Peer Review File

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The author thanks both reviewers for their candid perspectives and thoughts related to the submitted paper. Author maintains the paper is coherently organized.

- Introduced the concept of destiny in relation to the clinical trial
- Questioned whether the outcomes of the trial were destined to happen
- Supplied tangible data to support the idea that the results were not unexpected
- Discussed the potential implications of the disparate tumor targets
- Provided insight regarding the down- and up-sides of unequal randomization
- Detailed the features of the ADC which may contribute to its efficacy
- Proffered final comments

Below are responses to each reviewer's comments. All modifications are indicated in red.

Reviewer A

1. This is a commentary written by a pharmacologist in a tone that is not helpful for the reader. Although literary or public comparisons may add interest to a paper the inital 2 sentences do not make sense in the greater context of the paper. Why personifies a drug?

Reply: First, the author is not a pharmacologist but rather an academician with significant clinical and research/scholarship responsibilities. Second, the temper (of the text) was not intended to be condescending, but rather illuminating. Furthermore, simply stating that the paper is written "in a tone that is not helpful for the reader" is an extremely vague (i.e., not helpful in what manner?) criticism. Nonetheless, the author modified the first two sentences which, incidentally, were written initially to humanize the concept of destiny, NOT to personify the drug as inferred (see Page 2, lines 29-31).

2. The comments about Destiny imply that this ADC would have had great efficacy regardless or that AstraZeneca had some prior knowledge about the drug before launching their trials Names of trials are sometimes chosen after the phase I and this may have been done but it is not very relevant to the paper.

Reply: The reality is that the author used phases 2 and 3clinical trial data to support the argument related to the posited efficacy of the ADC in DESTINY 02, NOT what the reviewer implies as the thoughtless rumination of the author alluding to any preconceived (prior to early clinical trials) knowledge of the efficacy of T-DXd. In addition, the text contains the following statement "since the closure of the phase 2 DESTINY 01 trial coincided with the opening of DESTINY 02, it is conceivable that some of the positive outcomes (with T-DXd) from the earlier trial were already beginning to materialize in a population of subjects whose prior therapies included trastuzumab and T-DM1; and in who, more than 50% previously received pertuzumab or other anti-HER2 therapies" (see Page, lines 56-60). Furthermore, this author has no knowledge of why the trial was called DESTINY rather than any other

name. Instead, the trial name was used in the manner explained in the beginning of the commentary. This author is also well aware that naming (of clinical trials) usually occurs after conclusion of phase 1 trials. Arguably, the name of this clinical trial is indeed relevant to all oncologists specializing in breast cancer because of its association with one particular ADC.

3. The results of the trials are presented in a confusing and difficult to read manner. For those of us very well versed in the development of this drug one can follow them but for anyone with less knowledge it is poorly organized.

Reply: while the commentary may generate widespread readership, this author suspects that most of the readers will be breast cancer specialists and familiar with available anti-HER2 agents; and therefore, as the reviewer implies, "very well versed" with the developmental process of this agent. Nevertheless, the author added a table (see Table 1) which organizes all of the relevant data of the various studies. Of note, reviewer B did not indicate any negative aspects regarding the organization of the material presented.

4. There are 2 sides to a therapy - one is the efficacy and the other the toxicity. The toxicity of the ADC is not mentioned and although as clinical researchers and physicians one balances that, a commentary needs to also comment and provide balance.

Reply: this comment has merit. In order "balance" the data, safety issues were added to the text (see Page 5, lines 113-122 and Table 1).

5. The comments on 2 to 1 randomization trivialize the concept. These designs do require more enrollment which one could argue provide more data on safety and that is good. They do increase the enthusiasm in some situations for participation. They often take longer to get OS results. None of this is discussed in the commentary. The disparaging tone is not appropriate.

Reply: although unequal allocation if not uncommon in the conduct of confirmatory trials, the inclusion of the discussion was to highlight some of the relevant issues associated with this type of randomization scheme. Moreover, it hardly seems trivial when the discussion involves ethics, statistical power, patient number and recruitment, as well as data acquisition. Nonetheless, parts of the section have been modified as appropriate to provide discussion balance (see Page 5, lines 131-149).

6. At the end of the commentary, we do know that T-DxD has been shown superiority in terms of PFS to TDM-1 but the commentary does not teach us anything new nor present the known data in a clear manner.

Reply: debatably, much of what is contained regarding the molecular construct of T-DXd is not common knowledge among practicing oncologist; the author sees no need to modify the message.

7. The mechanism of action discussion is comprehensive but out of date as the bystander effect is now being questioned as to the mechanism.

Reply: regarding the integrity of the bystander effect, the author realizes this effect is controversial and hence, chose to state that this "property is believed to facilitate", a statement that is not absolute. A partial disclaimer is added to the text (see Page 3, lines 66, 73, and 79).

Reviewer B

This editorial commentary deals with the DESTNY-Breast02 study, which compares T-DXd vs. TPC for patients with HER2-MBC previously treated with T-DM1.
I recommend the author to revise the following points.

1. Human EGFR-Related 2-positive (HER2+) should be corrected into Human epidermal growth factor receptor 2 (P2L34).

   Reply: modified as indicated (see Page 2, line 33).

2. The author needs to cite the DESTINY-Breast09 (NCT04784715). (p4L110).

   Reply: cited as indicated (NCT number): NCT04784715 (see Page 4, line 108).