Peer Review File

Article information: https://dx.doi.org/10.21037/cco-23-72

Reviewer A

The authors have written an up-to-date review of HER2 targeted agents in GI cancers. Some clarification about recent studies needs to be made, as well as indicating that supposedly ongoing trials have actually been terminated. The review is modest and very readable with a clinical focus.

Specific comments are outlined below:

Introduction: The word "appertains" is poor phrasing. Specific nature of amplification should be clearly spelled out here, which can include gene amplification, mRNA expression, and actual protein expression (which appears to be the most clinically relevant to identify HER2 responsiveness).

- Reply: appreciate the comment on phrasing. About the nature of HER2 overexpression, we did specify gene amplification as the main mechanism, which would directly translate to overexpression of mRNA and, subsequently, of the protein.
- Changes in the text: line 44, changed "appertains" to "belongs". Line 45, specified "… mainly owing to gene amplification"

Page 6: The statement should be clarified with the added comment that trastuzumab was effective in IHC2+/FISH positive, albeit less than IHC 3+. The TOGA trial is mysteriously referenced to indicate the combination of trastuzumab with 3 drug regimens and with? bevacizumab? Any mention of bevacizumab should be deleted, this agent has no role in first line treatment. Is this reference citation incorrect? This has to be corrected or commentary deleted.

- Reply: thank you for the thoroughness, the reference was indeed incorrectly cited.
- Changes in the text: line 104, changed "this study" to "this metanalysis" to provide more clarity on the reference study. Line 105, corrected and updated the reference

Page 7: there is an incorrect comment that the published KEYNOTE 811 trial makes no mention of PDL-1 and efficacy. There is a Forrest plot in the paper indicating that for CPS cancers < 1% the response rate advantage falls to 5%. It should be commented that benefits were greater for IHC 3+ compared to IHC 2+/FISH+. The phrasing about comparable toxicity for the tras plus pembro arm was seen is poor and confusing. Just state that toxicity was not significantly enhanced with the addition of pembro.

- Reply: appreciate the comments on the phrasing. The subgroup analysis with

the forrest plot from KEYNOTE 811 did indeed suggest possible ORR benefit that is only associated with tumors with CPS of 1 or higher and IHC 3+. However, the interim analysis of this study (and the study itself) is not designed to detect significant differences based on this subgroup and the forrest plot was not the result of a multivariate analysis. Therefore, caution on overinterpretation of the subgroup analyses is warranted (please see Spears et al., Ann Oncol, 2017 for full commentary on subgroup analysis). Lastly, our comment on the efficacy based on PD-L1 subgroup was referring to survival outcomes (OS and PFS).

- Changes in the text: line 110 – line 113: we added brief commentary about subgroup analysis. Line 112-line113: as suggested, we rephrased and simplified that the safety profile of this regimen was manageable. Line 115: we changed "efficacy" to "survival benefit" avoid confusion.

The comment that TDXD had "no advantage" for IHC2+/FISH+ is an overstatement. This was a relative minority of patients, and perhaps "lesser benefit" compared to IHC3+ is more accurate.

- Reply: appreciate the suggestion on the phrasing
- Changes in the text: line 136 – added "less likely (with the IHC22/FISH+ group)."

The MAHOGANY trial has been terminated by the company; it is not ongoing. The authors cite the ongoing first line zanidatamab trial which should be more explicitly spelled out (the HERIZON trial), and there has to be discussion of the predecessor phase 2 trial combining zanidatamab with first line chemo regimens indicated striking response (75%) and PFS (1 year) and OS (exceeding 1 year). The phase 2 needs to be cited and discussed as this provided the rationale for the phase 3 trial.

- Reply: appreciate the thoroughness and the information about the MAHOGANY trial, which was indeed terminated by the company, but its information on clinicaltrial.gov was outdated and misleading, therefore, generating confusion from our end. About HORIZON, appreciated the comment
- Changes in the text: line 143-147 – deleted the comments on the MAHOGANY trial to simplify the content and avoid confusion. Line 150 – 155: we added the phase 2 data on zanidatamab plus chemothrapy

Page 9: What does "as opposed to GEC, chemotherapy remains the first-line choice in CRC." This is a fallacious statement. We do not give HER2+ GEJ cancers HER2 targeted therapy without chemotherapy. This statement needs to be corrected.

- Reply: appreciated the comment
- Changes in the text: line 166-167 – we rephrased and specified that anti-HER2 therapy is "part of the first-line therapy (for gastroesophageal cancer)".

Clarifications are required. MOUTAINEER did not allow prior HER2 targeted therapy. However, DESTINY-CRC02 has some prior HER2 treated patients. Activity was seen in both HER2 prior treatment and no prior HER2 treatment. Also as reported at ASCO

this year activity was also seen in RAS mutant patients, which distinguishes this agent from the others discussed. It should be clarified that the lower TDXd dose was favored on this trial.

- Reply: appreciated the comment
- Changes in the text: line 207-210 – added ORRs based on anti-HER2 therapy exposure, and specified the lower incidence of ILD in patients receiving lower dosage of T-DXd

Page 12: Future perspectives. Loss of HER2 expression is likely not the only resistance mechanism. Indeed, the Japanese Destiny phase 2 trial did not require repeat HER2 testing or HER2 overexpression retention. The Western DESTINY 02 trial however was more stringent and required HER2 overexpression be retained. Despite this the two trials yielded identical results. There also should be some comment about the demonstrable activity for TDXd seen in lower HER2 expressing gastric cancers, but not the case in CRC.

Other resistance pathways, including developing of amplification of MET, EGFR, and other abnormalities affecting cross resistance pathways such as activating mutations in the PI3kinase/AKT pathway, need to be mentioned.

- Reply: appreciated the comment
- Changes in the text: line 248-249 – rephrased and added PI3K pathway as an example of mechanism of resistance

Reviewer B

1. Please indicate the full name of "HR", "CI", "PD-L1" in the main text. All abbreviated terms should be full when they first appear.
- addressed

2. Tables: - addressed

1) Table 3 is missing to cite in the main text.

2) Please indicate the full name of "T-DXd" in Table 2 footnote.

3) Table 1: "HR" is missing in below data.

Bang et al. (ToGA) (22)	First line	Gastric or gastroesophageal adenocarcinoma	3	Cisplatin plus a fluoropyrimidine	Trastuzumab plus control	47% vs. 35%	13.8 vs. 11. months (0.74, 95% CI 0.60-0.91, p=0·0046)	Post-hoc analysis showed OS benefit only in the IHC2+/FISH+

4) Table 2: Should the below word be "IHC"?

Siena et al. (DESTINY-CRC01) (49)	Two or more previous regimens, including prior	2	NA	Fam-trastuzumab deruxtecan	Cohort A (ICH3+ and 2+/FISH positive): 45.3%	Cohort A: 5.4 months