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Gotistobart In Combination With Pembrolizumab In Patients With Advanced Melanoma Who Have Progressed On PD-1 Inhibitors With Or Without CTLA-4 Inhibitors

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Background

- Approximately 50% of patients with non-resectable metastatic melanoma achieve long-term disease control using ipilimumab in combination with nivolumab.[1] However, around 40% of patients do not respond to treatment, and prognosis is poor for those who are refractory or progress.[1]
- 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.[2-5]
- We hypothesized that gotistobart in combination with pembrolizumab could improve outcomes of patients who previously progressed on anti-PD-1 mAb ± anti-CTLA-4 mAb. We also aimed to evaluate differences in efficacy and safety between gotistobart 3 mg/kg Q3W vs 6 mg/kg while combining with pembrolizumab 200 mg Q3W.

Study design and objectives

- PRESERVE-001 (NCT04140526) is an open label, phase 1/2 study that is evaluating safety and efficacy of gotistobart as a single agent and in combination with pembrolizumab in patients with advanced or metastatic solid tumors.[6,7]
- Here we present safety and efficacy results from 67 patients with advanced/metastatic melanoma who were refractory to/relapsed on immunotherapy, including ipilimumab and nivolumab, and were treated with either 3 mg/kg or 6 mg/kg gotistobart plus 200 mg of pembrolizumab, Q3W (PRESERVE-001 Part B [melanoma patients only] and Part C Arms G and G2).

- **Primary endpoints:** ORR by investigator assessment in accordance with RECIST 1.1 and incidence of TRAEs
- **Secondary endpoints:** DoR, BoR and DCR
- **Exploratory endpoints:** Included PFS by investigator assessment in accordance with RECIST 1.1 and iRECIST, OS, and an ad-hoc analysis of next-treatment free survival (NTFS; next treatment was identified as initiation of a new anti-neoplastic agent)

Patient characteristics

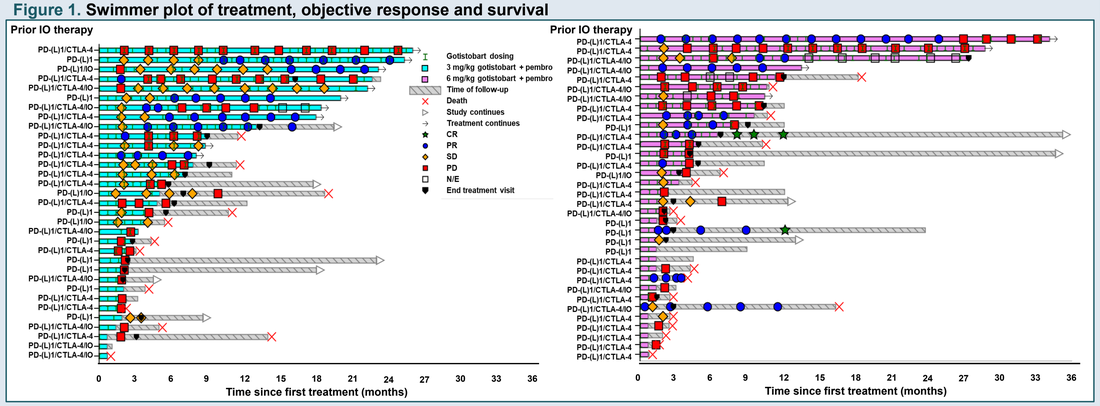
Table 1. Baseline patient and disease characteristics

Baseline characteristics	Gotistobart 3 mg/kg + pembro (n=33)	Gotistobart 6 mg/kg + pembro (n=34)
Median age, years (range)	62 (29–83)	66 (24–81)
Gender, n (%)		
Female	12 (36%)	12 (35%)
Male	21 (64%)	22 (65%)
Race, n (%)		
White	29 (88%)	31 (91%)
Black	0	1 (3%)
Asian	1 (3%)	0
Other	3 (9%)	2 (6%)
ECOG score, n (%)		
0	15 (45%)	18 (53%)
1	18 (55%)	16 (47%)
Baseline tumor burden >10cm	11 (33%)	9 (26%)
BRAF mutant, n (%)	11 (33%)	17 (50%)
Median number of prior regimens (range)	3 (1–7)	2 (1–14)
Prior treatment with PD-(L)1	33 (100%)	34 (100%)
Prior treatment with CTLA-4	22 (67%)	27 (79%)
Prior treatment with ipilimumab and nivolumab	22 (67%)	23 (68%)

Clinical activity

- At data cut off (March 28, 2025), median follow-up associated with OS was 16.3 and 12.9 months, for gotistobart 3 mg/kg and 6 mg/kg groups, respectively.
- Treatment beyond progression was allowed at the physician's discretion.

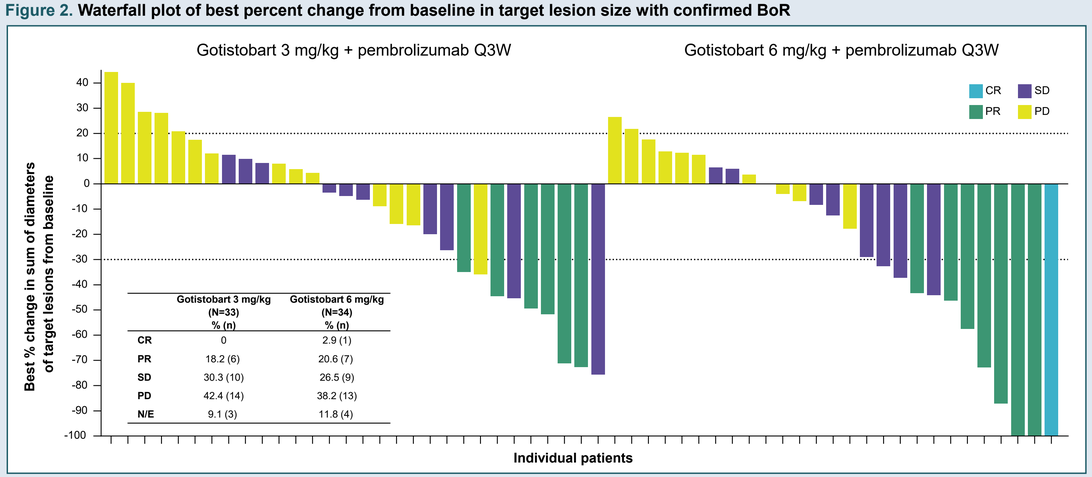
Figure 1. Swimmer plot of treatment, objective response and survival



N/E, non-evaluable: patients were missing post-baseline scan

- Confirmed ORR (cORR) was 18.2% (6/33) and 23.5% (8/34), in gotistobart 3 mg/kg and 6 mg/kg groups, respectively.
- Of patients who had prior ipilimumab and nivolumab, cORR was 18.2% (4/22) and 21.7% (5/23), respectively.
- Efficacy was noted regardless of BRAF mutation status (cORR wild type: 13.6% [3/22] and 29.4% [5/17], in gotistobart 3 mg/kg and 6 mg/kg groups, respectively vs cORR in patients with BRAF mutations: 27.3% [3/11] and 17.7% [3/17], respectively).
- NTFS rates at 12 months were 47.2% (95% CI 28.0–64.3) and 32.6% (95% CI 16.6–49.5), respectively.
- OS rates at 24 months were 51.1% (95% CI 28.4–69.9) and 37.4% (17.3–57.6), respectively.

Figure 2. Waterfall plot of best percent change from baseline in target lesion size with confirmed BoR



N/E, non-evaluable: patients were missing post-baseline scan

Safety

Table 2. Adverse events

	Gotistobart 3 mg/kg + pembro (n=33)	Gotistobart 6 mg/kg + pembro (n=34)	Overall (N=67)
Any TRAEs, n (%)	29 (87.9)	30 (88.2)	59 (88.1)
TRAEs of grades ≥3, n (%)	17 (51.5)	21 (61.8)	38 (56.7)
≥5% incidence:			
Colitis	4 (12.1)	7 (20.6)	11 (16.4)
Diarrhea	4 (12.1)	6 (17.6)	10 (14.9)
AST increased	3 (9.1)	3 (8.8)	6 (9.0)
ALT increased	3 (9.1)	2 (5.9)	5 (7.5)
Immune-mediated enterocolitis	2 (6.1)	2 (5.9)	4 (6.0)
Adrenal insufficiency	2 (6.1)	1 (2.9)	3 (4.5)
Cytokine release syndrome	0	2 (5.9)	2 (3.0)
TRAEs of grade 5, n (%)	0	1 (2.9)	1 (1.5)
Any serious TRAEs, n (%)	14 (42.4)	17 (50.0)	31 (46.3)
TRAEs leading to treatment discontinuation, n (%)	1 (3.0)	7 (20.6)	8 (11.9)

- Grade ≥3 TRAEs were observed in 51.5% and 61.8% of patients in the gotistobart 3 mg/kg and 6 mg/kg groups, respectively.
- Colitis/diarrhea or AST/ALT increase were the most common grade ≥3 TRAEs.
- TRAEs leading to study drug discontinuation were observed in 3.0% and 20.6% of patients in the gotistobart 3 mg/kg and 6 mg/kg groups, respectively.
- One patient in the gotistobart 6 mg/kg group died due to immune-mediated enterocolitis.

Conclusions

- To our knowledge, this is one of the largest cohorts studied in patients with advanced melanoma refractory or relapsed on prior anti-PD-1 ± anti-CTLA-4 therapy (including prior ipilimumab and nivolumab treatment).
- Gotistobart at 3 mg/kg combined with 200 mg pembrolizumab Q3W was associated with ORR comparable to that achieved with 6 mg/kg dosing, with favourable tolerability observed at the 3 mg/kg dose.
- Durable clinical benefit was observed with 3 mg/kg gotistobart plus 200 mg pembrolizumab; nearly half of the patients were free from additional systemic anti-cancer treatment at 1 year, and 2-year survival rate was >50%.

References

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Trial registration: NCT04140526

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BoR, best overall response; BRAF, B-Raf proto-oncogene; CR, complete response; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IO, immunotherapy; mAb, monoclonal antibody; NCT, National Clinical Trial; N/E, non-evaluable; NTFS, next-treatment free survival; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PFS, progression-free survival; PR, partial response; Q3W, every three weeks; SBIR, Small Business Innovation Research; SD, stable disease; TRAEs, treatment-related adverse events.

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