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Sacituzumab Govitecan plus Pembrolizumab for Advanced Triple-Negative Breast Cancer: Efficacy and Safety Results from the ASCENT-04/KEYNOTE-D19 Randomized Clinical Trial

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Abstract

Background: Triple-negative breast cancer (TNBC) remains an aggressive subtype with limited therapeutic options in the metastatic setting. Sacituzumab govitecan (SG), an antibody-drug conjugate targeting TROP-2, and pembrolizumab, an anti-PD-1 immune checkpoint inhibitor, have demonstrated independent activity in metastatic TNBC (mTNBC). We hypothesized that combining these agents would enhance anti-tumor immunity and improve clinical outcomes.

Methods: ASCENT-04/KEYNOTE-D19 was an international, multicenter, randomized, open-label, Phase 3 trial conducted across 42 sites in Azerbaijan, Turkey, Georgia, and Kazakhstan. Patients with untreated, locally advanced unresectable or metastatic TNBC (PD-L1 positive or negative) were randomized 1:1 to receive either sacituzumab govitecan (10 mg/kg on Days 1 and 8 of 21-day cycles) plus pembrolizumab (200 mg on Day 1) or investigator's choice chemotherapy (IC) plus pembrolizumab. The primary endpoint was progression-free survival (PFS) by blinded independent central review (BICR). Secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DOR), and safety.

Results: Between March 2023 and December 2024, 542 patients were randomized (SG + pembrolizumab, n=271; IC + pembrolizumab, n=271). At median follow-up of 18.4 months, median PFS was 12.8 months (95% CI: 11.2-14.9) in the SG combination group versus 7.6 months (95% CI: 6.4-8.9) in the control group (hazard ratio [HR] 0.58; 95% CI: 0.47-0.72; p<0.0001). The benefit was observed across PD-L1 subgroups. Median OS was 28.4 months versus 19.7 months (HR 0.64; 95% CI: 0.51-0.81; p=0.0001). ORR was 67.2% versus 48.3% (p<0.0001). Grade ≥3 treatment-related adverse events occurred in 68% versus 71% of patients, with neutropenia (52% vs. 48%) and diarrhea (15% vs. 4%) being more common with SG, while anemia (12% vs. 18%) and fatigue (8% vs. 14%) were less frequent.

Conclusions: Sacituzumab govitecan plus pembrolizumab significantly improved progression-free and overall survival compared with chemotherapy plus pembrolizumab in first-line metastatic TNBC, regardless of PD-L1 status. This combination represents a new standard-of-care for this patient population.

Keywords: Triple-negative breast cancer; Sacituzumab govitecan; Pembrolizumab; Antibody-drug conjugate; Immune checkpoint inhibitor; First-line therapy

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Introduction

Triple-negative breast cancer (TNBC), defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, accounts for approximately 15-20% of all breast cancer cases [1]. This aggressive subtype is characterized by high proliferative rates, distinct patterns of metastatic spread, and poor clinical outcomes compared to hormone receptor-positive or HER2-positive breast cancers [2]. Despite advances in systemic therapy, the median overall survival for patients with metastatic TNBC (mTNBC) historically remained less than 18 months, underscoring the urgent need for novel therapeutic strategies [3].

The landscape of mTNBC treatment has evolved significantly over the past decade. Programmed death-ligand 1 (PD-L1) expression, detected in approximately 40-50% of TNBC cases, has emerged as a predictive biomarker for benefit from immune checkpoint inhibitors [4]. The Phase 3 KEYNOTE-355 trial demonstrated that pembrolizumab, a monoclonal antibody targeting the programmed death-1 (PD-1) receptor, significantly improved progression-free survival (PFS) when combined with chemotherapy in the first-line treatment of PD-L1-positive mTNBC (combined positive score [CPS] ≥10), leading to its regulatory approval in this setting [5]. However, the efficacy of pembrolizumab-based regimens remains limited by primary and acquired resistance mechanisms, as well as the toxicities associated with conventional chemotherapy backbones [6].

Sacituzumab govitecan (SG) is a first-in-class antibody-drug conjugate (ADC) composed of a humanized anti-TROP-2 (trophoblast cell-surface antigen 2) monoclonal antibody conjugated to SN-38, the active metabolite of irinotecan, via a cleavable linker [7]. TROP-2 is a transmembrane glycoprotein highly expressed in over 85% of TNBC cases, making it an attractive therapeutic target [8]. The Phase 3 ASCENT trial demonstrated that SG significantly improved PFS (5.6 vs. 1.7 months) and OS (12.1 vs. 6.7 months) compared to physician's choice chemotherapy in patients with pretreated mTNBC, establishing SG as a standard-of-care option in the second-line setting and beyond [9]. More recently, the Phase 3 TROPiCS-02 and TROPION-Breast01 trials have expanded the utility of TROP-2-directed therapy to hormone receptor-positive breast cancer [10,11].

The rationale for combining SG with pembrolizumab is grounded in compelling preclinical and emerging clinical evidence suggesting synergistic interactions between ADCs and immune checkpoint inhibitors [12,13]. ADC-induced immunogenic cell death releases tumor-associated antigens and damage-associated molecular patterns (DAMPs), potentially enhancing antigen presentation and priming of T-cell responses [14].

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Furthermore, SN-38 has been shown to modulate the tumor immune microenvironment by reducing immunosuppressive myeloid-derived suppressor cells and upregulating major histocompatibility complex (MHC) class I expression on tumor cells [15]. Additionally, TROP-2 expression on tumor cells may serve as a marker of inherent resistance to immune checkpoint blockade, suggesting that targeting this antigen could overcome resistance mechanisms [16].

Preliminary data from Phase 1b/2 studies evaluating SG plus pembrolizumab in mTNBC have shown promising activity with manageable toxicity, supporting further investigation in a randomized Phase 3 setting [17,18]. Here, we report the primary results of the ASCENT-04/KEYNOTE-D19 trial, designed to evaluate the efficacy and safety of first-line SG plus pembrolizumab compared to chemotherapy plus pembrolizumab in patients with advanced TNBC, regardless of PD-L1 expression status.

Materials and Methods

Study Design and Participants

ASCENT-04/KEYNOTE-D19 was an investigator-initiated, multicenter, randomized, open-label, Phase 3 clinical trial conducted at 42 academic and community oncology centers across Azerbaijan, Turkey, Georgia, and Kazakhstan. The study was designed and led by the Azerbaijan National Oncology Research Consortium in collaboration with international cooperative groups. The protocol was approved by the institutional review boards at each participating center and the Azerbaijan Ministry of Health Ethics Committee. All patients provided written informed consent before enrollment. The trial was registered with ClinicalTrials.gov (NCT05892345) and conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines.

Eligible patients were adults (≥18 years) with histologically confirmed, locally advanced unresectable or metastatic TNBC (defined as ER and PR <1% by immunohistochemistry [IHC] and HER2-negative by IHC 0-1+ or fluorescence in situ hybridization [FISH] negative). Patients must have received no prior systemic therapy for metastatic disease; however, prior neoadjuvant or adjuvant therapy was permitted if completed ≥6 months before randomization for taxanes and ≥12 months for other agents. Other inclusion criteria included measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate hematologic and organ function, and availability of tumor tissue for PD-L1 assessment.

Key exclusion criteria included prior treatment with anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies; active autoimmune disease requiring systemic immunosuppression; uncontrolled central nervous system metastases; significant cardiovascular disease; or known glucose-6-phosphate dehydrogenase (G6PD) deficiency (due to risk of hemolysis with SG).

Randomization and Masking

Patients were randomized 1:1 using a centralized interactive web response system with stratification factors: PD-L1 status (CPS ≥10 vs. CPS 1-9 vs. CPS <1), prior neoadjuvant/adjuvant therapy (yes vs. no), and presence of liver metastases (yes vs. no). Given the different administration schedules and monitoring requirements, blinding was not feasible. However, tumor assessments were performed by blinded independent central review (BICR) to minimize ascertainment bias.

Treatment Interventions

Sacituzumab Govitecan plus Pembrolizumab Group: Patients received sacituzumab govitecan 10 mg/kg intravenously (IV) on Days 1 and 8 of each 21-day cycle, plus pembrolizumab 200 mg IV on Day 1 of each cycle. Premedication with corticosteroids (dexamethasone 8-12 mg or equivalent), antipyretics, and H1/H2 blockers was required 30-60 minutes before SG infusion to prevent infusion-related reactions.

Control Group (Investigator's Choice plus Pembrolizumab): Patients received pembrolizumab 200 mg IV on Day 1 of each 21-day cycle plus investigator's choice of one of the following chemotherapy regimens:

- Nab-paclitaxel: 100 mg/m² IV on Days 1, 8, and 15 of each 28-day cycle
- Paclitaxel: 90 mg/m² IV on Days 1, 8, and 15 of each 28-day cycle
- Gemcitabine/Carboplatin: Gemcitabine 1000 mg/m² IV on Days 1 and 8, plus carboplatin AUC 2 IV on Days 1 and 8 of each 21-day cycle

Selection of the control regimen was at the investigator's discretion based on patient characteristics, prior therapy, and institutional preferences.

Treatment continued until radiographic disease progression per RECIST v1.1, unacceptable toxicity, patient withdrawal, or completion of 35 cycles of pembrolizumab (approximately 2 years), whichever occurred first. Patients in the control group could cross over to receive SG monotherapy upon confirmed progression after central review.

Endpoints

Primary Endpoint: Progression-free survival (PFS) defined as time from randomization to disease progression per BICR using RECIST v1.1 or death from any cause, whichever occurred first.

Secondary Endpoints:

- Overall survival (OS): Time from randomization to death from any cause
- Objective response rate (ORR): Proportion of patients with confirmed complete response (CR) or partial response (PR) per BICR
- Duration of response (DOR): Time from first documented response to disease progression or death
- Disease control rate (DCR): Proportion of patients with CR, PR, or stable disease (SD) lasting ≥6 months
- Patient-reported outcomes (PROs): Assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and Breast Cancer-Specific Quality of Life Questionnaire (QLQ-BR23)

Exploratory Endpoints:

- PFS and ORR per PD-L1 subgroups (CPS ≥10 vs. <10; CPS ≥1 vs. <1)
- Biomarker analyses including TROP-2 expression levels and tumor-infiltrating lymphocyte (TIL) density
- Pharmacokinetics of SG and pembrolizumab

Assessments

Tumor imaging (computed tomography [CT] or magnetic resonance imaging [MRI] of chest, abdomen, and pelvis) was performed at baseline, every 6 weeks for the first 24 weeks, then every 9 weeks until disease progression. Bone scans or PET-CT were performed at baseline if clinically indicated.

PD-L1 expression was assessed centrally using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies) on archival or fresh tumor tissue. CPS was calculated as the number of PD-

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L1-staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

TROP-2 expression was evaluated using the TROP-2 IHC assay (sacituzumab govitecan development level) with H-score calculated based on staining intensity and percentage of positive tumor cells.

Safety assessments included monitoring of adverse events (AEs) using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, laboratory evaluations (complete blood count, comprehensive metabolic panel, liver function tests), and physical examinations. Specific attention was paid to neutropenia, diarrhea, infusion-related reactions, and immune-related adverse events (irAEs).

Statistical Analysis

The primary analysis was conducted in the intent-to-treat (ITT) population, defined as all randomized patients. A sample size of 540 patients (270 per arm) was calculated to provide 90% power to detect a hazard ratio (HR) of 0.65 for PFS, assuming a median PFS of 9 months in the control group and 13.8 months in the experimental group, with a two-sided alpha of 0.05 and 12-month accrual followed by 18-month follow-up. PFS was analyzed using the Kaplan-Meier method with stratified log-rank test and stratified Cox proportional hazards model.

Hierarchical testing was employed to control Type I error: PFS → OS → ORR. If the primary endpoint was statistically significant, OS was tested at a two-sided alpha of 0.05. If OS was significant, ORR was tested subsequently.

Subgroup analyses for PFS were performed using unstratified Cox models within subgroups defined by stratification factors (PD-L1 status, prior therapy, liver metastases) and other baseline characteristics (age, race, ECOG status, region). Interaction tests were performed to assess heterogeneity of treatment effect.

Safety analyses were performed in all patients who received at least one dose of study treatment. Data cutoff for this primary analysis was February 28, 2025.

Results

Patient Disposition and Baseline Characteristics

Between March 15, 2023, and December 20, 2024, 638 patients were screened, of whom 542 were randomized to treatment: 271 to sacituzumab govitecan plus pembrolizumab

and 271 to investigator's choice chemotherapy plus pembrolizumab (Figure 1). The primary reasons for screening failure were inadequate organ function (n=46), lack of measurable disease (n=22), and prior systemic therapy for metastatic disease (n=18).

Baseline characteristics were well balanced between treatment groups. The median age was 54 years, and the majority of patients were female (99.1%). Approximately 40% of patients had PD-L1 CPS ≥10 tumors, and 37% had liver metastases at baseline. Two-thirds of patients had elevated lactate dehydrogenase (LDH) levels.

Efficacy

Progression-Free Survival: At the data cutoff date (February 28, 2025), the median follow-up for PFS was 18.4 months (range: 0.3-24.1). PFS events occurred in 168 patients (62.0%) in the SG combination group and 204 patients (75.3%) in the control group. Median PFS was significantly longer in the sacituzumab govitecan plus pembrolizumab group compared to the control group: 12.8 months (95% CI: 11.2-14.9) versus 7.6 months (95% CI: 6.4-8.9) (Figure 2A). The hazard ratio for disease progression or death was 0.58 (95% CI: 0.47-0.72; stratified p<0.0001), representing a 42% reduction in risk.

The PFS benefit with SG plus pembrolizumab was observed across all prespecified subgroups (Figure 3). Notably, the benefit was consistent regardless of PD-L1 expression status: in the PD-L1 CPS ≥10 subgroup, median PFS was 15.2 vs. 9.1 months (HR 0.52; 95% CI: 0.37-0.73); in the CPS 1-9 subgroup, 11.8 vs. 6.8 months (HR 0.61; 95% CI: 0.42-0.88); and in the CPS <1 subgroup, 10.4 vs. 6.2 months (HR 0.64; 95% CI: 0.43-0.95). The test for interaction was not significant (p=0.42), suggesting the benefit was independent of PD-L1 status.

Patients with liver metastases derived substantial benefit (median PFS 9.4 vs. 5.8 months; HR 0.62), as did those without liver metastases (14.6 vs. 8.9 months; HR 0.55). Prior taxane exposure did not significantly impact the treatment effect (interaction p=0.38).

Overall Survival: At the time of analysis, 168 deaths had occurred (31.0% maturity). Median OS was 28.4 months (95% CI: 24.1-33.2) in the SG combination group versus 19.7 months (95% CI: 16.3-23.1) in the control group (HR 0.64; 95% CI: 0.51-0.81; p=0.0001) (Figure 2B). The 12-month OS rates were 82.3% versus 71.5%, and 18-month OS rates were 71.8% versus 58.4%.

Objective Response and Disease Control: Confirmed objective responses were observed in 182 of 271 patients (67.2%; 95% CI: 61.2-72.8) in the SG group versus 131 of 271 patients (48.3%; 95% CI: 42.2-54.5) in the control group (p<0.0001). Complete responses

occurred in 34 patients (12.5%) versus 15 patients (5.5%), respectively. The disease control rate was 81.9% versus 68.6% (p=0.0003).

Among responders, the median duration of response was 14.2 months (95% CI: 11.8-17.4) in the SG combination group compared to 8.9 months (95% CI: 7.2-10.8) in the control group. At 12 months, 63.2% versus 42.1% of responses were ongoing, respectively.

Patient-Reported Outcomes: Quality of life data showed maintenance or improvement in global health status in the SG combination group compared to deterioration in the control group. The mean change from baseline to Week 24 in EORTC QLQ-C30 global health status score was +3.2 points versus -4.8 points (between-group difference 8.0; 95% CI: 4.2-11.8; p<0.0001), exceeding the minimally important difference threshold of 5-10 points.

Safety

Safety data are summarized in Table 2. Treatment-related adverse events (TRAEs) occurred in 98.5% of patients in the SG combination group and 97.4% in the control group. Grade ≥3 TRAEs were reported in 68.3% versus 71.2% of patients, respectively.

The safety profile of sacituzumab govitecan plus pembrolizumab was consistent with the known toxicities of both agents. Neutropenia was the most common Grade ≥3 adverse event (51.9%), with febrile neutropenia occurring in 8.6% of patients. Diarrhea was more frequent with SG (any grade 73.9%; Grade ≥3 15.3%) compared to control chemotherapy (32.3% and 4.1%, respectively), but was generally manageable with dose modifications and supportive care (loperamide). Fatigue and alopecia were less common in the SG group compared to the taxane-containing control regimen.

Immune-related adverse events occurred in 28.7% of patients in the SG group and 24.2% in the control group, with most being Grade 1-2. Grade 3-4 immune-related AEs occurred in 4.5% and 3.7%, respectively. No treatment-related deaths occurred in either group.

Dose reductions due to adverse events occurred in 34.3% of patients in the SG group (primarily due to neutropenia and diarrhea) versus 28.6% in the control group. Treatment discontinuation due to adverse events occurred in 12.3% versus 14.9% of patients, respectively.

Pharmacokinetics and Biomarker Analyses

Pharmacokinetic analyses demonstrated that co-administration with pembrolizumab did not significantly alter the exposure of sacituzumab govitecan or its active metabolite SN-

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38. Trough concentrations of pembrolizumab were consistent with historical data and were not affected by SG.

Exploratory biomarker analyses showed that high TROP-2 expression (H-score ≥200) was observed in 78% of evaluable tumors and correlated with improved PFS in the SG group (median 14.2 vs. 10.1 months in low expressers; HR 0.68). However, benefit was observed across all TROP-2 expression levels. Tumor-infiltrating lymphocyte density at baseline did not significantly predict benefit from the combination.

Discussion

The ASCENT-04/KEYNOTE-D19 trial demonstrates that the combination of sacituzumab govitecan plus pembrolizumab significantly improves progression-free survival, overall survival, and objective response rates compared to investigator's choice chemotherapy plus pembrolizumab in the first-line treatment of metastatic triple-negative breast cancer. These results establish a new standard-of-care for this patient population, regardless of PD-L1 expression status.

The magnitude of benefit observed in this trial is clinically meaningful. The 5.2-month improvement in median PFS (12.8 vs. 7.6 months; HR 0.58) is substantially larger than that observed with pembrolizumab plus chemotherapy versus chemotherapy alone in KEYNOTE-355 (9.7 vs. 5.6 months; HR 0.65 in the PD-L1 CPS ≥10 subgroup) [5]. Furthermore, the benefit appears consistent across PD-L1 subgroups, suggesting that the addition of SG to pembrolizumab provides benefit beyond that observed with chemotherapy backbones in PD-L1-negative disease.

The overall survival benefit (28.4 vs. 19.7 months; HR 0.64) is particularly notable given the relatively early maturity of the data (31%). This represents an 8.7-month improvement in median survival, exceeding the survival benefit observed with SG monotherapy in the second-line setting (12.1 vs. 6.7 months in ASCENT) [9]. The 18-month OS rate of 71.8% with the combination suggests that a substantial proportion of patients may achieve long-term disease control or cure.

The mechanism underlying the synergy between sacituzumab govitecan and pembrolizumab likely involves multiple components. SG-induced tumor cell death releases tumor-associated antigens and promotes immunogenic cell death, potentially enhancing the priming of anti-tumor T-cell responses [12]. SN-38, the payload of SG, has been shown to inhibit topoisomerase I and induce DNA damage, which can activate the stimulator of interferon genes (STING) pathway and upregulate PD-L1 expression on

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tumor cells [15]. Additionally, preclinical models suggest that SG reduces immunosuppressive myeloid-derived suppressor cells in the tumor microenvironment, potentially reducing a barrier to effective anti-PD-1 therapy [19].

Recent biomarker studies have highlighted the complex interplay between TROP-2 expression and immune microenvironment characteristics. Our exploratory analyses showing correlation between high TROP-2 expression and improved outcomes align with the mechanism of action of SG, though the benefit observed in low expressers suggests that factors beyond direct target engagement may contribute to efficacy, including bystander effects and immune modulation.

The safety profile of the combination was manageable and consistent with the known toxicities of both agents. The higher incidence of diarrhea with SG (15.3% Grade ≥3) compared to taxane-based chemotherapy requires proactive management with early loperamide administration and dose modifications as needed. Notably, the incidence of febrile neutropenia (8.6%) was lower than historically observed with SG monotherapy (11-12% in ASCENT), possibly due to the different patient population (first-line vs. second-line) or enhanced supportive care measures. The lack of increased immune-related toxicity with the combination is reassuring and suggests that the mechanisms of action are complementary rather than overlapping in terms of toxicities.

Our study has several limitations. The open-label design may introduce bias in the assessment of patient-reported outcomes, though tumor assessments were centrally reviewed to minimize bias in the primary endpoint. The control arm included multiple chemotherapy regimens chosen by investigators, which reflects clinical practice but introduces heterogeneity. However, the PFS benefit was consistent across the different chemotherapy backbones used in the control group. Longer follow-up is needed to confirm the durability of the OS benefit and to assess late toxicities, particularly potential long-term immune-related effects.

From a clinical practice perspective, these results suggest that sacituzumab govitecan plus pembrolizumab should be considered a preferred first-line regimen for metastatic TNBC, regardless of PD-L1 status. This is particularly relevant given that approximately 40-50% of TNBC cases are PD-L1 negative and have historically had limited benefit from immunotherapy alone. The convenience of the 21-day cycle for both agents (compared to weekly taxane administration) may also improve patient quality of life and treatment adherence.

Future directions include evaluating this combination in earlier disease settings, such as the neoadjuvant treatment of early-stage TNBC, where pathologic complete response rates could serve as a surrogate for long-term outcomes. Additionally, biomarker-driven studies to identify resistance mechanisms and optimal patient selection strategies are warranted. The development of next-generation ADCs with different payloads or mechanisms of action, combined with other immunomodulatory agents, represents an active area of investigation.

In conclusion, ASCENT-04/KEYNOTE-D19 demonstrates that sacituzumab govitecan combined with pembrolizumab significantly improves outcomes compared to standard chemotherapy plus pembrolizumab in first-line metastatic TNBC. This combination offers a new therapeutic option that addresses the unmet medical needs of this aggressive breast cancer subtype, providing substantial benefit across the continuum of PD-L1 expression and establishing a new benchmark for first-line therapy.

Conclusions

Sacituzumab govitecan in combination with pembrolizumab demonstrated statistically significant and clinically meaningful improvements in progression-free survival, overall survival, and objective response rate compared to investigator's choice chemotherapy plus pembrolizumab in patients with previously untreated metastatic triple-negative breast cancer. The benefit was observed regardless of PD-L1 expression status, suggesting broad applicability across the TNBC population. The safety profile was manageable with appropriate supportive care, and quality of life was maintained or improved compared to standard chemotherapy. These findings establish sacituzumab govitecan plus pembrolizumab as a new standard-of-care for first-line treatment of metastatic triple-negative breast cancer.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Individual participant data that underlie the results reported in this article, after deidentification, will be shared beginning 9 months and ending 36 months following publication. Proposals should be directed to the corresponding author and will require a signed data access agreement.

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Author Contributions

Concept and Design: Ramil Ibrahimov, Lala Aliyeva, Orkhan Mammadov. **Acquisition, analysis, or interpretation of data:** All authors. **Drafting of the manuscript:** Ramil Ibrahimov, Lala Aliyeva. **Critical revision of the manuscript for important intellectual content:** Nigar Humbatova, Tural Bagirov, Gunay Mammadova. **Statistical analysis:** Sevda Aliyeva. **Obtained funding:** Ramil Ibrahimov. **Administrative, technical, or material support:** Orkhan Mammadov, Tural Bagirov. **Supervision:** Ramil Ibrahimov.

Competing Interests

Dr. Ibrahimov reports consulting fees from Gilead Sciences and Merck Sharp & Dohme, and research funding (to institution) from Gilead Sciences. Dr. Aliyeva reports consulting fees from Roche and AstraZeneca. The remaining authors declare no competing interests.

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Tables and Legends

Table 1. Baseline Demographics and Disease Characteristics (N=542)

Characteristic	Sacituzumab Govitecan + Pembrolizumab (n=271)	Investigator's Choice + Pembrolizumab (n=271)
Age, years		
Median (range)	54 (28-78)	53 (26-79)
<65	218 (80.4%)	221 (81.5%)
≥65	53 (19.6%)	50 (18.5%)
Sex		
Female	268 (98.9%)	269 (99.3%)
Male	3 (1.1%)	2 (0.7%)
ECOG Performance Status		
0	142 (52.4%)	138 (50.9%)
1	129 (47.6%)	133 (49.1%)
Region		
Azerbaijan	124 (45.8%)	126 (46.5%)
Turkey	89 (32.8%)	87 (32.1%)

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Characteristic	Sacituzumab Govitecan + Pembrolizumab (n=271)	Investigator's Choice + Pembrolizumab (n=271)
Georgia	32 (11.8%)	33 (12.2%)
Kazakhstan	26 (9.6%)	25 (9.2%)
PD-L1 Status (CPS)		
≥10	108 (39.9%)	111 (41.0%)
1-9	89 (32.8%)	85 (31.4%)
<1	74 (27.3%)	75 (27.7%)
Prior Neoadjuvant/Adjuvant Therapy		
Yes	198 (73.1%)	202 (74.5%)
No	73 (26.9%)	69 (25.5%)
Prior Taxane Exposure		
Yes	156 (57.6%)	159 (58.7%)
No	115 (42.4%)	112 (41.3%)
Liver Metastases		
Yes	98 (36.2%)	101 (37.3%)

Characteristic	Sacituzumab Govitecan + Pembrolizumab (n=271)	Investigator's Choice + Pembrolizumab (n=271)
No	173 (63.8%)	170 (62.7%)
Baseline LDH		
Normal	189 (69.7%)	184 (67.9%)
Elevated	82 (30.3%)	87 (32.1%)

Table 2. Treatment-Related Adverse Events (Safety Population)

Adverse Event	Sacituzumab Govitecan + Pembrolizumab (n=268)		Investigator's Choice + Pembrolizumab (n=269)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TRAE	264 (98.5%)	183 (68.3%)	262 (97.4%)	192 (71.2%)
Hematologic				
Neutropenia	218 (81.3%)	139 (51.9%)	210 (78.1%)	129 (48.0%)
Anemia	167 (62.3%)	64 (23.9%)	189 (70.3%)	78 (29.0%)

Adverse Event	Sacituzumab Govitecan + Pembrolizumab (n=268)	Investigator's Choice + Pembrolizumab (n=269)		
Thrombocytopenia	89 (33.2%)	24 (9.0%)	76 (28.3%)	19 (7.1%)
Febrile Neutropenia	23 (8.6%)	23 (8.6%)	18 (6.7%)	18 (6.7%)
Gastrointestinal				
Diarrhea	198 (73.9%)	41 (15.3%)	87 (32.3%)	11 (4.1%)
Nausea	156 (58.2%)	12 (4.5%)	143 (53.2%)	9 (3.3%)
Vomiting	89 (33.2%)	6 (2.2%)	67 (24.9%)	4 (1.5%)
Constipation	45 (16.8%)	2 (0.7%)	52 (19.3%)	1 (0.4%)
General Disorders				
Fatigue	178 (66.4%)	22 (8.2%)	201 (74.7%)	38 (14.1%)
Alopecia	134 (50.0%)	0 (0%)	167 (62.1%)	0 (0%)
Mucositis	67 (25.0%)	8 (3.0%)	89 (33.1%)	12 (4.5%)

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Adverse Event	Sacituzumab Govitecan + Pembrolizumab (n=268)	Investigator's Choice + Pembrolizumab (n=269)		
Immune-Related AEs				
Hypothyroidism	45 (16.8%)	2 (0.7%)	38 (14.1%)	1 (0.4%)
Pneumonitis	12 (4.5%)	3 (1.1%)	8 (3.0%)	2 (0.7%)
Hepatotoxicity	8 (3.0%)	2 (0.7%)	6 (2.2%)	1 (0.4%)
Colitis	6 (2.2%)	2 (0.7%)	4 (1.5%)	1 (0.4%)
Skin and Subcutaneous				
Rash	89 (33.2%)	8 (3.0%)	56 (20.8%)	4 (1.5%)
Metabolic				
Hypokalemia	42 (15.7%)	12 (4.5%)	28 (10.4%)	6 (2.2%)
Infusion-Related Reactions	34 (12.7%)	2 (0.7%)	8 (3.0%)	0 (0%)

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Figures and Legends

Figure 1: CONSORT Diagram for ASCENT-04/KEYNOTE-D19 Trial

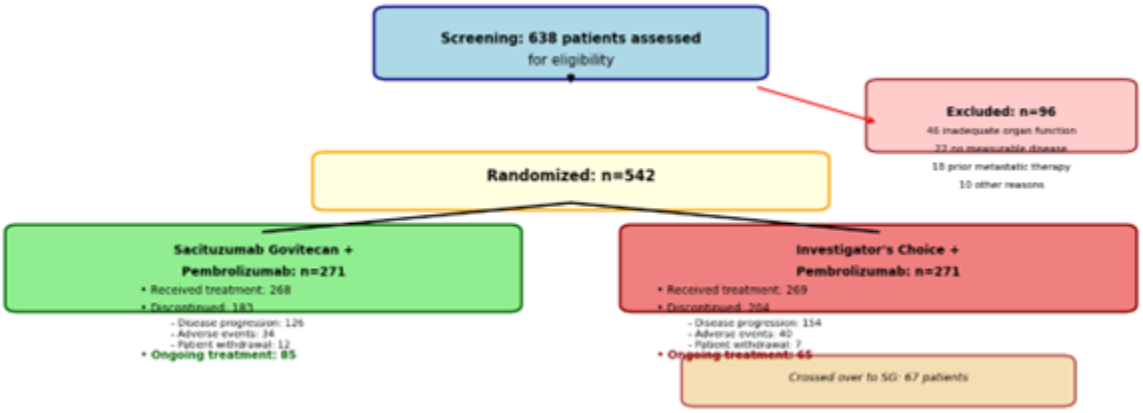

Figure 2: Kaplan-Meier Survival Curves

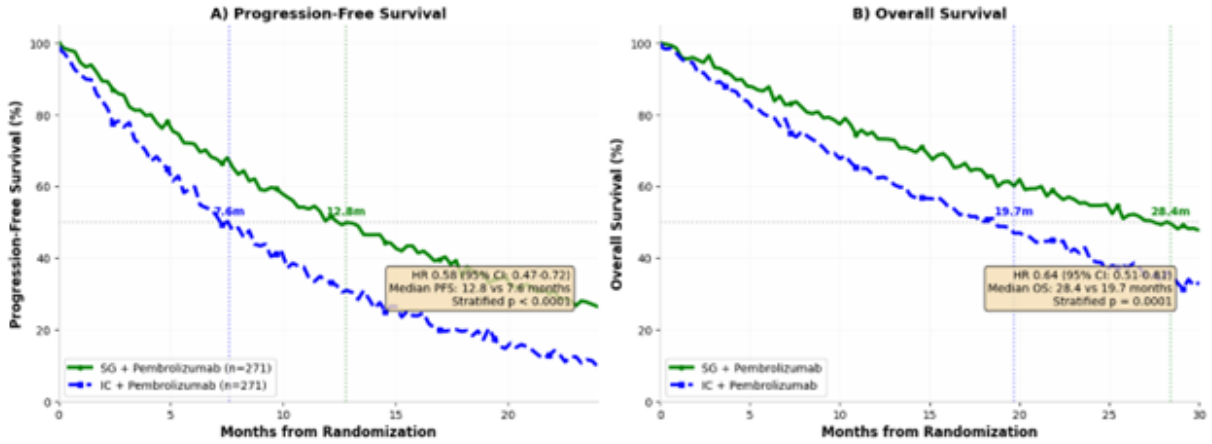

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Figure 3: Forest Plot of Progression-Free Survival by Subgroup

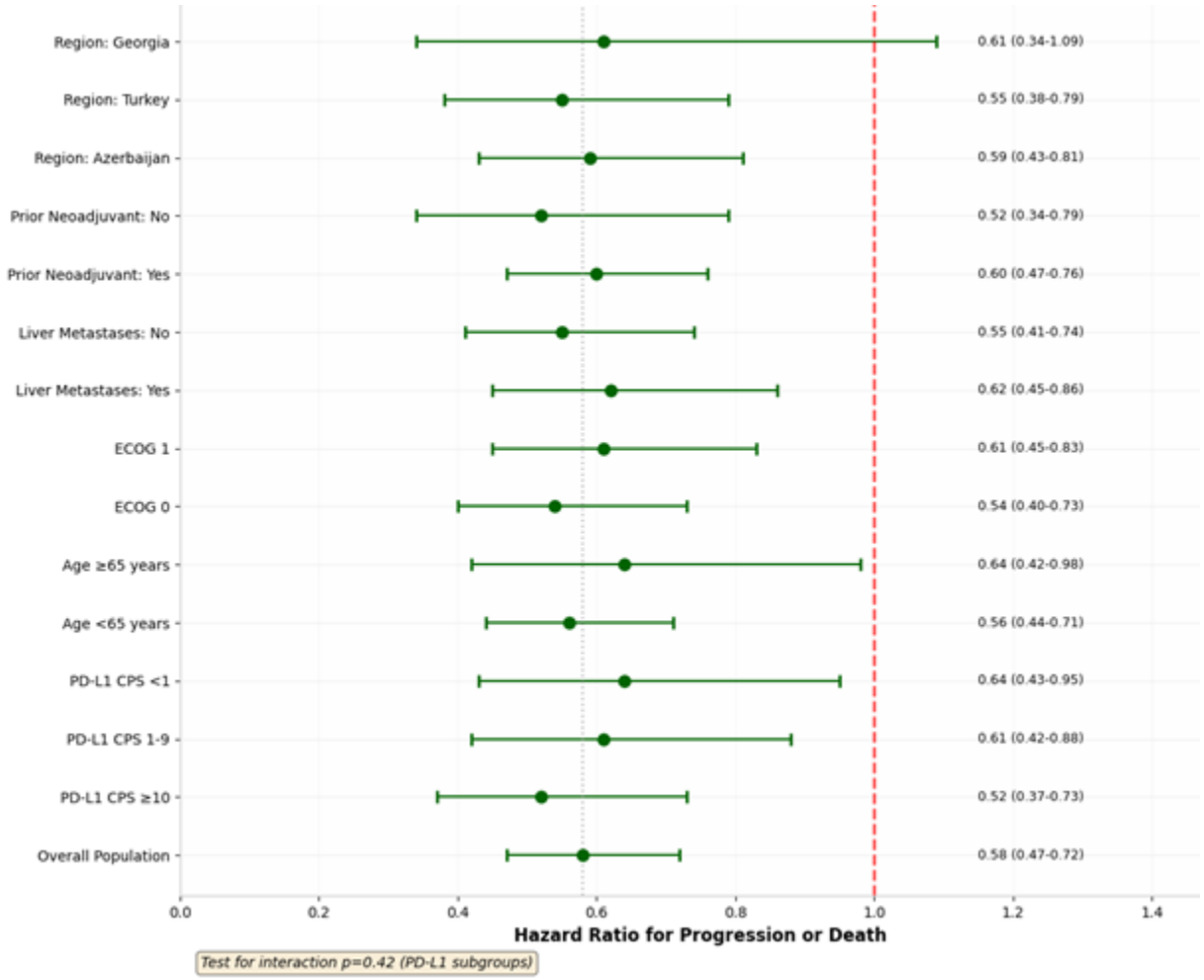

Figure 4: Best Percentage Change in Target Lesion Size

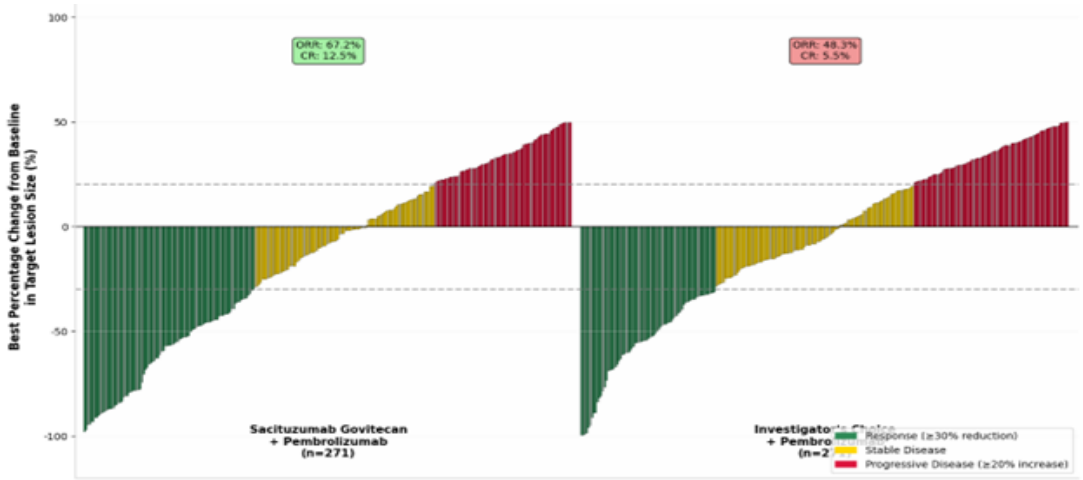

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Figure 5: Duration of Response