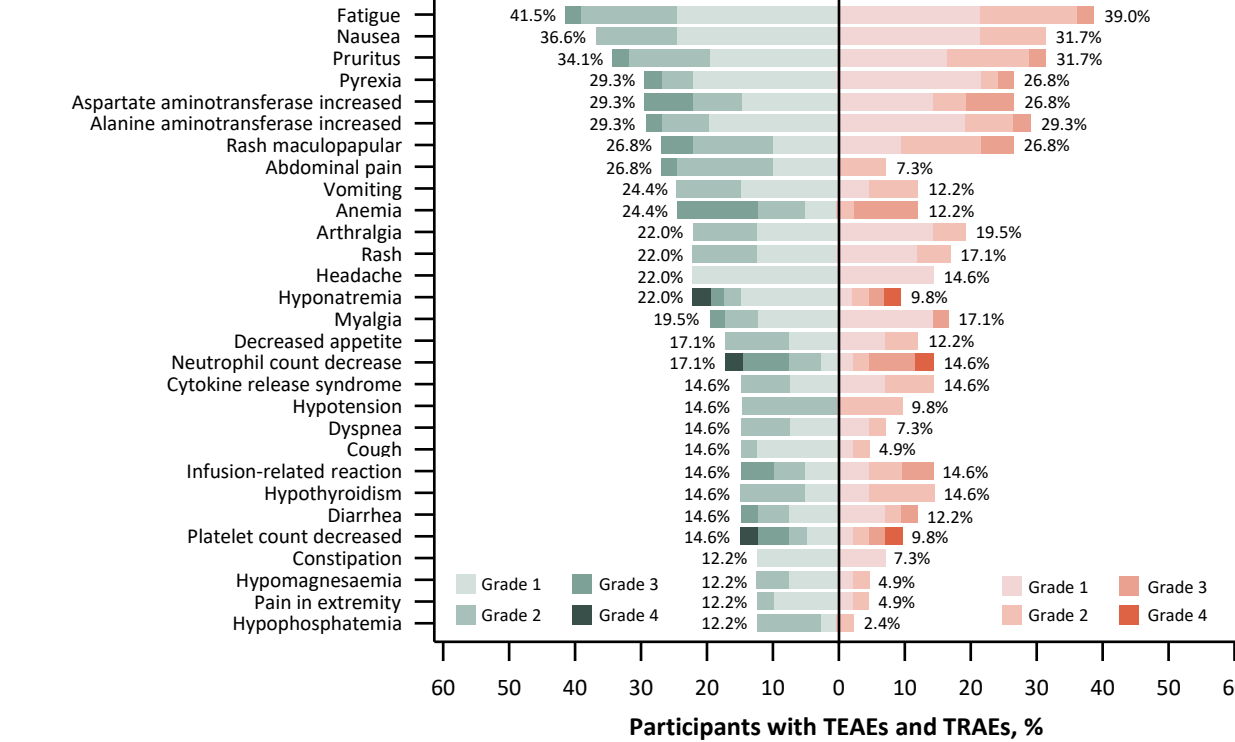
Events, n (%)	PROC (cohort A) n=24	CCGC (cohort B) n=17	Overall N=41
TEAE	24 (100)	17 (100)	41 (100)
TEAE grade ≥3 ^a	16 (66.7)	11 (64.7)	27 (65.9)
TRAE ^b	23 (95.8)	17 (100)	40 (97.6)
TRAE grade ≥3 ^{a,b}	12 (50.0)	8 (47.1)	20 (48.8)
Serious TEAE	15 (62.5)	8 (47.1)	23 (56.1)
Serious TRAE ^{c,d}	12 (50.0)	6 (35.3)	18 (43.9)
Serious TRAE grade ≥3 ^{a,b}	10 (41.7)	5 (29.4)	15 (36.6)
Fatal TRAE ^b	1 (4.2)	0	1 (2.4)
TRAEs of special interest ^b	14 (58.3)	9 (52.9)	23 (56.1)
Cytokine release syndrome	3 (12.5)	3 (17.6)	6 (14.6)
Infusion-related reaction	3 (12.5)	3 (17.6)	6 (14.6)
Immune-mediated hepatotoxicity	3 (12.5)	1 (5.9)	4 (9.8)
Immune-mediated cardiac toxicity	1 (4.2)	0	1 (2.4)
Other immune-related TRAEs ^d	9 (37.5)	6 (35.3)	15 (36.6)
Capillary leak syndrome	0	0	0
TRAEs leading to dose interruption ^b	10 (41.7)	11 (64.7)	21 (51.2)
TRAEs leading to drug discontinuation ^b	7 (29.2)	3 (17.6)	10 (24.4)

^aBased on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. ^bIncluded events with causality assessments of "Probably," "Possibly," or "Definitely" related to lorigerlimab. ^cThe only serious TRAE occurring in more than 1 participant was pyrexia (n=2) in cohort A, including, but not limited to, diarrhea, colitis, pneumonia, dermatitis, toxicity, hematologic toxicity, myelitis, hypophosphatemia, hypothyroidism, hyperthyroidism, and neurotoxicity. ^dCCGC, clear cell gynecologic cancer; PROC, platinum-resistant ovarian cancer; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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Figure 5. Adverse Events Occurring in ≥10% of Participants in Overall Safety Population (N=41)

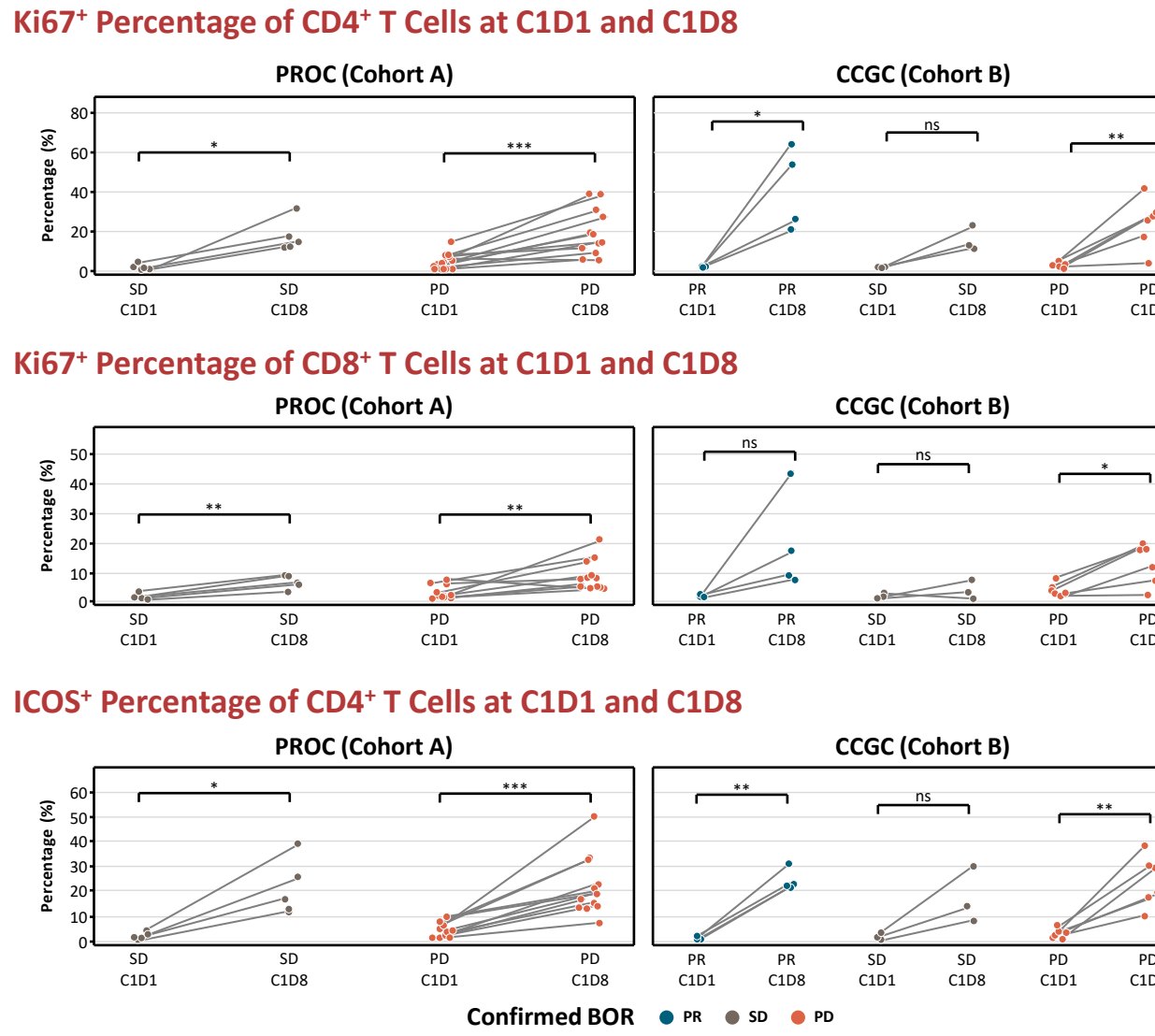


AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Exploratory Pharmacodynamic Analyses

- Paired Cycle 1, Day 1–Cycle 1, Day 8 analyses demonstrated on-treatment induction of proliferating (Ki67⁺) CD4⁺ and CD8⁺ T cells and activated (inducible costimulator [ICOS⁺]) CD4⁺ T cells in peripheral blood across both cohorts and across best overall response groups (Figure 6)
- These data are consistent with target engagement and early pharmacodynamic activity induced by the dual PD-1/CTLA-4 receptor binding and inhibitory activity of lorigerlimab

Figure 6. Treatment-Associated Pharmacodynamic Activity



CONCLUSIONS

- As of the September 1, 2026 data cutoff, lorigerlimab demonstrated encouraging preliminary clinical activity in participants with CCGC, achieving a confirmed ORR of 25.0% and a DCR of 43.8%
- The safety profile of lorigerlimab was manageable and consistent with dual PD-1/CTLA-4 blockade; higher rates of grade ≥3 serious TRAEs were observed in the more heavily pretreated PROC cohort
- Peripheral blood immunophenotyping data demonstrated T-cell activation, consistent with the mechanism of action of lorigerlimab, in both PROC and CCGC cohorts, and across BOR groups
- Further evaluation of lorigerlimab in participants with CCGC may be warranted
 - Enrollment is ongoing in cohort C evaluating lorigerlimab 3 mg/kg Q3W in participants with CCGC