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Commentary

Sacituzumab govitecan in the first-line treatment of triple-negative breast cancer: balancing therapeutic sequencing with patient-relevant benefits

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The management of advanced triple-negative breast cancer (TNBC) has historically posed major clinical challenges, with chemotherapy representing the mainstay of treatment but with limited overall benefit.[1] The advent of immune checkpoint inhibitors (ICIs) combined with chemotherapy has improved outcomes for patients with PD-L1-positive TNBC, yet a substantial therapeutic void persists. Within this context, the ASCENT-04/KEYNOTE-D19 trial sought to interrogate whether the Trop2-directed antibody-drug conjugate (ADC) sacituzumab govitecan (SG), approved in the setting of pretreated TNBC, could be repositioned as a frontline agent in combination with pembrolizumab in patients with PD-L1-positive TNBC.[2] Preclinical data suggest that SG's SN-38 payload induces DNA damage activating cGAS–STING/type I interferon and antitumor immunity, potentially enhanced by ICI. Phase 2 trials are exploring this in TNBC (NCT04468061) and post-neoadjuvant settings (NCT05633654), while in advanced hormone-receptor positive disease, no added benefit over SG alone was observed.[3,4]

ASCENT-04 touches two main aspects of the current drug development in TNBC:

i. how to best sequence available therapeutic options or otherwise, what is the benefit in moving drugs approved in later line to the upfront setting, and
ii. whether new treatments tackle the most clinical challenging presentations, especially pertaining those patients at risk of more adverse outcomes.

The primary analysis of ASCENT-04 was presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in June 2025.[2] After a median follow-up of 14 months, SG-pembrolizumab yielded a median PFS of 11.2 months (95% CI, 9.3-16.7) compared to 7.8 months (95% CI, 7.3-9.3) with chemotherapy-pembrolizumab, corresponding to a hazard ratio (HR) of 0.65 (95% CI, 0.51-0.84; $P < 0.001$). The objective response rate was also higher in the SG arm (60% vs 53%), with a median duration of response of 16.5 months vs 9.2 months. Crucially, overall survival (OS) data remain immature at a 26% event rate, with 43% of control-arm patients crossing over to SG upon disease progression. Patient-reported outcome data were not presented.

The most rigorous way to assess the impact of early frontline drug use is through an OS-powered trial with crossover permitted; if early SG use shows no OS advantage over sequential use, its upfront deployment may be futile.[5] ASCENT-04/KEYNOTE-D19, however, was designed around PFS, with OS tested hierarchically, leaving SG's true frontline value unresolved. In TNBC, where PFS is a questionable surrogate and quality of life (QoL) data are lacking, a + 3.4-month median PFS gain demands scrutiny on whether it translates into tangible OS benefit.

To further clinically contextualize the results of this trial, one must examine stratification factors and clinically relevant subgroup data. In ASCENT-04, prior exposure to an anti-PD-(L)1 therapy in the curative setting was uncommon (only 5% of patients), with no apparent benefit of SG-pembrolizumab (PFS 6.6 vs 7.5 months, HR 1.08 [95% CI, 0.31-3.75]) in this subset of patients. Real-world evidence will help address this gap, but the future use of this regimen remains largely speculative in ICI-pretreated patients.

Moreover, the stratification by disease-free survival (DFS) interval proves particularly illuminating, in light of prior reports[6,7] indicating that early-relapsing TNBC is characterized by poor outcomes with ICI combinations, likely reflecting a less immunogenic biology,[8] and ultimately, no evident advantage from integrating an ICI.

In ASCENT-04, the most pronounced PFS benefit of SG in lieu of chemotherapy in the first-line was reported in the group of patients experiencing DFS >12 months, showing almost a doubling of the median PFS (16.6 vs 8.7 months; HR 0.52 [95% CI, 0.35-0.76]). Such a result was modest in patients experiencing prior 6-12 months DFS, reporting 9.9 and 7.2 months of median PFS, respectively (HR = 0.62, 0.36-1.08). To juxtapose, in IMpassion132[6] enrolling patients with TNBC relapsing <12 months after last chemotherapy dose in the curative setting, the addition of atezolizumab to chemotherapy in PD-L1–positive TNBC conferred no OS benefit (HR 0.93 [95% CI, 0.73-1.20]; $P = 0.59$). Similarly, in KEYNOTE-355[7] enrolling patients if at least 6 months had elapsed between completion of treatment

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with curative intent, the subgroup with DFS <12 months trended toward no OS benefit from the addition of pembrolizumab (OS 19.7 vs 17.1 months, HR = 1.44 in PD-L1 CPS ≥ 10). By contrast, a sub-analysis of the pivotal ASCENT trial showed that SG demonstrated superior PFS and OS compared with chemotherapy in patients with disease recurrence within 12 months of (neo)adjuvant treatment and a prior line of chemotherapy in the metastatic setting—suggesting a therapeutic role in early-recurring TNBC.[9] These findings indicate intrinsic biological resistance in early-relapsing TNBC to ICI and a potential benefit of the ADC, calling into question the therapeutic role of the combination in an unselected patient population.

Eventually, patients with *de novo* metastatic TNBC appeared to benefit the least with the novel combination (HR = 0.89, 0.59-1.34; median PFS 8.1 vs 7.7 months). In *de novo* metastatic TNBC, intrinsic heterogeneity and resistance likely contribute to observed outcomes, as these tumors more frequently harbor *TP53* mutations and *MYB* amplifications, whose co-occurrence is associated with a more aggressive phenotype and reduced sensitivity to ICI.[10,11]

In essence, ASCENT-04 does not show major benefit in the most challenging TNBC scenarios, particularly in patients relapsing after prior ICI. SG outperforms chemotherapy in pretreated and early-relapsing cases, while the benefit of adding ICIs is uncertain, with potential value mainly in first-line, non-early relapsing disease.

The SG-pembrolizumab combination increased nausea, diarrhea, and vomiting, though overall moderate-to-severe adverse events were similar across arms, yielding no clear safety advantage. Addition of ICI raised immune-related risks—including pneumonitis, colitis, endocrine disorders, and skin reactions (each occurring in ≤2% of patients)—generally mild to moderate but potentially irreversible, underscoring the need to select patients most likely to benefit.

Critically, QoL outcomes were not reported. In a setting where symptom burden and treatment fatigue shape patient experience, the absence of patient-reported data limits assessment of whether PFS gains translate into meaningful benefit. To navigate the requirements to fulfill patient-centric improvements in clinical trials, we developed a data synthesis table for ASCENT-04 based on the Common-Sense Oncology checklist[12] (Table 1).

Table 1. Report of the data from ASCENT-04 clinical trial based on the CSO checklist.

Section	Item	Reported?	Comment
Abstract (overall)	Explicit definition of the primary endpoint	**Yes**	PFS by BICR clearly defined as primary endpoint.
	Hazard ratio for primary endpoint and OS, with CIs and absolute benefit	**Yes (PFS)/ Partial (OS)**	HR for PFS reported (0.65; 95% CI, 0.51-0.84). OS data immature; early trend noted.
	Objective summary of grades 3-5 toxicity, time with chronic toxicities, discontinuation	**Partial**	Grade ≥3 AEs summarized, no mention of chronic toxicities or time lived with toxicity.
	Statement about HRQOL	**No**	No data on the quality of life yet provided.
	Lay-language summary of main results	**Yes**	A lay-language summary of the results provided
Methods	Patient/public involvement in design/approval	**Unclear**	Not reported.
	Justification of the control group as the current SoC	**Yes**	Control arm was chemo + pembrolizumab, current standard in PD-L1+ advanced TNBC per KN355 trial.
	Justification of primary endpoint/surrogacy evidence	**No**	Not reported.
	Statistical basis for sample size and detectable benefit	**Partial**	Alpha 1-sided at 2.5% reported, hierarchical testing planned. No explicit reporting of assumed effect size or power to be clinically meaningful.
	Strategies to reduce drop-out and censoring	**No**	Not reported. No mention of specific retention or censoring mitigation strategies.
	Plans for crossover, indication if mandated and funded	**Partial**	Crossover to 2 L sacituzumab govitecan offered (43% of control arm).
	Criteria for interim analysis and early stopping	**Yes**	A hierarchical design was provided, including mention of event-driven interim analysis for PFS and OS, no rule for it is explained.
Results	Time-to-event curves for primary and OS, with numbers at risk and censored.	**Partial**	PFS curve available. OS immature. Numbers at risk reported, no explicit statement on censoring.
	Absolute measure of benefit	**Yes**	Median PFS benefit of +3.4 months reported (11.2 vs 7.8 mo).
	Reasons for drop-out and censoring, sensitivity analysis	**No**	Not reported.
	Number of control patients crossing over, post-progression treatments	**Partial**	43% crossover reported; post-progression treatments not fully detailed.
	Objective toxicity assessment, patient-reported toxicity	**Partial**	Grade ≥3 AEs objectively reported; no patient-reported outcomes for toxicity.
	ESMO MCBS substantial benefit criterion met (MCBS > 3 or A-B)	**No**	Estimated, non-official ESMO-MCBS v2.0 score is 3.
Discussion	Summary of main results	**NA**	Summary present, stating significant PFS benefit, tolerability, and early OS trend.
	Comprehensive risk–benefit including physical, financial, time toxicity	**NA**	Only physical toxicity is partially discussed. No mention of financial or time toxicity burden.

The table was developed with the data derived from the ASCO 2025 meeting abstract and the slides used to present the results, limiting the availability of the overall data. MCBS 2.0 score estimated using the available forms (form 2b), not an official ESMO score. Whether OS will be provided, and it shows improvement, it will prevail and scoring should be done according to form 2a. Whether QoL as at least secondary outcome will be provided, it may provide an upgrade.
Abbreviations: 2L, second line; AE, adverse event; BICR, blinded independent central review; CI, confidence interval; ESMO MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; HR, hazard ratio; HRQOL, health-related quality of life; NA, not available; OS, overall survival; PFS, progression-free survival; TNBC, triple-negative breast cancer.

We believe that ASCENT-04 signals therapeutic activity while highlighting unresolved dilemmas in trial design, including frontline use of later-line-approved agents and the true value of novel therapeutics.

Ethically, offering SG access post-progression, as provided in this trial, is not a liability but a standard every trial should uphold; concerns that cross-over will confound the OS results is unfounded: it will consolidate the notion on whether the upfront use of a new drug with no major advantage in term of safety is "truly" needed, as opposed to the current use in later lines. Speculatively, the anticipated OS gain in ASCENT-04 hovers between +1 and +3 months—based on the PFS gain, a magnitude that would fall markedly short of thresholds established by leading international benchmarks for substantial clinical benefit. According to the World Health Organization (WHO), a meaningful survival improvement in this setting requires a gain exceeding 6 months.[13] Similarly, under the ESMO Magnitude of Clinical Benefit Scale (MCBS v2.0),[14] considering the PFS in the control arm falling between 6 and 12 months (noncurative setting, form 2B), no OS data, no better safety and no QoL data, the anticipated MCBS 2.0 score for this new combination would be 3. In settings with limited OS, trials powered for survival can remain feasible, as focusing on clinically meaningful gains reduces required events and keeps time to analysis manageable and scientifically justified.[15,16] We advocate for future frontline TNBC trials to be powered for OS and QoL as primary endpoints, incorporating cross-over by design as appropriate, and reflect immunotherapy-pretreated modern cohorts. We strongly support the inclusion of biomarkers by design when using targeted agents, as we already vocalized in reviewing the overall landscape of ADCs clinical development in solid tumors.[17] We also emphasize the need for predefined biomarkers to assess ICI benefit, as the trial assumed its activity parallels chemo-immunotherapy. The pursuit of expedited approvals should never eclipse the epistemic duty to demonstrate tangible, patient-centered benefit. ASCENT-04 highlights that meaningful therapeutic progress depends not only on statistical significance or on endpoints that are difficult to communicate to patients, like PFS[18]—but in survival and people's well-being, guiding the treatment selection around patient-centric metrics. How, then, should ASCENT-04 be integrated into clinical practice? In its current form, the combination may offer value for patients experiencing relapse after a DFS of more than 12 months and could be considered an alternative in the frontline setting for more biologically aggressive disease for those patients who could not be treated with chemotherapy—with a case-by-case evaluation of ICI combinations, particularly for patients previously treated with ICI. However, its definitive role is still dependent on forthcoming OS and QoL data, which will be crucial in determining whether this strategy offers a patient-centered, practice-changing benefit by moving SG to the upfront treatment approach for all eligible patients.

Author contributions

Dario Trapani (Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Visualization, Writing—original draft), Carmine Valenza (Data curation, Investigation, Writing—original draft, Writing—review & editing), and Giuseppe Curigliano (Conceptualization, Funding acquisition, Supervision, Validation, Writing—original draft, Writing—review & editing). All authors reviewed and approved the final version of the manuscript.

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Conflicts of interest

G.C. reports financial interests with AstraZeneca, Celcuity, Daiichi Sankyo, Exact Sciences, Lilly, Merck, Novartis, Pfizer, Roche, Veracyte, Ellipsis, Astellas, Blueprint Medi-cine, BMS, Kymab, Merck, Novartis, Philogen, Relay Therapeutics, Sanofi; and non-financial interests with the Italian National Health Council as Advisor for Ministry of Health ESMO, ESMO as Clinical Practice Guidelines Chair, Europa Donna as Member of the Scientific Council, EUSOMA as member of the Advisory Council, Fondazione Beretta, Lega Italiana Lotta ai Tumori as member of Board of Directors. All the competing interests were outside the submitted work. All other authors have no potential conflicts of interest to disclose.

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