Peer Review File

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Reviewer A Comments:
This is an interesting commentary to the Ascent trial results, written by experts in Trop2 biology. Some minor points should be addressed:

Comment 1: The discussion on the Pfizer mAb is a bit too long - since the development of that drug has been discontinued.

Reply 1: We have updated the text accordingly.

Comment 2: The commentary could probably benefit from a very short discussion on the newest mAb in class, datopotamab-DXd. Its early phase results have been reported at the SABCS symposium: different toxicity (due to the difference in the linker?) but apparently cross-resistance with SG (same class of payload) and could nicely fit in the pro/cons discussion of SG.

Reply 2: Thank you for your update request. We have integrated our text accordingly.

Reviewer B Comments:
Comment 1: Consider rephrase the title to: "The anti-Trop-2 antibody-drug conjugated sacituzumab govitecan - effectiveness, pitfalls and promises".

Reply 1: We have rephrased the title as suggested.

Comment 2: Line 32: consider to change 'shown' to 'confirmed', since the 2020 accelerated approval was not based on ascent but on IMMU-132-01phase 1/2 basket study results in the TNBC cohort. Now it reads as the accelerated approval was based on ASCENT. Consider to add the info on the basket truly shortly. (I later saw it was in in line 49, maybe this info better suits after info on accelerated approval).

Reply 2: This is a good point. Of course, ASCENT was a randomized trial, with corresponding added value. We thus shifted our taking from 'shown' to 'validated'.
Appropriate reference to the IMMU-132-01phase 1/2 trial has been added at the first mention of the FDA approval.

Comment 3: Line 34: 468 pts was the number in primary analysis population (without baseline brain mets), total number of randomized pts was larger.

Reply 3: We have rephrased the text accordingly.

Comment 4: Line 42: essentially no impact might be considered a too strong statement, given the small subgroups and abundance of statistical analysis in this subanalysis. Only the PFS in this arm

is mentioned, as such the impact of SG is not really shown. I would reconsider phrasing here. Same for OS: profited the most might not be the optimal terminology, benefit of SG vs TPC in these separate subgroups was not assessed statistically. The differences seemed lower in trop2 low group, but this was also the smallest group, with also worse outcomes in the comparator arm in this cohort. Now prognostic and predictive associations seem to be confused with this wording from line 41 through line 48. The ORR was still 22% for SG in Trop2 low subgroup (which is a big deal in heavily pretreated TNBC).

Reply 4: Thank you for your comment. We have added specific comments and rephrased the text accordingly.

Comment 5: Line 45: here ORR is defined, but objective response is noted in line 39; better to align and define the abbreviation at first use.

Reply 5: We have rephrased the text accordingly.

Comment 6: Line 47-48: 'supporting SG clinical efficacy in TNBC through specific targeting of Trop-2': little unclear, when this statement would relate to the fact that it can be concluded from this subgroup to implement trop2 as predictive biomarker to decide whether or not to use S, this could be considered suboptimal in current landscape. Tissue samples in ASCENT evaluated for Trop2 could be both from early and advanced setting, and it is unclear in what extent temporal changes in Trop2 expression may occur in TNBC. Limitations could have been mentioned.

Reply 6: This is a good point. A major limitation of this analysis inevitably was its post-hoc nature.

Comment 7: Line 55-57: here ORR is written in full, and objective is used, in line 57 abbreviation ORR is used; align throughout.

Reply 7: We have aligned the text throughout.

Comment 8: Line 60: strange to mention RECIST criteria here, I would do this at first definition of ORR, and not later in the manuscript.

Reply 8: We have re-drafted the text accordingly.

Comment 9: Line 63: consider to mention here somewhere the approval of SG for bladder cancer.

Reply 9: We have added it to the manuscript, thank you.

Comment 10: Line 70: this trial was not limited to TNBC, but a basket trial as outlined in lines 49-53.

Reply 10: We have clarified this point.

Comment 11: Line 142: This together with some considerations above truly makes the manuscript in its current form read as positively biased towards datopotamab deruxtecan. Moreover, one would expect to see Trop2 ADC's listed in table 1 when reading this sentence in the conclusion, but the table gives an overview of the FDA approved ADC's which might be considered less appropriate in this editorial commentary.

Reply 11: Thank you for raising this and the preceding issues. No bias was implied, and a more balanced mention of datopotamab deruxtecan is provided. We have re-drafted the remainder of these sections accordingly.
We agree that an overview of the FDA approved ADC's may be less appropriate in this context, versus the paucity of citable anti-Trop-2 ADCs. We have re-drafted our text accordingly.

Reviewer C Comments:
This is a concise, well written and balanced review of the anti-Trop2 antibody drug conjugate sacituzumab Govitecan, which is a "first in class" innovative treatment for a very difficult disease to treat, namely advanced triple negative BC. After summarizing the key efficacy/safety features of the drug in the pivotal phase 3 "Ascent" trial, the authors underline specific weaknesses of the compound, the most important ones being a suboptimal selectivity of preferential Trop2 targeting on cancer cells and a large systemic release of the payload. They rightly conclude that research of improved Trop2 antibody drug conjugates is worthwhile. Here are 3 proposed additions to the review:

Comment 1: A reminder that until SG no topoisomerase I inhibitor was used in metastatic TNBC: irinotecan as a free drug was too toxic and pegylated irinotecan's development was not pursued. So, SG brings on board a "new" cytotoxic in the treatment of a disease that still heavily depends on "chemotherapy".

Reply 1: Thank you for your comment. We have re-drafted the text accordingly.

Comment 2: A brief explanation on why Trop2 levels do not need to be measured in the clinic: indeed, only a modest proportion of advanced TNBC have low levels of Trop2 (10-15%).

Reply 2: Thank you for raising this issue. We have introduced comments to this end, for a better discussion of the issue.

Comment 3: A reference to the recently demonstrated clinical activity of DATOPOTAMAB deruxtecan in advanced TNBC (San Antonio breast cancer conference 2021) and how this drug differs from SG.

Reply 3: We have added this reference to the manuscript.

Reviewer D Comments:
The editorial is generally well written, but there are several issues that the authors should address.

Comment 1. Page 2 line 39: Might be useful to include breakdown of PR and CR for this % (as done below).

Reply 1: We have added the corresponding data to the manuscript.

Comment 2: Page 2 line 41: Please mention how the level of Trop-2 expression was determined, i.e., by immunohistology.

Reply 2: We have mentioned that Trop-2 expression was determined by immunohistochemistry.

Comment 3: Page 3 line 64: Another early trial showed efficacy in SCLC.

Reply 3: We have added reference to the Gray et al. trial.

Comment 4: Page 3 Line 86. It would be important here to note that drug associated with the Trop-2 antibody; i.e., a Dolastatin 10 analogue, which is akin to the more potent auristatin agents that are microtubule inhibitors.

Reply 4: Thank you for raising this issue. We have highlighted this information to the text.

Comment 5: Page 4 line 103: I think this comment is misleading.
First, stating that there is a large systemic release of SN-38 might infer the conjugate falls apart quickly. Preclinical data (Sharkey et al. Clin Cancer Res. 2015 Nov 15;21(22):5131-8) and the data by Ocean et al., ref #18, and to some degree by Pandey et al, Anal Chem. 2020 Jan 7;92(1):1260-1267.) does not substantiate this claim.
Secondly, the statement infers that the anti-tumor activity of the conjugate is related primarily to release of SN-38 into the serum; however, other publications have indicated there is specific uptake of the conjugate related to Trop-2 targeting (Goldenberg et al. Oncotarget. 2015 Sep, 8;6(26):22496-512).
Thus, the sentence should be revised.

Reply 5: Thank you for raising this issue. Data in the literature provide a multi-faceted scenario. We have extended this discussion and revised our text accordingly.

Comment 6. Page 4 line 121: I think this last sentence is over-reaching. Yes, the targeting of normal tissues with an anti-trop-2 antibody coupled stably with a very potent drug appears to lead to target-related toxicities to some of the Trop-2 expressing normal tissues, but there is no evidence suggesting that the efficacy of the agent was affected by a reduction in the level of conjugate reaching the tumor.
Your next paragraph better explains the different toxicity profile. Thus, the agent was discontinued due to the different toxicity profile compared to sacituzumab govitecan, which likely represented the targeting of accessible Trop-2 on normal tissues (such as the skin) with a much more potent and stably-linked drug.

Reply 6: We appreciated your comments, and revised the text accordingly.

Comment 7: For a more complete assessment of ADCs targeting Trop-2, the authors should also cite the work with Datopotmab deruxtecan, and anti-Trop-2 conjugate with a camptothecin derivative.

Reply 7: Thank you for suggesting this integration. We have added a reference to ongoing work on Datopotmab deruxtecan as from the 2021 SABCS.