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Galaxy Publication

An Fc-Enhanced Anti–CTLA-4 Antibody Combined with PD-1 Blockade Induces Durable Responses in Treatment-Refractory Ovarian Cancer

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ABSTRACT

Patients whose ovarian cancer no longer responds to platinum-based therapy have limited treatment options and poor prognoses, emphasizing the need for alternative therapeutic approaches. This phase 1b investigation examined the tolerability and antitumor activity of botensilimab (BOT), an Fc-modified monoclonal antibody targeting cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), administered with the programmed cell death protein 1 (PD-1) inhibitor balstilimab (BAL), in an expanded population of individuals with advanced, treatment-refractory ovarian malignancies. Eligible patients received intravenous BOT at either 1 mg/kg or 2 mg/kg every six weeks in combination with intravenous BAL at a dose of 3 mg/kg every two weeks, with treatment continuing for up to two years. Safety and tolerability constituted the primary study endpoints. Measures of antitumor efficacy included objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS), evaluated using RECIST version 1.1 criteria. Overall survival (OS) was assessed exploratorily. Forty-four patients were included in the safety analysis, having received a median of three prior systemic regimens, with a median observation period of 9.6 months (range, 0.6–36.6 months). Thirty-five patients were evaluable for response. Gastrointestinal immune-related toxicity, particularly diarrhea or colitis, was the most frequently reported treatment-related adverse event, occurring in 43% of patients; grade 3 events were observed in 16%, and no deaths attributable to study therapy were reported. Confirmed radiographic responses were observed in 23% of evaluable patients (8 of 35; 95% CI, 10%–40%), comprising one complete remission and seven partial tumor regressions. Sustained disease control lasting at least 24 weeks, including responses and prolonged stable disease, was achieved in 31% of patients (95% CI, 17%–49%). The median DOR was 9.7 months, while median PFS was 2.8 months. Median OS reached 14.8 months, with an estimated 75% of patients alive at 12 months. Correlative immune analyses revealed that therapeutic benefit was associated with increased frequencies of FcγRIIIA^{+}CD11c^{+} immune cells, elevated tumor PD-L1 expression, and the presence of pre-existing T-cell–inflamed tumor microenvironments. Distinct immune patterns were also noted among different histopathologic subtypes. Dual checkpoint inhibition with the Fc-engineered CTLA-4 antibody botensilimab and PD-1 blockade via balstilimab produced meaningful and durable clinical activity in a heavily pretreated ovarian cancer population lacking effective standard treatments. Traditional RECIST criteria underestimated the overall therapeutic impact, as a subset of patients experienced prolonged disease stabilization with clinical relevance. Adverse events were generally manageable and reversible. These findings, together with the observed immune biomarker associations, support continued clinical evaluation of this combination regimen.

Keywords: Antibody, PD-1, Ovarian Cancer, CTLA-4

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Introduction

Ovarian cancer accounts for approximately 13,000 deaths each year in the United States and nearly 200,000 deaths worldwide [1, 2]. In the setting of recurrent or persistent disease, immune checkpoint blockade targeting programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) as monotherapy has yielded

limited clinical benefit, with objective response rates of approximately 8–10% and median progression-free survival of about two months in large clinical trials [3, 4]. Modest improvement in progression-free survival to 3.9 months has been observed with the addition of the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor ipilimumab [5]. Numerous combination strategies incorporating immune checkpoint inhibitors with chemotherapy, poly(ADP-ribose) polymerase (PARP) inhibitors, and/or antiangiogenic agents have also been explored [3, 6–11]. However, overall outcomes have remained unsatisfactory, with meaningful benefit largely restricted to select patient subpopulations [11]. Among the prognostic variables investigated, the presence of intraepithelial $CD8^+$ tumor-infiltrating lymphocytes has been consistently associated with improved survival in ovarian cancer [12–14].

Botensilimab (BOT) is a next-generation anti–CTLA-4 monoclonal antibody designed with an Fc-engineered IgG1 domain that enhances affinity for activating Fc gamma receptors (FcγRs), thereby enabling immune mechanisms not achieved with earlier CTLA-4 antibodies such as ipilimumab or tremelimumab [15]. This Fc optimization facilitates improved interactions between T cells, antigen-presenting cells, and natural killer cells, leading to enhanced T-cell priming, expansion, memory differentiation, and activation of myeloid compartments [15, 16]. In addition, BOT mediates depletion of regulatory T cells through antibody-dependent cellular cytotoxicity and phagocytosis [15]. Balstilimab (BAL) is a fully human IgG4 monoclonal antibody targeting PD-1 with high affinity, effectively disrupting PD-1 interactions with both PD-L1 and PD-L2, and demonstrating pharmacodynamic activity comparable to approved PD-1 inhibitors [17, 18]. When administered together, BOT and BAL provide complementary immunologic effects: CTLA-4 inhibition promotes early T-cell activation by enhancing FcγR-dependent immune synapse formation and modulating regulatory T-cell suppression, while PD-1 blockade restores the function of exhausted tumor-infiltrating T cells [19]. The combined targeting of CTLA-4 and PD-1 has the potential to generate potent antitumor immune responses and may help overcome the immunosuppressive tumor microenvironment characteristic of ovarian cancer [19, 20].

Earlier findings from an open-label, phase 1b trial evaluating BOT as monotherapy or in combination with BAL have demonstrated encouraging antitumor activity across multiple treatment-refractory and immunologically "cold" malignancies. These included tumor types traditionally resistant to first-generation immune checkpoint inhibitors, such as microsatellite-stable metastatic colorectal cancer and sarcomas [15, 20–22].

In the present report, we describe the clinical outcomes of BOT combined with BAL in a cohort of patients with advanced ovarian cancer that was refractory to standard therapies, the majority of whom had platinum-resistant or platinum-refractory disease.

Materials and Methods

Study design and patient population

C-800–01 is a multicenter, open-label, phase 1b clinical trial designed to evaluate the safety, tolerability, and preliminary efficacy of botensilimab administered alone or in combination with balstilimab (ClinicalTrials.gov identifier NCT03860272). Patients with treatment-refractory ovarian cancer were enrolled between April 1, 2019, and November 8, 2023, across nine clinical sites in the United States. Detailed descriptions of the study design, dose-escalation strategy, and outcomes from previously reported cohorts, including microsatellite-stable metastatic colorectal cancer and sarcoma, have been published elsewhere [21, 23].

Eligible participants were adults (≥18 years) with histologically confirmed recurrent ovarian cancer for which no established standard treatment options remained or for which prior standard therapies had failed. Additional eligibility criteria included measurable disease according to RECIST version 1.1, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic and organ function. Prior exposure to immune checkpoint inhibitors was permitted. Complete inclusion and exclusion criteria are provided in the published study protocol.

Procedures

In the initial dose-finding phase, botensilimab (BOT) was administered intravenously either every three weeks or every six weeks at doses spanning 0.1–3 mg/kg. Balstilimab (BAL) was given intravenously at a fixed dose of 3 mg/kg every two weeks. Treatment with either agent, alone or in combination, could continue for up to two years. During the expansion phase, BOT dosing was standardized to 1 mg/kg or 2 mg/kg every six weeks and combined with BAL at 3 mg/kg every two weeks. Patients receiving BOT alone were allowed to transition to combination

therapy, and continuation of treatment beyond radiographic progression was permitted when investigators judged ongoing clinical benefit. Enrollment into the C-800–01 trial has been completed.

End points

The primary objective of the study was characterization of safety, including identification of dose-limiting toxicities during dose escalation. These results have been previously reported, and no maximum tolerated dose was identified [21]. BOT doses up to 2 mg/kg were determined to be acceptable from a safety standpoint [21]. Secondary objectives included evaluation of treatment-emergent adverse events and laboratory abnormalities graded according to NCI-CTCAE version 5.0, as well as assessment of antitumor activity. Efficacy outcomes included objective response rate (complete or partial response), duration of response (time from initial response to progression or death), disease control rate (response or stable disease maintained for at least six weeks), and progression-free survival (time from first dose to progression or death). Tumor responses were assessed by investigators using RECIST version 1.1 criteria, with imaging performed every six weeks (±3 days).

Exploratory analyses included overall survival and clinical benefit rate, defined as response or stable disease sustained for a minimum of 24 weeks. Additional post hoc subgroup analyses examined outcomes according to platinum sensitivity. Platinum-resistant or refractory disease was defined as a platinum-free interval of six months or less, including primary platinum-refractory disease characterized by progression during initial platinum therapy or within one month of treatment completion. Platinum-sensitive disease was defined by a platinum-free interval exceeding six months. The platinum-free interval was calculated from the last administered dose of platinum therapy to the date of documented progression or recurrence.

Statistical analysis

The prespecified data cutoff was December 5, 2024. All patients who received at least one dose of study medication were included in the safety population (n = 44). Patients with at least one post-baseline radiographic assessment at six weeks were included in the efficacy-evaluable population (n = 35). Continuous variables were summarized using descriptive statistics, and categorical variables were summarized using frequencies and proportions.

Complete and partial responses required confirmation on subsequent imaging. Time-to-event endpoints, including duration of response, progression-free survival, and overall survival, were estimated using Kaplan–Meier methods, with medians and corresponding 95% confidence intervals reported. Safety data were summarized by dose cohort, and adverse event severity was graded using NCI-CTCAE criteria where applicable.

Correlative studies

Multiplex immunofluorescence and digital pathology

Pretreatment tumor biopsies preserved as formalin-fixed, paraffin-embedded tissue were analyzed using multiplex immunofluorescence. Staining was performed on a Leica Bond automated platform using Opal multiplex reagents (Akoya Biosciences) and immune marker panels. Antibody conditions and staining sequences were optimized using single-marker chromogenic and fluorescent assays prior to multiplex application. Each antibody was assigned a unique fluorophore. Slides were counterstained with DAPI and mounted using antifade media.

Whole-slide images were acquired using the PhenoImager Fusion system and processed for spectral unmixing. Quantitative analysis, including cell identification and phenotyping, was performed using HALO software. Tumor immune phenotypes were defined by evaluating the spatial distribution of $CD3^{+}CD8^{+}$ T cells across tumor and stromal regions in digitized slides scanned at 20× magnification. Tumors were categorized as immune-infiltrated, immune-excluded, or immune-desert based on established spatial criteria reflecting T-cell density and localization.

Tumor mutational burden

Tumor mutational burden was assessed using clinically validated, tumor-based next-generation sequencing assays conducted at local reference laboratories. Results were reported as the number of somatic mutations per megabase of sequenced DNA.

Cytokine analysis

Pretreatment peripheral blood samples were collected from consenting participants under Institutional Review Board–approved protocols. Plasma was isolated from sodium heparin–treated blood samples, processed immediately, and stored at −80°C until analysis. Plasma interleukin-6 concentrations were measured using a commercially available electrochemiluminescence assay (Meso Scale Discovery V-PLEX Plus Proinflammatory Panel 1), with testing performed by a centralized laboratory.

PD-L1 immunohistochemistry

PD-L1 expression was assessed in pretreatment tumor specimens using the PD-L1 28–8 pharmDx immunohistochemistry assay following manufacturer guidelines. Tumor presence was confirmed on hematoxylin and eosin–stained sections by a certified pathologist. Samples containing fewer than 100 viable tumor cells were excluded from analysis. PD-L1 expression was quantified using the combined positive score. Non-tumor tissue, necrotic regions, and technical artifacts were excluded, and samples stained more than six months after sectioning were not evaluated.

Results and Discussion

Patient population

At the time of the prespecified analysis, a total of 44 individuals with advanced ovarian cancer that was refractory to prior therapies had received study treatment and were included in the safety analysis. Of these, 7 patients were enrolled during the dose-escalation phase and 37 during the dose-expansion phase. Thirty-five patients underwent at least one tumor assessment at the scheduled six-week post-treatment time point and therefore comprised the efficacy-evaluable population **(Figure 1).** The remaining nine treated patients were not included in efficacy analyses because they discontinued study participation before the first post-baseline imaging evaluation due to early clinical deterioration, withdrawal of consent, death, or treatment-related toxicity.

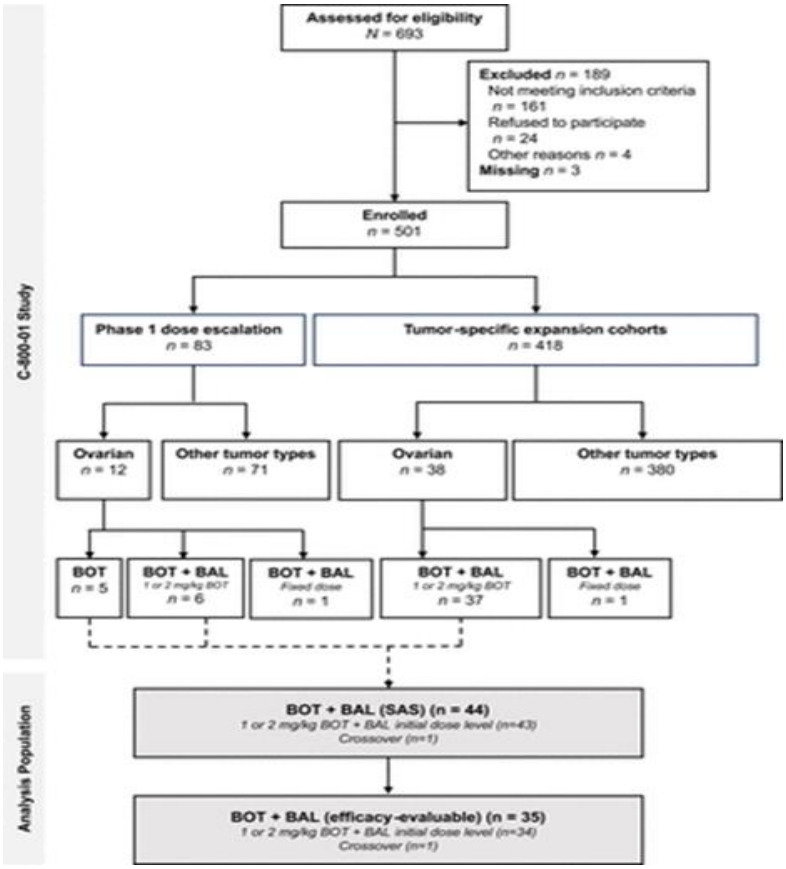


Figure 1. Study flow diagram illustrating patient disposition in the C-800–01 trial among individuals with treatment-refractory ovarian cancer (n = 44). BOT, botensilimab; BAL denotes balstilimab; SAS, safety analysis set; CONSORT, Consolidated Standards of Reporting Trials.

The safety analysis set comprised 44 treated patients and reflected the expected clinical profile of a heavily pretreated ovarian cancer population **(Table 1).** The median patient age was 66 years (range, 37–79 years), and functional status was evenly distributed, with 50% of patients having an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 50% having a status of 1. Participants had undergone extensive prior therapy, with a median of three previous systemic regimens (range, 1–14). All patients had received platinum-based combination chemotherapy. Additional prior treatments included bevacizumab in 77% of patients, poly(ADP-ribose) polymerase (PARP) inhibitors in 59%, PD-(L)1–directed immunotherapy in 14%, and mirvetuximab soravtansine-gynx in 5%. None of the enrolled patients had been previously treated with a CTLA-4–targeting agent.

With respect to platinum sensitivity, 27% of patients were classified as platinum sensitive, 55% as platinum resistant, and 18% as having primary platinum-refractory disease, resulting in 73% of the cohort falling into the platinum-resistant or refractory category. Histopathologic evaluation showed that high-grade serous carcinoma predominated (82%), followed by clear cell carcinoma (11%), endometrioid adenocarcinoma (2%) and carcinosarcoma (5%).

Regarding study treatment exposure, 21 patients received botensilimab at 1 mg/kg in combination with balstilimab, 22 patients received botensilimab at 2 mg/kg plus balstilimab, and one patient transitioned from botensilimab monotherapy at 0.1 mg/kg administered every three weeks to combination therapy with botensilimab and balstilimab.

Among patients who underwent molecular testing, pathogenic BRCA1 or BRCA2 alterations were identified in 35% (8 of 23 tested). Nearly all tumors were microsatellite stable (41 patients), with microsatellite status unavailable for three patients. Tumor mutational burden assessment was performed in a limited subset of patients (n = 13), with only one individual (8%) demonstrating a high TMB (>10 mutations per megabase). Programmed death-ligand 1 (PD-L1) expression was evaluated in 25 patients, of whom the majority (84%, 21 of 25) were PD-L1 positive, defined as a combined positive score of at least 1%.

Table 1. Baseline demographic and clinical characteristics of all treated patients with treatment-refractory ovarian cancer (n = 44)

Patient Characteristic	Overall (N=44)
Female sex, n (%)	44 (100)
Median age, years (range)	66 (37–79)
Prior lines of therapy	
Median (range)	3 (1–14)
ECOG performance status at baseline, n (%)	
0	22 (50)
1	22 (50)
Selected prior therapies, n (%)	
Prior mirvetuximab soravtansine-gynx	2 (5)
PD-(L)1 inhibitor	6 (14)
Radiotherapy	9 (20)
Platinum-based doublet chemotherapy	44 (100)
Bevacizumab	34 (77)
PARP inhibitor	26 (59)
Number of prior lines, n (%)	
0	0 (0)
1	4 (9)
2	11 (25)
≥3	29 (66)
Study dose level, n (%)	
Crossover§	1 (2)
1 mg/kg BOT + BAL	21 (48)
2 mg/kg BOT + BAL	22 (50)
Disease setting, n (%)	
Primary platinum-refractory‡	8 (18)
Multiple sites of metastasis, n (%)	33 (75)

Platinum-sensitive*	12 (27)
Platinum-resistant†	24 (55)
Visceral liver metastases, n/N (%)	6/44 (14)
Tumor histology, n (%)	
Endometrioid adenocarcinoma	1 (2)
High-grade serous	36 (82)
Carcinosarcoma	2 (5)
Clear cell (including 1 mixed)	5 (11)
Selected biomarkers	
PD-L1 positive (CPS ≥1%), n/N (%)	21/25 (84)
Tumor mutational burden >10 mut/Mb, n/N (%)¶	1/13 (8)
BRCA1/2 mutation, n/N (%)	8/23 (35)
Microsatellite stable (MSS), n/N (%)	41/41 (100)
Elevated CA-125 (>35 U/mL), n/N (%)	29/39 (74)

*Platinum-sensitive disease was defined as relapse or progression occurring more than 6 months after completion of first-line or subsequent platinum-based therapy.

†Platinum-resistant disease was defined as relapse or progression occurring between 1 and 6 months after first-line platinum therapy, or within 6 months of the last dose of any later platinum-based regimen.

‡Primary platinum-refractory disease was defined as relapse or progression within 1 month after completion of first-line platinum therapy.

§One patient in the crossover group initially received 0.1 mg/kg BOT monotherapy every 3 weeks, and subsequently received 1 mg/kg BOT every 6 weeks in combination with BAL.

¶A single patient had a tumor mutational burden exceeding 10 mutations per megabase (TMB = 11).

TMB, tumor mutational burden; BOT, botensilimab; BAL, balstilimab; CA-125, cancer antigen 125; BRCA, breast cancer gene; MSS, microsatellite stable; CPS, combined positive score; PARP, poly-ADP ribose polymerase; muts/Mb, mutations per megabase; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-(L)1, programmed cell death (ligand) 1.

Safety

Among the 44 patients included in the safety population, two individuals experienced toxicities that met criteria for dose limitation during the dose-escalation phase. One case involved a patient initially treated with botensilimab (BOT) alone who developed a grade 2 maculopapular eruption that necessitated a temporary interruption of dosing and was therefore classified as a DLT. After recovery, this patient resumed treatment, achieved extended disease stabilization, and later transitioned to combination therapy with BOT and balstilimab (BAL), resulting in a partial tumor response. The second DLT occurred in a patient treated upfront with the combination regimen who developed grade 4 thrombocytopenia; although the event resolved with supportive care, further exposure to BOT was discontinued.

Adverse events of any cause were universal in the safety population, with severe events (grade ≥3) observed in approximately two-thirds of patients **(Table 2)**. Events attributed to study treatment were reported in the majority of patients (89%), with high-grade treatment-related toxicities occurring in 41%. Gastrointestinal immune-mediated toxicities were the most prominent, with diarrhea or colitis reported in 43% of patients, including grade 3 manifestations in 16%. Fatigue and nausea were also common, each affecting 36% of patients, although high-grade events were infrequent. Single cases of grade 4 treatment-related autonomic neuropathy, acute kidney injury, and thrombocytopenia were documented. No fatalities related to study treatment occurred.

Serious immune-mediated toxicities affecting organ systems outside the gastrointestinal tract were rare. Pneumonitis was reported in one patient at grade 2 severity, and immune-related myocarditis occurred in one patient at grade 3 severity. No cases of hypophysitis were identified in this cohort. Overall, treatment discontinuation due to toxicity occurred in 19 patients (43%). The leading causes of discontinuation were inflammatory bowel toxicities, most commonly immune-mediated enterocolitis and colitis.

Table 2. Treatment-related adverse events reported in at least 10% of treated patients with refractory ovarian cancer (n = 44)

Adverse Event Category / Event	Grade ≥3, n (%)	Any Grade, n (%)
Lower gastrointestinal disorders		
Diarrhea or colitis*	7 (16%)	19 (43%)
Abdominal pain	1 (2%)	6 (14%)
Immune-mediated enterocolitis	2 (5%)	9 (20%)
Overall (N=44 patients)		

Any treatment-related adverse event	18 (41%)	39 (89%)
General/constitutional symptoms		
Joint pain (arthralgia)	0 (0%)	8 (18%)
Fatigue	3 (7%)	16 (36%)
Headache	0 (0%)	7 (16%)
Decreased appetite	0 (0%)	8 (18%)
Fever	0 (0%)	5 (11%)
Chills	0 (0%)	5 (11%)
Upper gastrointestinal disorders		
Vomiting	0 (0%)	5 (11%)
Nausea	1 (2%)	16 (36%)
Blood disorders		
Anemia	0 (0%)	5 (11%)
Skin disorders		
Maculopapular rash	2 (5%)	6 (14%)
Itching (pruritus)	0 (0%)	8 (18%)

*Diarrhea and colitis were evaluated collectively rather than as individual events, with both preferred terms grouped for analysis.
TRAE, treatment-related adverse event.

Nearly three-quarters of treated patients (73%) developed at least one toxicity considered potentially immune driven, regardless of severity. For the purposes of this analysis, immune-mediated events were defined as adverse effects attributed to study therapy that necessitated systemic corticosteroids, additional immunosuppressive therapy, or endocrine replacement at any point during the episode. Events were categorized using predefined grouped terms described in the corresponding table footnotes. Gastrointestinal inflammation represented the dominant immune-mediated toxicity, with diarrhea/colitis affecting 43% of patients, including grade 3 manifestations in 23%. Cutaneous toxicities occurred in 27% of patients (5% grade 3), followed by nausea (20%, grade 3 in 2%) and hepatitis (11%, grade 3 in 2%). Only a single grade 4 immune-mediated adverse event—thrombocytopenia—was reported, and no fatal immune-related toxicities were observed.

To manage steroid-responsive immune-mediated diarrhea/colitis, the protocol allowed the use of tumor necrosis factor–alpha (TNF-α) blockade, including agents such as infliximab, with the intent of accelerating symptom resolution, reducing corticosteroid exposure, and enabling continuation of therapy [24]. Resumption of study treatment was permitted once toxicity improved to below grade 2. In instances where a grade 3 immune-mediated adverse event was attributed to botensilimab but not to balstilimab, patients were allowed to remain on balstilimab monotherapy. Continued treatment was contingent upon tapering systemic corticosteroids to an oral prednisone-equivalent dose of no more than 10 mg daily. Management of other immune-mediated toxicities followed established treatment recommendations and was left to investigator judgment [24, 25].

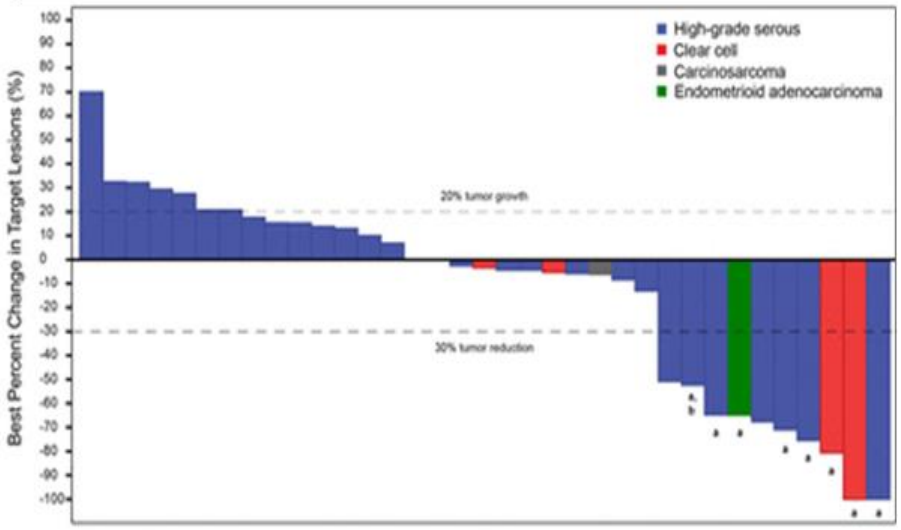
Among the 20 patients who developed immune-mediated diarrhea/colitis requiring intervention, combined corticosteroid and TNF-α inhibitor therapy was administered in 14 cases, corticosteroids alone in five cases, and TNF-α inhibition alone in one case. Recurrent episodes of immune-mediated diarrhea/colitis were documented in 65% of affected patients; however, none remained on active corticosteroid or immunosuppressive therapy at the time of analysis. All gastrointestinal immune-mediated events ultimately resolved.

Efficacy

Efficacy outcomes were restricted to responses confirmed by RECIST criteria and assessed by investigators in patients with at least one post-baseline tumor evaluation (n = 35); **(Table 3 and Figure 2a).** Objective tumor regression was documented in eight patients, yielding an overall response rate of 23% (95% CI, 10%–40%). This included one complete response and seven partial responses. Responding tumors spanned multiple histologic subtypes, including high-grade serous carcinoma (n = 5), clear cell carcinoma (n = 1), mixed clear cell and endometrioid histology (n = 1), and endometrioid adenocarcinoma (n = 1).

Disease stabilization or response lasting at least 6 weeks was observed in 60% of patients (95% CI, 42%–76%), while durable clinical benefit—defined as response or prolonged stable disease—was achieved in 31% (95% CI, 17%–49%). Median duration of response was 9.7 months (95% CI, 2.8 months to not reached); **(Figure 2b)**, with individual responses persisting between 1.4+ and 17.5+ months. At the time of data cutoff, one patient remained in ongoing response follow-up.

Median progression-free survival was 2.8 months (95% CI, 1.4–5.5); **(Figure 3a).** Overall survival outcomes included a median survival of 14.8 months (95% CI, 12.1 months to not reached) and a 12-month survival probability of 75% (95% CI, 55%–86%); **(Figure 3b).** The observed median follow-up duration was 9.6 months (range, 0.6–36.6 months); using reverse Kaplan–Meier methodology, median follow-up was calculated as 14.6 months (95% CI, 9.2–21.2).



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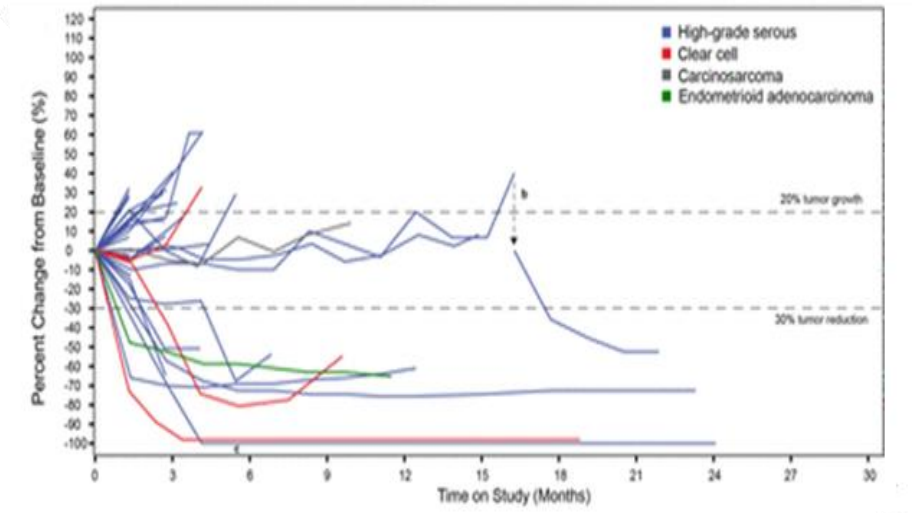
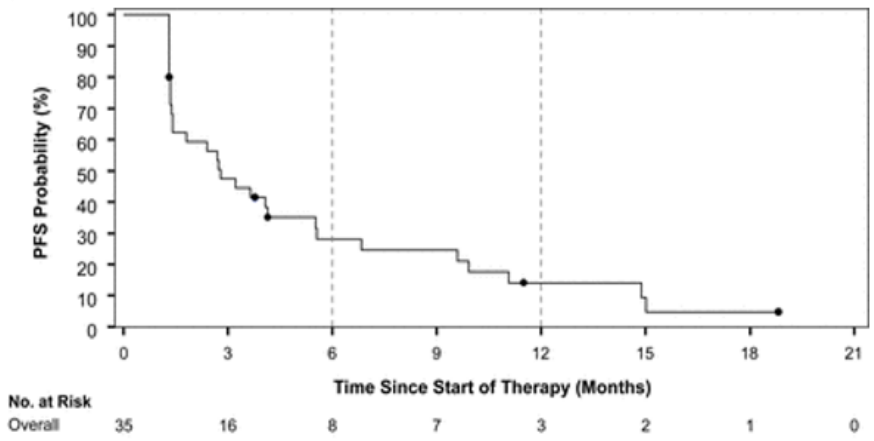


b)

Figure 2. Antitumor activity observed in patients with refractory ovarian cancer who were evaluable for efficacy (n = 35). Panel (a) illustrates the maximum tumor response achieved by each patient, while panel (b) depicts longitudinal changes in tumor burden over the course of treatment. [a] Indicates responses confirmed as complete or partial according to RECIST version 1.1. [b] Identifies the patient who transitioned from initial botensilimab (BOT) monotherapy (0.1 mg/kg) to combination therapy; the discontinuity in the spider plot in panel (b) marks the new baseline at initiation of BOT plus balstilimab (BAL) at 1.0 mg/kg. [c] Denotes a patient who underwent localized radiotherapy at approximately 24 weeks for a single progressing lesion, with no further detectable disease thereafter. RECIST, Response Evaluation Criteria in Solid Tumors; BOT, botensilimab; BAL, balstilimab.



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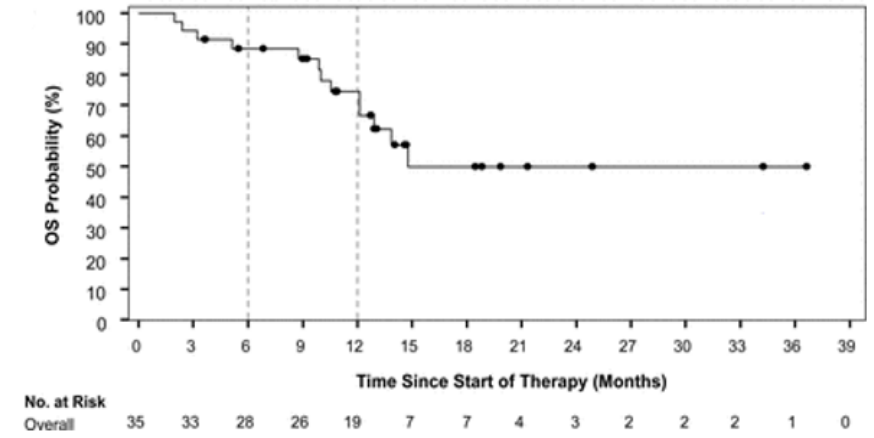


b)

Figure 3. Time-to-event efficacy outcomes among all patients included in the efficacy analysis population with treatment-refractory ovarian cancer (n = 35). Panel (a) shows progression-free survival, and panel (b) displays overall survival. Data points marked with circles represent censored observations. PFS, progression-free survival; OS, overall survival.

Table 3. Overview of investigator-assessed efficacy outcomes in patients with treatment-refractory ovarian cancer who were evaluable for response, as defined by RECIST version 1.1 (n = 35).

Efficacy Measure	Value
Overall (N=35 patients)	
Objective Response Rate (ORR)	
95% Confidence Interval	10% to 40%
n (%)	8 (23%)
Best Overall Response (BOR), n (%)	
Partial Response (PR)	7 (20%)
Complete Response (CR)	1 (3%)
Progressive Disease (PD)	14 (40%)
Stable Disease (SD)	13 (37%)
Clinical Benefit Rate (CBR)	
95% Confidence Interval	17% to 49%
n (%)	11 (31%)
Disease Control Rate (DCR)	
95% Confidence Interval	42% to 76%
n (%)	21 (60%)
Progression-Free Survival (PFS)	
Median (95% CI), months	2.8 (1.4 to 5.5)

6-month PFS rate (95% CI)	28% (14% to 44%)
9-month PFS rate (95% CI)	25% (11% to 40%)
Duration of Response (DOR)	
Median (95% CI), months	9.7 (2.8 to not reached)
Overall Survival (OS)	
Median (95% CI), months	14.8 (12.1 to not reached)
12-month OS rate (95% CI)	75% (55% to 86%)
18-month OS rate (95% CI)	50% (28% to 69%)
Median follow-up duration, months (range)	9.6 (0.6 to 36.6)

Best overall response (BOR); clinical benefit rate (CBR); complete response (CR); disease control rate (DCR); duration of response (DOR); not reached (NR); objective response rate (ORR); overall survival (OS); progressive disease (PD); progression-free survival (PFS); partial response (PR); Response Evaluation Criteria in Solid Tumors (RECIST); stable disease (SD).

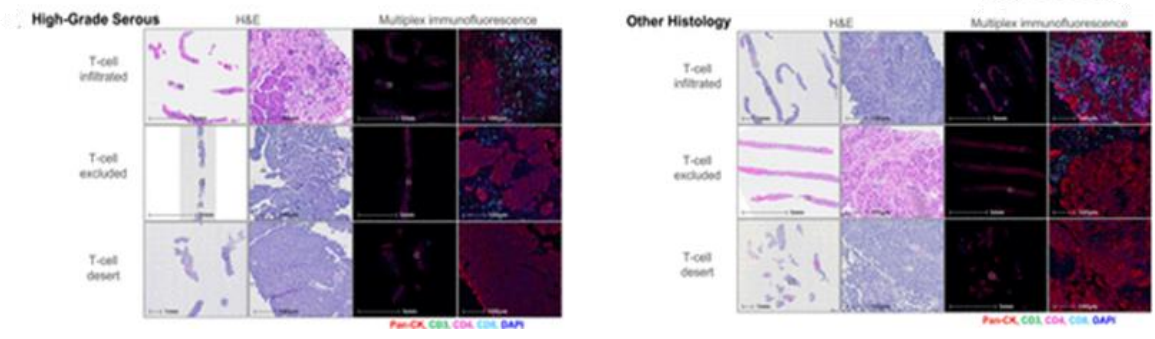
Clinical benefit extended beyond conventional RECIST-defined responses. A total of 11 patients maintained disease stabilization or better for at least 24 weeks, meeting criteria for clinical benefit; among these, one patient remained stable for up to 36 weeks and another for as long as 60 weeks. In addition, two patients who initially responded (one complete response and one partial response) experienced limited or localized disease progression and continued treatment beyond progression. By the time of data lock, prolonged treatment-free intervals were becoming evident: one responding patient had not initiated subsequent systemic therapy despite receiving study treatment for approximately 3 months after progression, while another had remained off new systemic therapy since 2023 after continuing treatment for roughly 13 months beyond progression.

Exploratory post hoc subgroup analyses showed comparable antitumor activity in patients with platinum-refractory or platinum-resistant disease (n = 25) and those with platinum-sensitive ovarian cancer (n = 10). Notably, among the four evaluable patients with primary platinum-refractory disease—defined as progression during initial platinum exposure or within one month of treatment completion—clinical activity was observed in three patients, including two partial responses and one complete response, with the remaining patient achieving stable disease.

Correlative studies

Comprehensive histologic and immune profiling demonstrated marked heterogeneity in tumor immune architecture across ovarian cancer histologic subtypes. Tumors segregated into three previously described immune phenotypes—T-cell infiltrated, T-cell excluded, and T-cell desert—based on spatial patterns of lymphocyte localization [26] **(Figures 4a and 4b).** Quantitative analyses suggested higher densities of cytotoxic CD3+CD8+ T cells and helper CD3+CD4+ T cells in non–high-grade serous (non-HGS) tumors relative to high-grade serous (HGS) tumors **(Figures 4c and 4d),** although these differences did not achieve statistical significance.

In contrast, the distribution of immune phenotypes differed significantly by histology. Non-HGS tumors were substantially more likely to exhibit a T-cell–infiltrated phenotype and correspondingly less likely to demonstrate immune exclusion or immune desert patterns compared with HGS tumors **(Figure 4e)**; ($p = 0.0004$). Furthermore, tertiary lymphoid structures—defined by spatial co-localization of CD20+, CD3+, HLA-DR+, and CD11c+ immune cells **(Figure 4f)**—were detected at a markedly higher frequency in non-HGS tumors (69%) than in HGS tumors **(Figure 4g)**; ($p < 0.0001$). These organized immune aggregates were predominantly associated with tumors displaying a T-cell–infiltrated microenvironment, consistent with active local immune responses.



a) b)

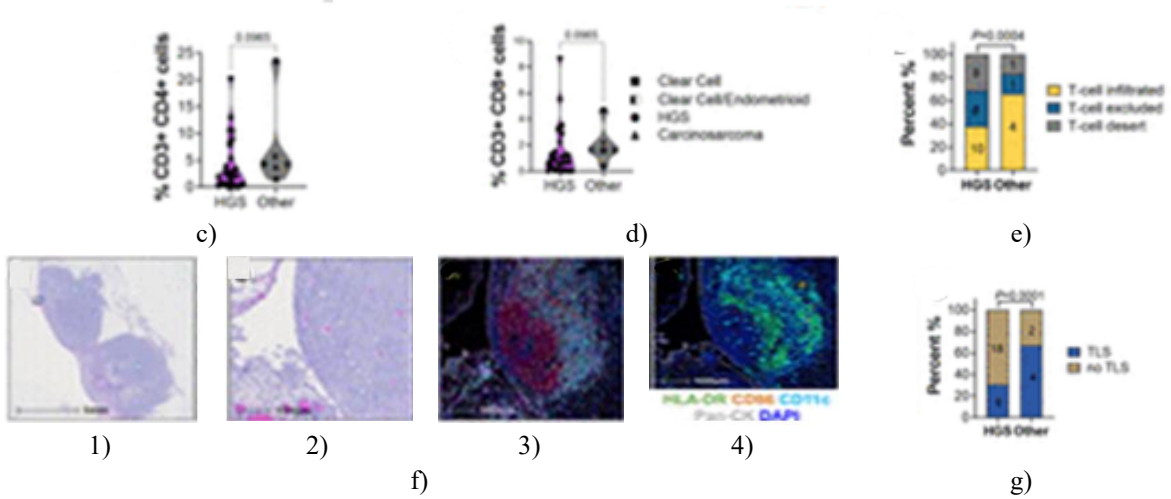


Figure 4. Baseline analysis using multiplex immunofluorescence (mIF) highlights substantial variability in tumor microenvironment (TME) composition among study participants. Representative histopathologic and immune features are illustrated across ovarian cancer subtypes. In panels (a–b), hematoxylin and eosin (H&E)–stained sections on the left depict classic morphologic characteristics of (a) high-grade serous (HGS) ovarian carcinoma, including compact solid tumor growth, columnar epithelial cells with eosinophilic cytoplasm, and marked nuclear pleomorphism, and (b) non-HGS tumors, which demonstrate gland-forming architecture and heterogeneous nuclear features. Corresponding mIF images on the right display staining for pan-cytokeratin (pan-CK; red), CD3 (green), CD4 (magenta), CD8 (cyan), and DAPI (blue), revealing three spatial immune patterns: infiltrated, excluded, and desert phenotypes. Whole-slide images are shown alongside magnified regions of interest, with scale bars provided.

Quantitative immune profiling by mIF was performed to characterize intratumoral lymphocyte populations. Panels (c) and (d) present distributions of CD3+CD4+ helper T cells and CD3+CD8+ cytotoxic T cells, respectively. Data are visualized using violin plots indicating medians (solid lines) and interquartile ranges (dashed lines), with individual symbols denoting tumor histologic subtype. Statistical comparisons were conducted using the Mann–Whitney test, with corresponding p values annotated. Panel (e) summarizes the proportion of patients assigned to each T-cell spatial phenotype based on CD3+CD8+ localization, stratified by histology (HGS versus non-HGS), with significance assessed via Fisher's exact test.

Tertiary lymphoid structures (TLS) are illustrated in panels (f) and (g). Panel (f) includes representative images: (1) a full-section H&E slide from an HGS tumor; (2) a higher-magnification view demonstrating organized immune aggregates resembling secondary lymphoid tissue; (3) matched mIF staining for CD20, CD3, CD4, CD8, pan-CK, and DAPI, showing germinal center–like regions enriched in CD20+ B cells encircled by T lymphocytes; and (4) staining for HLA-DR, CD86, CD11c, pan-CK, and DAPI, indicating enhanced antigen-presentation marker expression within TLS. Panel (g) displays the percentage of tumors with detectable TLS versus those lacking such structures, grouped by histologic subtype, with Fisher's exact test p values shown. H&E, hematoxylin and eosin; DAPI, 4′,6-diamidino-2-phenylindole; HGS, high-grade serous; pan-CK, pan-cytokeratin; mIF, multiplex immunofluorescence; TME, tumor microenvironment; TLS, tertiary lymphoid structure; HLA-DR, human leukocyte antigen-DR.

Immune correlates of clinical activity

Associations between immune architecture and treatment outcomes were observed. Tumors classified as T-cell infiltrated were predominantly found among patients achieving complete response, partial response, or durable stable disease, whereas tumors from patients with progressive disease were more frequently categorized as immune excluded or immune desert ($p < 0.0001$). Although overall survival did not differ significantly across immune phenotypes, patients with infiltrated tumors demonstrated a numerically favorable survival trend (HR = 0.31, $p = 0.12$).

Clinical benefit was also strongly linked to the presence of TLS ($p < 0.0001$). While TLS status did not significantly stratify overall survival, a lower hazard of death was observed among TLS-positive patients (HR = 0.56, $p = 0.25$). Further immune profiling revealed enrichment of CD56+ pan-CK– cells, CD11c+ myeloid cells, CD86+ antigen-presenting cells, and FcγRIIIA+CD11c+ populations in patients with CR, PR, or stable disease

compared with those experiencing progression. However, survival analyses based on FcγRIIIA+CD11c+ cell frequency did not demonstrate statistically significant differences (HR = 0.65, p = 0.55).

PD-L1 expression, measured using the 28–8 research-use-only assay, had a cohort-wide median combined positive score (CPS) of 6 (range 0–65). Non-HGS tumors exhibited significantly elevated CPS values relative to HGS tumors (median 35 vs 3; Mann–Whitney p = 0.0015). Higher PD-L1 expression was also associated with clinical benefit (CR/PR/SD) compared with progressive disease (p = 0.02), although CPS-based stratification did not yield statistically significant survival differences (p = 0.43). Correlative analyses showed positive relationships between CPS and densities of CD3+CD8+, CD3+CD4+, CD11c+, and CD20+ immune cells, indicating concordance between PD-L1 expression and immune infiltration within the TME.

Systemic inflammatory assessment demonstrated a nonsignificant trend toward lower baseline plasma interleukin-6 levels in patients with CR, PR, or stable disease compared with those with progression (p = 0.32), with no observed association with survival outcomes.

Tumor mutational burden was evaluable in 13 patients, with a median value of 4 mutations per megabase (range 1–11). A single tumor exceeded 10 mut/Mb; this case involved clear cell/endometrioid histology and corresponded to stable disease.

Baseline cancer antigen 125 (CA-125) measurements were available for 39 patients, yielding a median concentration of 233 U/mL (range 7–6,464); elevated levels (>35 U/mL) were present in 74% of cases. Higher baseline CA-125 values were observed in HGS tumors compared with non-HGS tumors. During therapy, reductions in CA-125 occurred primarily in patients achieving CR or PR and in three individuals with stable disease, whereas persistent elevation was common among patients with ongoing stable disease or progression.

Findings from the phase 1b C-800–01 expansion cohort indicate that the combination of botensilimab and balstilimab exhibits meaningful antitumor activity in a population with advanced, treatment-refractory ovarian cancer. This cohort was characterized by extensive prior therapy exposure: all participants had received platinum-based chemotherapy, most had platinum-resistant or platinum-refractory disease, and prior bevacizumab use was common. High-grade serous carcinoma predominated, with fewer patients harboring clear cell tumors. Despite these adverse prognostic features, treatment with BOT/BAL resulted in a confirmed objective response rate of 23%, durable disease control lasting at least 24 weeks in nearly one-third of patients, and sustained benefit beyond radiographic progression in select cases, while maintaining an acceptable and manageable toxicity profile.

Historically, immune checkpoint inhibition in recurrent ovarian cancer has produced limited clinical success, and no immunotherapy regimens have received regulatory approval in this setting. Earlier trials combining first-generation CTLA-4 and PD-1 inhibitors reported modest outcomes. For example, a phase 1 study of ipilimumab plus nivolumab in a heavily pretreated, platinum-resistant population demonstrated an ORR of approximately 10% [27]. In contrast, a subsequent phase 2 trial of the same combination—conducted in a less heavily pretreated cohort with a greater proportion of platinum-sensitive disease and higher representation of clear cell histology—reported a higher ORR of 31% [5]. Clear cell histology in that study was associated with substantially increased response likelihood and has been linked to elevated tumor mutational burden in prior reports [5, 28, 29]. Additionally, dual checkpoint blockade with durvalumab and tremelimumab yielded an ORR of only ~3% in an unselected platinum-resistant ovarian cancer population [30]. When viewed against these historical benchmarks, the activity observed with BOT/BAL suggests a potential advantage, including in traditionally “immune-cold” tumors such as relapsed or refractory high-grade serous ovarian cancer, which has generally shown limited responsiveness to immune checkpoint blockade.

Exploratory subgroup analyses revealed that clinical responses occurred in both platinum-sensitive and platinum-resistant/refractory disease subsets. Notably, the ovarian cancer expansion cohort included four efficacy-evaluable patients with primary platinum-refractory disease, a group associated with particularly poor outcomes and often excluded from later-phase trials [31–34]. Among these patients, responses included one complete response, two partial responses, and one case of stable disease. Although interpretation is constrained by the limited sample size and the non-randomized design inherent to a phase 1b study, these observations raise the possibility that BOT/BAL may offer durable benefit even in patients with primary platinum resistance.

Recently, mirvetuximab soravtansine-gynx—an antibody–drug conjugate targeting folate receptor-alpha—received approval for PROC after demonstrating a 32% ORR in a cohort of 104 patients [35]. In randomized studies, responses to mirvetuximab correlated with improvements in both progression-free and overall survival [34]. By contrast, immunotherapy regimens incorporating CTLA-4 blockade have often shown relatively modest

response rates but disproportionate effects on long-term survival, with progression-free survival frequently underestimating clinical benefit in the minority of patients who derive durable responses [36]. While mirvetuximab expands therapeutic options, patients whose disease progresses after treatment or whose tumors lack sufficient FRα expression continue to face limited alternatives. The enrollment of patients previously treated with mirvetuximab in the present study underscores the ongoing unmet need and suggests a potential role for BOT/BAL in this setting.

Management of immune-related toxicity has evolved across immuno-oncology, with increasing emphasis on early use of tumor necrosis factor-alpha inhibition in steroid-responsive cases to shorten steroid exposure and minimize treatment interruption [24, 37, 38]. This strategy was incorporated into the C-800–01 trial and contributed to the overall reversibility and manageability of BOT/BAL-associated toxicities. No novel safety signals were identified in this ovarian cancer cohort, and diarrhea/colitis remained the most frequently observed treatment-related adverse event (43%, with 16% grade 3). Prior studies have suggested that immune-mediated adverse events—including higher-grade events—may correlate with therapeutic benefit, and that durable responses can persist even after early discontinuation of treatment [39–41]. Broader adoption of optimized toxicity management approaches may therefore enhance the clinical utility of CTLA-4–based combinations and emerging immunotherapeutic strategies.

Correlative analyses offered insight into immune features associated with response to BOT/BAL. Patients experiencing clinical benefit were enriched for tumors exhibiting a T-cell–infiltrated phenotype, with higher densities of CD8+ cytotoxic T cells, CD4+ helper T cells, and tertiary lymphoid structures. Increased frequencies of FcγRIIIA+CD11c+ cells were also observed in responding patients, aligning with the Fc-engineered design of botensilimab and its reliance on FcγR-mediated immune activation [15]. Although these cell populations did not demonstrate independent prognostic significance, their association with response supports the proposed mechanism of action. PD-L1 expression was higher in responders and correlated with immune infiltration but was not predictive of survival outcomes, indicating that its role as a biomarker remains uncertain. Reductions in CA-125 levels among responders and some patients with stable disease further support its utility as a pharmacodynamic marker, whereas baseline IL-6 levels and tumor mutational burden showed limited predictive value. Consistent with prior experience, no single biomarker emerged as definitively predictive, underscoring the need for continued refinement of immune-based selection strategies.

Several limitations warrant consideration. As with many early-phase studies, patient heterogeneity and early censoring of time-to-event end points may have influenced efficacy estimates; nine treated patients were not evaluable for response. The short median progression-free survival reflects inclusion of patients with rapidly progressive disease who were unlikely to benefit from immunotherapy. These findings highlight the importance of selecting patients without imminent clinical deterioration and with sufficient time for immune-mediated responses to manifest. Additionally, the small and diverse study population—spanning platinum-sensitive, platinum-resistant, and platinum-refractory disease—complicates definitive interpretation of subgroup outcomes.

Conclusion

In summary, BOT/BAL produced durable responses, including complete remissions, in a heavily pretreated population dominated by platinum-resistant or refractory ovarian cancer, with a tolerable safety profile. Given the paucity of effective therapies for this group, these results support continued evaluation of this combination in larger, randomized clinical trials.

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