Editorial Commentary

Sacituzumab govitecan: ascending the treatment algorithm in triple negative breast cancer

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Sacituzumab govitecan has emerged as a promising new therapy in metastatic triple negative breast cancer (TNBC). Sacituzumab govitecan is an antibody-drug conjugate composed of an antitrophoblast cell surface antigen 2 (Trop-2) IgG1 kappa antibody coupled through a hydrolyzable linker to SN-38, a topoisomerase inhibitor and active metabolite of irinotecan. It received full Food and Drug Administration (FDA) approval on April 7th, 2021 for the treatment of unresectable locally advanced and metastatic TNBC after at least two prior lines of therapy based on the confirmatory results of the phase 3 ASCENT trial (1).

The ASCENT trial confirmed improved progression free survival (PFS) and overall survival (OS) with sacituzumab govitecan compared to chemotherapy. Accelerated FDA approval was first granted in April 2020 based on phase I/II data from a single group basket trial which showed a response rate of 33% in heavily pretreated 108 patients with metastatic TNBC, PFS of 5.5 months, and a median OS of 13 months (2). Subsequently, the ASCENT phase III trial randomized 468 patients in a 1:1 ratio to either sacituzumab govitecan or chemotherapy of the physician's choice (eribulin, vinorelbine, capecitabine, or gemcitabine). The primary endpoint was PFS and secondary endpoints were OS, objective response, and safety. The median PFS was 5.6 months (95% CI: 4.3–6.3 months) with sacituzumab govitecan *vs.* 1.7 months (95% CI: 1.5–2.6 months) with physician's choice chemotherapy (HR 0.41, 95% CI: 0.32–0.52, P<0.001). The median OS was 12.1 months (95% CI: 10.7–14.0 months) with sacituzumab govitecan *vs.* 6.7 months (95% CI: 5.8–7.7 months) with chemotherapy (HR 0.48, 95% CI: 0.38–0.59, P<0.001). The objective response rate was 35% with sacituzumab govitecan *vs.* 5% with standard chemotherapy drugs.

Interestingly, the benefit in PFS was seen in all predefined subgroups, regardless of age, >3 previous therapies, liver metastases, or previous use of PD-1 or PD-L1 inhibitors. Exploratory biomarker analysis suggests a benefit regardless of Trop-2 expression or *BRCA1/2* germline mutation status, however there were too few patients with low Trop-2 expression or positive *BRCA1/2* germline mutations in the trial to assess for statistical significance. Eighty percent of patients in the ASCENT trial had high or medium Trop-2 expression and only eleven patients had no Trop-2 expression. Patients with low Trop-2 expression had a numerically lower PFS (2.7 months, 95% CI: 1.4–5.8 months) compared to patients with high Trop-2 expression (6.9 months, 95% CI: 5.8–7.4 months). However, patients with low Trop-2 expression still had improved PFS with Sacituzumab govitecan compared to chemotherapy (1.6 months, 95% CI: 1.4–2.7 months) and the sample size was too small to make a definitive conclusion. Only 11% of patients in the Sacituzumab govitecan arm had a germline pathogenic variant in BRCA1 or *BRCA2* and mutation status did not appear to affect PFS (4.6 months in *BRCA1/2* positive *vs.* 4.9 months in *BRCA1/2* negative) (3).

The most common adverse events in the Sacituzumab

govitecan treatment arm were neutropenia (63%), diarrhea (59%), nausea (57%), alopecia (46%) and fatigue (45%). No grade 1 or grade 2 interstitial lung disease was reported, and one patient developed grade 3 pneumonitis. Serious treatment related adverse events were reported in 39 patients (15%) with sacituzumab compared to 19 patients (8%) with chemotherapy. However, discontinuation rates due to adverse events were similar in the two groups, occurring in 12 patients (5%) in each group. An exploratory analysis revealed that patients with UGT1A1 homozygous *28/*28 genotype (only 13.6% of the patient population in the ASCENT trial) were at a modestly higher risk of neutropenia, however the risk of diarrhea was not increased. UGT1A1 status did not alter recommendation for treatment or toxicity management but recommended close monitoring for known UGT1A1 *28 homozygosity (4).

The high response rates and improvements in PFS and OS seen with Sacituzumab govitecan in this third-line setting in metastatic TNBC are encouraging. Other single agent chemotherapies in this setting such as eribulin, carboplatin or docetaxel have similar median OS of 13.1 months (95% CI: 11.8–14.3 months) (5), 12.8 months (95% CI: 10.6–15.3 months), and 12.0 months (95% CI: 10.2–13.0 months) respectively (6). However, these drugs are often used in the first or second line setting, and indeed in the ASCENT trial, 100% of patients had received a prior taxane and 63% had received prior carboplatin.

Targeted therapies such as olaparib have shown an improved OS of 18.8 months after prior chemotherapy in the second or third line setting, however only 5% of all breast cancer patients carry a germline deleterious mutation in *BRCA1* and/or *BRCA2* (7). A clinical need remains for developing more treatment options in the second/third line setting in this rapidly progressing patient population. Thus, sacituzumab govitecan is an effective treatment option in this challenging clinical situation.

It is unclear whether patients with brain metastases benefit from sacituzumab govitecan. Patients with brain metastases that were stable for at least 4 weeks were allowed on the trial but capped at 15% and they were excluded from the primary end point analysis. A total of 61 patients in the trial had brain metastases at baseline and had previously received a median of 5 prior anticancer regimens. When these patients were included in the full patient population the median PFS (4.8 months, 95% CI: 4.1–5.8 months) and median OS (11.8 months, 95% CI: 10.5–13.8 months) were similar to the patient population that did not have brain metastases at baseline. However, subgroup analysis revealed median PFS of 2.8 months (95% CI: 1.5–3.9 months) with sacituzumab govitecan compared to 1.6 months (95% CI: 1.3–2.9 months) with chemotherapy and median OS of 6.8 months (95% CI: 4.7–14.1 months) with sacituzumab govitecan compared to 7.5 months (95% CI: 4.7–11.1 months) with chemotherapy. It is difficult to make conclusions in this small sample size but the small improvement in PFS and worse OS suggests that sacituzumab govitecan may have limited benefit in this patient population (8).

Several other clinical trials utilizing sacituzumab govitecan are currently underway. Efficacy in earlier lines is being investigated in NeoSTAR which is a phase II study of Sacituzumab in the neoadjuvant setting (NCT04230109) and in SASCIA which is investigating efficacy in patients with residual disease after neoadjuvant treatment (NCT04595565). Several combination trials are also currently underway including in combination with immunotherapy and PARP inhibitors (NCT04468061, NCT03424005, NCT03992131, NCT04039230). There are encouraging phase II data in the hormone positive breast cancer population and we eagerly await the results of TROPiCS-02 phase III data investigating Sacituzumab govitecan *vs.* chemotherapy in hormone positive metastatic breast cancer (NCT03901339).

The field of antibody drug conjugates (ADC)s is very promising and in the future there may be opportunities to sequence different ADC for maximal response. For example, the TROPION-PanTumor01 phase I trial showed datopotamab deruxtecan (a humanized anti-TROP2 IgG1 monoclonal antibody conjugated with DNA topoisomerase I inhibitor TOP1) had activity in a heavily pretreated population including patients with TNBC previously treated with Sacituzumab govitecan (9). Hopefully as more ADCs are developed, clinical trial data will inform where in the treatment algorithm these drugs are most effective and what is the optimal sequence. Ultimately, we need more therapeutics for patients with this very aggressive subtype of breast cancer.

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