**Peer Review File**

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**Reviewer A Comments:**

The treatment of triple negative breast cancer has been in full evolution in recent years. New treatment strategies are being incorporated, such as neoadjuvant treatment, already fully implemented, and the constant incorporation of new drugs, including Sacituzumab govitecan. The demonstration of its efficacy in late phases of the disease opens the door to its use in early phases. In this article, the authors provide a clear and concise review of the current status of Sacituzumab govitecan in the treatment of triple-negative breast cancer, as well as ongoing trials. Given the constant appearance of articles on new drugs in this disease, this type of article is well received when the subject is treated rigorously, as is the case.

**Reply:** Thank you for this review.
**Changes in text:** None

**Reviewer B Comments:**

This is an interesting and relevant topic to review.
More detail regarding the phase 1 study and stating the primary endpoint of studies would be important to include in your revision.
**Reply:** Considering the word count limitations, we are unable to add more details about the phase I trial (IMMU-132-01) without removing other information that we feel is more in line with the overall goals of the article. Primary endpoints of the ASCENT and TROPION-PanTumor01 trial have been added.
**Changes in text**: The primary endpoint was PFS--added for the ASCENT trial. The primary objectives were safety and tolerability--added for the TROPION-PanTumor01 trial.

Furthermore, discussion of the antibody, drug ratios, different linkers and payloads and the impact these have on efficacy would improve your manuscript
**Reply:** This information has been added into a table, as it could not be added to the main text due to word count limitations.
**Changes in text:** Table 3 (also included below).

Table 3: Components and Characteristics of Sacituzumab Govitecan and Datopotamab Deruxtecan

| Antibody-Drug Conjugate | Antibody | Target | Linker | Payload | Drug-to-Antibody Ratio |
|---|---|---|---|---|---|
| Sacituzumab govitecan | RS7 | Trop-2 | Hydrolysable | SN-38 | 7.6:1 |
| Datopotamab deruxtecan | Datopotamab | Trop-2 | Tetrapeptide-based, cleavable | Deruxtecan | 4:1 |

Trop-2, trophoblast cell surface antigen 2

Additionally, the following areas require some revision:

1. Introduction; to give the necessary context, it would be worth adding the timing of approval of TDM1 in advanced breast cancer.

**Reply 1:** I have added the dates for approvals of ado-trastuzumab emtansine and trastuzumab deruxtecan.
**Changes in text:** This led to FDA drug approvals for ado-trastuzumab emtansine in 2013 and the accelerated approval for trastuzumab deruxtecan in 2019 (3, 4).

2. Sacituzumab govitecan; line 62; whilst the overall rate of any grade toxicities is important, the rate of grade 3 or higher is also relevant and should be added here.

**Reply 2:** We have added the grade 3 toxicities.
**Changes in text**: The most frequent ≥ grade 3 adverse events with SG versus chemotherapy included neutropenia (51% vs 33%), leukopenia (10% vs 5%), diarrhea (10% vs <1%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%).

3. Data from the sub-group analysis in patients with brain metastases must be discussed given this affects 50% of patients with metastatic TNBC. Given the apparently low intracranial efficacy and poor prognosis in these patients, how do we best use this drug for this key patient group?

**Reply 3:** Results of this subgroup analysis are now included.
**Changes in text**: A subgroup analysis of 61 patients with brain metastases was also conducted (12). Compared to chemotherapy, SG improved PFS (2.8 months (95% CI, 1.5-3.9) vs 1.6 months (95% CI, 1.3-2.9)) and ORR (3% vs 0%) but not overall survival (6.8 months (95% CI, 4.7-14.1) vs 7.5 months (95% CI, 4.7-11.1)). Evaluation of this subgroup bears importance as many patients with TNBC develop brain metastases. However, the small sample size for the analysis impedes conclusive determination of the effect of SG on outcomes for patients with brain metastases.

4. Trop-2 expression; line 81; having a target for ADCs that is minimally expressed in normal tissues is key, this should be discussed for Trop-2.

**Reply 4:** Thank you for pointing this out. We have now noted that Trop-2 expression is lower in normal tissues.
**Changes in text**: Trop-2 is a transmembrane calcium signal transducer. It's expression is increased in multiple solid tumors when compared to it's expression in normal tissues, and therefore, is a reasonable drug target. Specifically, it has been shown that the majority of breast cancers express Trop-2, with increased levels associated with increased tumor growth and poor prognosis (5, 15, 16).

5. Trop-2 expression; line 98; there was a trend towards more benefit in patients with high expression of the target Ag which should be mentioned.

**Reply 5**: Added trend in benefit based on expression level of target Ag.
**Changes in text:** However, patients with high and medium Trop-2 expressing tumors treated with SG appeared to have numerically better ORR, PFS, and overall survival than tumors with low Trop-2 expression. In fact, ORR and PFS for the patients with high/medium Trop-2 expressing tumors were almost double that of the patients with low Trop-2 expressing tumors. The magnitude

of benefit in patients with low Trop-2 H-scores is difficult to decipher given the low number of patients in this group.

6. Line 105; please add a sub-heading for Dato-DXd. Would you agree that there appears to be some cross-resistance? Is this due to the target and/or payload?

**Reply 6:** Subheading for Dato-DXd has been added. Cross-resistance is possible; however, this would be speculation as we currently do not have enough knowledge to say from what exactly.
**Change in text:** Datopotomab Deruxtecan

7. There are some combination data for Dato-DXd with durvalumab from the BEGONIA trial (ASCO 2021 and ESMO breast 2022) which should be added and discussed here.

**Reply 7:** BEGONIA is mentioned in line 154 and in Table 2. We have added results from ESMO 2022.
**Changes in text**: BEGONIA is a phase Ib/II multi-arm trial investigating durvalumab in combination with multiple different agents, including Dato-DXd, in the first line setting for patients with metastatic TNBC. At a median follow-up of 3.9 months, initial results for the 27 patients receiving Dato-DXd plus durvalumab demonstrated an ORR of 74% (7% CR and 67% PR), warranting further enrollment and analysis in the expansion phase (32).

8. Line 114; given the incidence of ILD with this payload in Enhertu, you must comment specifically on cases of ILD with this drug (8% in the Tropion PanTumour01 including 3 grade 5 events).

**Reply 8:** Incorporated the incidence of ILD in the NSCLC dose analysis results
**Changes in text**: No drug-related interstitial lung disease (ILD) was observed in this TNBC cohort. However, during the dose analysis of 175 patients with metastatic NSCLC, 8% of patients experienced ILD, with three patients experiencing a grade 5 ILD (24). The rates of ILD were higher in the 8 mg/kg group (15%) than in the 6 mg/kg group (2%) and the 4 mg/kg group (2%). In the TNBC cohort, 95% of the patients were treated at a dose of 6 mg/kg and only 5% were treated at a dose of 8 mg/kg.

9. Lines 16-18; this is highly speculative and should be removed.

**Reply 9**: We have now added more information on TROPION-Breast02 and removed suggested speculation.
**Changes in text:** An ongoing randomized phase III trial, TROPION-Breast02 (NCT05374512), is comparing Dato-DXd versus investigator's choice chemotherapy (either paclitaxel, nab-paclitaxel, carboplatin, capecitabine, or eribulin mesylate). This trial is being conducted in the first-line setting for patients with metastatic TNBC who are not candidates for treatment with immune checkpoint inhibitors. If results confirm efficacy, Dato-DXd could become another option for treating metastatic TNBC.

10. Looking to the future; line 123; the results of the TROPICS-02 trial in ER+/HER2- breast cancer will be presented at ASCO, and Dato-DXd is already under study in this population, so these drugs are already being investigated outside TNBC, so your comment doesn't fit.

**Reply 10:** We have changed the wording to make the intention of our statement clearer.
**Changes in text:** Results of studies of the Trop-2-targeted ADCs have been clinically meaningful, and it remains to be seen whether using these agents as an earlier line of therapy or combining

them with other drugs could broaden their applicability. Additionally, as Trop-2 is expressed in most solid epithelial cancers, a role for Trop-2-targeted agents may exist in treating other subtypes of breast cancer as well. Multiple ongoing trials are evaluating Trop-2–targeted agents in these settings.

**11.** Looking to the future; please discuss advanced disease strategies first, then move on to early disease where we currently have no data. As above, TROPICS-02 is about to report. Also please add the SG/pembro first line study for PDL1+ TNBC.

**Reply 11:** Incorporating your feedback, we have re-ordered some paragraphs, and our discussion of advanced disease strategies now precedes the discussion of early disease. We also now discuss TROPiCs-02 results. Details of the Ascent-04 trial have been added to Table 1.

**Changes in text:** In the randomized phase III trial, TROPiCS-02 (NCT03901339), SG was evaluated in patients with metastatic HR+/HER2-negative breast cancer. Patients must have progressed on at least two, but no more than four, prior chemotherapy regimens. Prior taxane, hormonal treatment, and cyclin-dependent kinase 4/6 inhibitors were all required for eligibility. Patients were randomized to either SG or physician's choice of chemotherapy (eribulin, capecitabine, gemcitabine, or vinorelbine). Primary results were presented at the 2022 American Society of Clinical Oncology Annual Meeting. Median follow-up was 10.2 months. PFS, the primary outcome, was longer in the SG arm than in the chemotherapy arm (5.5 versus 4.0 months (HR 0.66 [95% CI, 0.53 – 0.83]; $P = .0003$)) (25). Results of this first interim analysis showed that overall survival was longer with SG, albeit not significantly (13.9 versus 12.3 months (HR 0.84 [95% CI, 0.67 – 1.06]; $P = .143$). Results of subgroup analyses demonstrated improved benefit from SG across all subgroups, including older patients (> 65 years), patients with visceral metastases, and those with ≥ three lines of chemotherapy in the metastatic setting. These are encouraging results, especially since patients with metastatic HR+/HER2-negative breast cancer who exhaust their oral treatment options often have less durable responses with each additional line of cytotoxic chemotherapy. On the basis of these primary results, SG could be considered another potential treatment option for patients with metastatic HR+/HER2-negative disease who have progressed through multiple lines of chemotherapy.

**12.** Lines 140-142; even if SASCIA were positive, this needs to fit into newly approved regimens such as pembro for stage 2-3 TNBC, adjuvant Olaparib for BRCA mutation-associated high risk cancers. Please delete this sentence and comment on integration with current standards**.**

**Reply 12:** We have reworded the sentence to clarify that there are other options/SOC for this patient population.

**Changes in text:** A clear need exists for improving outcomes in patients who are deemed high risk and do not attain pCR. If the results of SASCIA show that SG improves invasive disease-free survival, then SG is likely to become another option for treating residual disease in patients with high-risk primary HER2-negative breast cancer.

**13.** Lines 150-151; a press release has already informed us that TROPICS-02 is positive, so it will become an option, but the question is more where to position it in relation to other SOC chemo as patients were permitted to have 2-4 prior lines of chemo, so it will be useful to see whether sub-group analysis shows any attrition of the benefit in later lines. Also need to consider toxicity compared to, e.g., oral regimens without the risk of hair loss.

**Reply 13**: Results of TROPICs-02 incorporated.

**Changes in text:** Please see Comment 11 for details of changes.

**14.** Conclusions; suggest re-write the final paragraph. You have not alluded to how patients may be selected/how we best sequence in the body of the review, so it feels rather cursory to add it here.

**Reply 14** Final paragraph has been rewritten to better reflect body and to include edits based on comments from Reviewer C.

**Changes in Text:**The treatment paradigm for metastatic TNBC has evolved since 2020 when the first checkpoint inhibitor was approved and when PARP and NTRK inhibitors became treatment options for patients harboring the appropriate biomarkers. ADCs represent the latest treatment advancement. ASCENT was the first trial to show that treatment with an ADC improved overall survival for metastatic TNBC in a patient population unselected for biomarkers. With the approval of SG in the second line setting and beyond, an effective treatment option now exists for patients, regardless of their biomarkers. Patients with PD-L1–positive tumors can receive SG after progression on their first line chemoimmunotherapy. In the ASCENT trial, 29% of patients had previous exposure to a PD-1/PD-L1 inhibitor. A subgroup analysis of PFS showed that regardless of previous exposure to PD-1/PD-L1 inhibitors, PFS was longer in patients receiving SG compared to chemotherapy. For patients with BRCA mutations, it is reasonable to sequence SG after a PARP inhibitor, as PARP inhibitors are effective in this population, and since these drugs are administered orally, treatment is less cumbersome. Patients with BRCA mutations who had received prior PARP inhibitors comprised 7% of the ASCENT population.

With the compelling overall survival results from the ASCENT trial and initial response rates from results of the TROPION-PanTumor01 trial, Trop-2 targeted ADCs appear to be not only efficacious, but appropriate for a broad patient population, as they do not require expression of a specific biomarker (based on the current data). It is possible that moving ADCs to the front-line, as monotherapy or in combination, could result in greater benefit. As previously described, efforts are underway to investigate ADCs in the metastatic setting in earlier lines, and in combination with other agents. Furthermore, multiple trials are now investigating ADC incorporation into the neoadjuvant/adjuvant setting for early-stage HER2-negative breast cancer. As these trials and other ADC trials in breast cancer continue to accrue and report results, more information will be available to guide further incorporation of Trop-2-targeted ADCs into our treatment algorithms.

**15.** Table 1: please add the first line SG +/- pembro study.

**Reply 15:** We have added details of the Ascent-04 trial; details of SACI-IO already in Table 1.
**Changes in Text:** Please see Table 1

**16.** Table 2: You haven't mentioned other Trop 2 ADCs in development such as SKB264 for which phase 1 data were presented at ESMO 2021.

**Reply 16:** Although we acknowledge other Trop-2 ADCs in development, given the word count limitations and request to provide commentary on the ASCENT trial specifically, we do not feel that we can provide enough insight into each trial/drug if we were to include other Trop-2 ADCs in development. We hope that by focusing on SG (Table 1) and Dato-DXd (Table 2), which are further in development/trials, we have provided more in-depth information and practical insight for the audience.

**Changes in Text**: This editorial commentary will focus on the Trop-2 directed ADCs that have thus far been evaluated in phase III trials.

## Reviewer C Comments:

1. Could you please add your perspectives on sequencing sacituzumab govitecan in mTNBC by specific biomarkers.

**Reply**: Incorporating your comment and that of another reviewers, changes have now been made to the final two paragraphs.
**Changes in text:**
The treatment paradigm for metastatic TNBC has evolved since 2020 when the first checkpoint inhibitor was approved and when PARP and NTRK inhibitors became treatment options for patients harboring the appropriate biomarkers. ADCs represent the latest treatment advancement. ASCENT was the first trial to show that treatment with an ADC improved overall survival for metastatic TNBC in a patient population unselected for biomarkers. With the approval of SG in the second line setting and beyond, an effective treatment option now exists for patients, regardless of their biomarkers. Patients with PD-L1–positive tumors can receive SG after progression on their first line chemoimmunotherapy. In the ASCENT trial, 29% of patients had previous exposure to a PD-1/PD-L1 inhibitor. A subgroup analysis of PFS showed that regardless of previous exposure to PD-1/PD-L1 inhibitors, PFS was longer in patients receiving SG compared to chemotherapy. For patients with BRCA mutations, it is reasonable to sequence SG after a PARP inhibitor, as PARP inhibitors are effective in this population, and since these drugs are administered orally, treatment is less cumbersome. Patients with BRCA mutations who had received prior PARP inhibitors comprised 7% of the ASCENT population.
With the compelling overall survival results from the ASCENT trial and initial response rates from results of the TROPION-PanTumor01 trial, Trop-2 targeted ADCs appear to be not only efficacious, but appropriate for a broad patient population, as they do not require expression of a specific biomarker (based on the current data). It is possible that moving ADCs to the front-line, as monotherapy or in combination, could result in greater benefit. As previously described, efforts are underway to investigate ADCs in the metastatic setting in earlier lines, and in combination with other agents. Furthermore, multiple trials are now investigating ADC incorporation into the neoadjuvant/adjuvant setting for early-stage HER2-negative breast cancer. As these trials and other ADC trials in breast cancer continue to accrue and report results, more information will be available to guide further incorporation of Trop-2-targeted ADCs into our treatment algorithms.

2. Relapse time (DFI<12mon)

**REPLY**: The relapse time frame is addressed in initial draft: This improvement in efficacy with SG was also observed in a subgroup analysis of patients who relapsed within 12 months of (neo)adjuvant therapy (10); this was notable because patients with early relapses (≤ 12 months) are likely to have more aggressive disease (11).
**Changes in text:** None

3. And toxicities respectively?

**REPLY:** The toxicities are addressed in initial draft: Treating providers must be prepared to support SG-treated patients with granulocyte colony-stimulating factors, dose reductions, and anti-diarrheal medications, as myelosuppression and diarrhea are common side effects. Neutropenia occurred in 63% of patients treated with SG versus 43% of those treated with chemotherapy, anemia in 34% versus 24%, and diarrhea in 59% versus 12%. The most frequent ≥ grade 3 adverse events with SG versus chemotherapy included neutropenia (51% vs 33%), leukopenia (10% vs 5%), diarrhea (10% vs < 1%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%). Additionally, an analysis of the effects of SG on health-related quality of life (HRQoL) in the ASCENT trial was conducted (13). HRQoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire, which was administered at baseline, on the first day of each cycle, and one month after therapy completion. The results showed that treatment with SG was associated with significantly better HRQoL outcomes than chemotherapy was, including improved global health status and extended time until quality of life deterioration. Although SG was more often associated with diarrhea, nausea, and vomiting, these outcomes did not significantly impact global health status, QoL, or functioning domains.
**Changes in Text:** None