PRESERVE-004/GOG-3081 (NCT05446298): A Phase 2 randomized dose optimization trial of gotistobart, a pH-sensitive anti-CTLA-4, in combination with pembrolizumab in platinum-resistant ovarian cancer

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Background and study design

- Gotistobart is a pH-sensitive CTLA-4-preserving antibody designed to dissociate from CTLA-4 in endosomes, thus avoiding antibody induced lysosomal degradation and allowing normal recycling of both CTLA-4 and gotistobart (**Figure 1**).[1-4]
- Through the recycling mechanism, preservation of CTLA-4 allows selective elimination of immunosuppressive regulatory T-cells in the tumor microenvironment without affecting peripheral regulatory T-cell function.[1-4]
- The objective of PRESERVE-004 is to assess safety and efficacy of gotistobart + pembrolizumab in patients with ovarian cancer who are resistant to platinum-based chemotherapy (**Figure 2**).[5]

Figure 1. Proposed mechanism of action for gotistobart

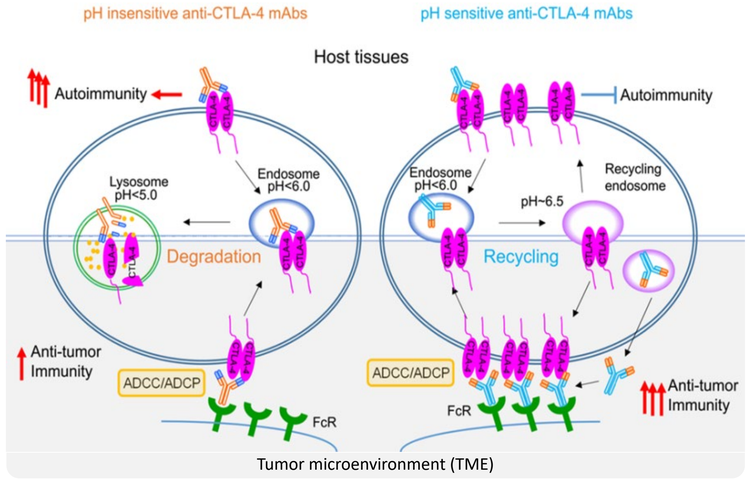
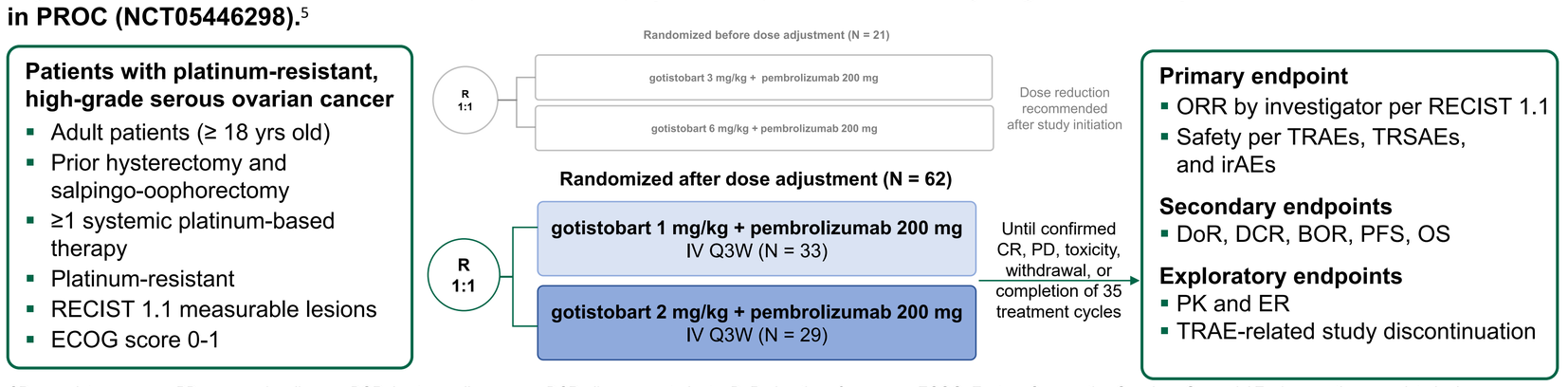


Figure 2. PRESERVE-004 is a Phase 2, randomized, open-label, multicenter study of gotistobart + pembrolizumab in PROC (NCT05446298).[5]



CR, complete response; PD, progressive disease; BOR, best overall response; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; irAEs, immunotherapy-related adverse effects; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; Q3W, once every 3 weeks; R, randomization; RECIST, response evaluation criteria in solid tumors; SAEs, severe adverse events; TRAE, treatment-related adverse events; TRSAEs, treatment-related serious adverse event. 1. ClinicalTrails.gov identifier: NCT05446298.

Results

Baseline patient and disease characteristics

- As of July 19, 2024, 62 patients were treated with either 1 mg/kg or 2 mg/kg gotistobart + pembrolizumab 200 mg.
- Treatment groups were well-matched **(Table 1).**
- Most patients had metastatic disease at enrollment.
- The median number of prior regimens was 4 and 3, respectively, in the 1 mg/kg and 2 mg/kg arms, with patients receiving up to 9 prior treatment regimens.
- Patients received a median of 3 treatment cycles.

Table 1. Baseline disease characteristics and study drug exposure

	gotistobart + pembrolizumab 200mg	
Characteristic	**1 mg/kg (n = 33)**	**2 mg/kg (n = 29)**
Age – mean (SD), years	65.2 (10.25)	63.5 (8.46)
Race – n (%)		
White/ Black/ Asian/ Other	27 (81.8)/ 1 (3.0)/ 1 (3.0)/ 4 (12.1)	25 (86.2)/ 2 (6.9)/ 1 (3.4)/ 1 (3.4)
ECOG performance-status score – n (%)		
0	19 (57.6)	15 (51.7)
1	14 (42.4)	14 (48.3)
Primary cancer diagnosis n (%)		
High-grade serous ovarian cancer	28 (84.8)	25 (86.2)
Primary peritoneal cancer	2 (6.1)	2 (6.9)
Fallopian tube cancer	3 (9.1)	2 (6.9)
Prior cancer regimens – median (range)	4.0 (2–9)	3.0 (1–8)
Study drug exposure		
Treatment duration, mean months (SD)	3.03 (2.43)	3.18 (2.45)
Gotistobart cycles, median (range)	3.0 (1–12)	3.0 (1–12)
Gotistobart dose intensity, median % (range)	98.4 (56.6–106.9)	98.4 (56.7–105.1)

Efficacy results

ORR (BICR) was 27.3% in the 1 mg/kg group and 34.5% in the 2 mg/kg group (**Table 3, Figure 4 and Figure 5**).

Table 3. Best overall response

	gotistobart + pembrolizumab 200mg	
	1 mg/kg	**2 mg/kg**
By investigator	n = 32	n = 29
ORR % (n)[a]	**25.0% (8)**	**27.6% (8)**
95% CI	11.5–43.4	12.7–47.2
CR[b]	3.1% (1)	6.9% (2)
PR[b]	21.9% (7)	20.7% (6)
By blinded independent central review	n = 33[c]	n = 29
ORR % (n)[d]	**27.3% (9)**	**34.5% (10)**
95% CI	13.3–45.5	17.9–54.3
Cr[e]	3.0% (1)	6.9% (2)
PR[e]	24.2% (8)	27.6% (8)

Figure 4. Swimmer plots of individual patient responses to treatment (investigator assessment)

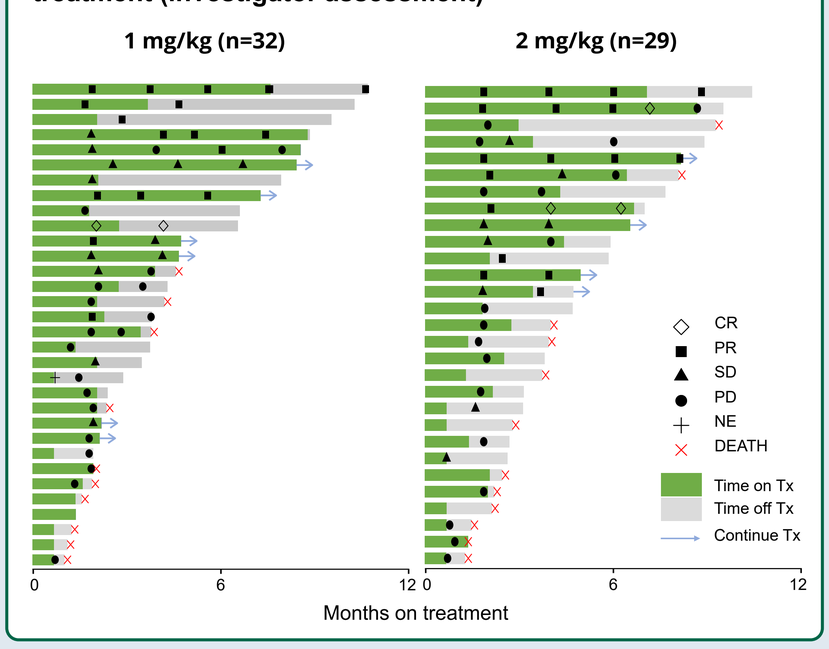
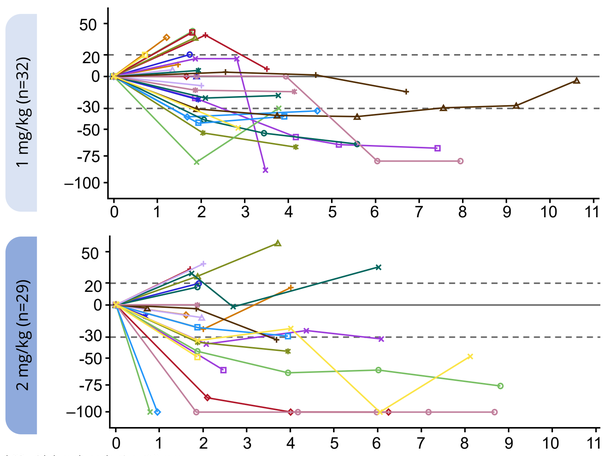


Figure 5. Spider plot indicating the percentage change from baseline in sum of target lesion diameters (investigator assessment)



One patient in the 1 mg/kg arm achieved CR with lymph node size <10 mm.

[a]Includes both confirmed and unconfirmed responses (3 unconfirmed responders in each treatment group); [b]One out of 3 unconfirmed responders are still on treatment, for both treatment groups; [c]At the time of data extraction, scans for one patient were included for BICR review while investigator response data for this patient were not entered in the electronic database collection; [d]3 and 5 unconfirmed responders in 1 mg and 2 mg groups, respectively; [e]1 unconfirmed responder is still on treatment in the 2 mg group.

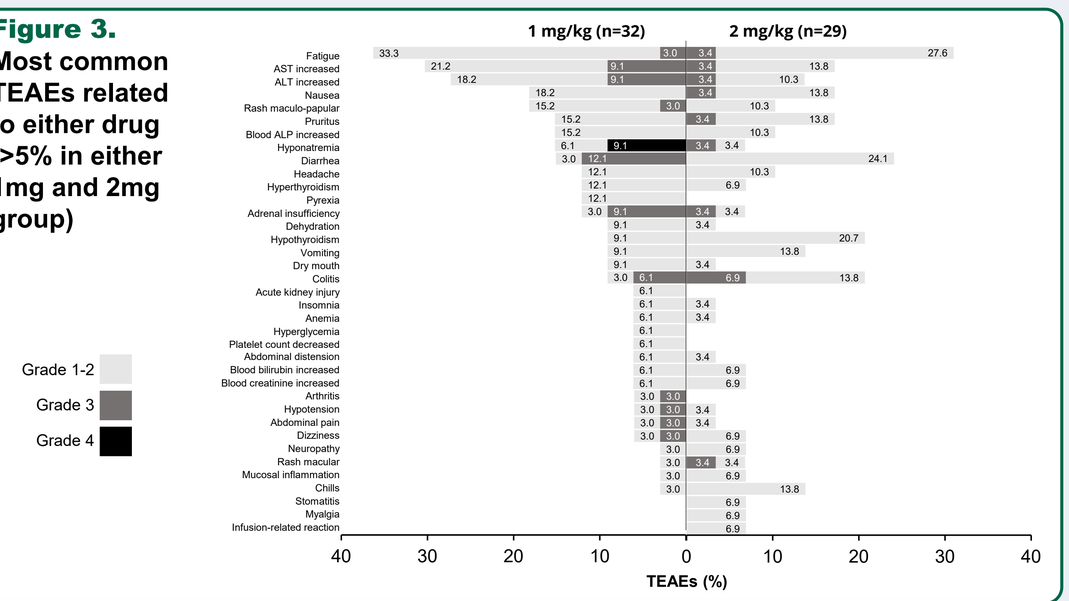
Safety results

The most common grade 3 TEAEs related to either drug (≥5%) were diarrhea, increased ALT and AST, adrenal insufficiency, and colitis. The most common grade 4 TEAE related to either drug was hyponatremia **(Table 2 and Figure 3).**

Table 2. Treatment-emergent adverse events

	gotistobart + pembrolizumab 200 mg	
	1 mg/kg (n = 33)	**2 mg/kg (n = 29)**
TEAEs, n (%)	33 (100.0)	28 (96.6)
Grade ≥ 3, n (%)	25 (75.8)	25 (86.2)
TEAEs related to either drug, n (%)	27 (81.8)	23 (79.3)
Grade ≥ 3, n (%)	15 (45.5)	12 (41.4)
Serious TEAEs, n (%)	9 (27.3)	8 (27.6)
irAE All grades, n (%)	15 (45.5)	18 (62.1)
Grade ≥ 3, n (%)	8 (24.2)	11 (37.9)
TEAEs leading to gotistobart discontinuation	7 (21.2)	8 (27.6)

Figure 3. Most common TEAEs related to either drug (>5% in either 1mg and 2mg group)



Gotistobart PK Analysis and Exposure-Response (E-R) Analysis

- Gotistobart C_{max}, C_{min}, and AUC increased proportionally with dose in combination.
  - The combination of gotistobart and pembrolizumab had a PK profile broadly consistent with gotistobart monotherapy, indicating lack of pembrolizumab effect on PK.
- There was a positive trend between gotistobart exposures and Grade ≥ 3 TRAE and ALT/AST elevation.
- No trend was observed for efficacy (ORR) or other safety endpoints.

Conclusions

- Early results from PRESERVE-004 demonstrate that gotistobart + pembrolizumab in PROC has a manageable tolerability profile at both dose levels, with no new safety signals.
- Preliminary results for efficacy are encouraging at both doses.
- Preliminary E-R supports potential recommended phase 2 dose selection of gotistobart at lower dosages (1-2 mg/kg) + pembrolizumab 200 mg Q3W for patients with PROC.
- The final dose selection will be based on the totality of safety, efficacy, and pharmacokinetics.
- If confirmed by further pre-planned analyses, the combination of gotistobart + pembrolizumab in PROC may be explored in a randomized setting.

Data cut off July 19, 2024. The authors would like to thank the patients and their families, and the staff, research coordinators and investigators at each participating institution. Support was provided by extended Oncoc4 and BioNTech teams, including Qiong Wang for statistical analysis, Lili Pan for translational analysis, Stephen Georgiou for medical writing support. The PRESERVE-004/GOG-3081 (NCT05446298) study is sponsored by OncoC4 Inc. and is conducted in collaboration with BioNTech SE, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and the GOG Foundation.

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