Peer Review File

Article Information: https://dx.doi.org/10.21037/jgo-24-284

Reviewer A

Comment 1:

The comment is very clear and easy to understand.

The PARADIGM study also presented a prognostic analysis stratified by biomarkers that can be measured in clinical practice and by tumor site (left/right).

(Kentaro Yamazaki et al., Efficacy of panitumumab in patients with left-sided disease, MSS/MSI-L, and RAS/BRAF WT: A biomarker study of the phase III PARADIGM trial.. JCO 41, 3508-3508(2023). DOI:10.1200/JCO.2023.41.16_suppl.3508)

It would be even more instructive to comment on this one as well.

Reply 1: we added some data to our text (see Line 35, page 01) and we added 1 reference to support it (see Line 158, page 04)

Changes in the text:

Furthermore, a prognostic analysis stratified by measurable biomarkers in clinical practice and by tumor side was performed. Its results support reinforce the use of panitumumab plus mFOLFOX6 as a first-line treatment for patients diagnosed with left-sided, microsatellite stable, RAS/BRAF wild-type tumors [8].

Reference added:

8.- Kentaro Yamazaki et al., Efficacy of panitumumab in patients with left-sided disease, MSS/MSI-L, and RAS/BRAF WT: A biomarker study of the phase III PARADIGM trial.. JCO 41, 3508-3508(2023). DOI:10.1200/JCO.2023.41.16_suppl.3508.
(see Line 158, page 04)

Reviewer B

The authors provide a brief commentary on the on the paper, "Negative hyperselection of resistance mutations for panitumumab maintenance in RAS wild-type metastatic colorectal cancer (PanaMa phase II trial, AIO KRK 0212)". The authors conclude that primary tumor location, as well as hyperselection based on solid or liquid DNA-testing, endorse the correct identification of mCRC patients who may benefit from first-line treatment with anti-EGFR combined with chemotherapy and that prospective validation is warranted to translate these findings into generalized clinical practice.

The manuscript is generally well written and discusses an important research question for precision medicine in colon cancer.

Comments

Major

1. Provide the definition of negative hyperselection that was used in the PanaMa trial [i.e., the genes included on the hotspot panel and/or IHC).

Reply 1: we have modified our text as advised (see Line 82, page 02)

Changes in the text: The negative hyperselected mutation subgroup was defined by the identification of one or more pathogenic tumor point mutations of the following genes: RAS, BRAF-V600E, AKT1, PTEN, PIK3CA-exon 9/20, ERBB2, ALK1 and or HER2/neu overexpression.

2. Confirm whether this analysis was prespecified. If one looks back at the ASCO presentation of this data from 2022, the definition of negative hyperselection was a little different in that HER2 overexpression by IHC was not included in the 2022 definition.

Reply 2: We confirmed that this analysis was prespecified according to the following publication Clin Cancer Res. 2024 Apr 1;30(7):1256-1263.
Line 2 - second paragraph of the referred publication, point out that the analysis was pre-specified.
Line 1 of the discussion of the referred publication indicates that the analysis was pre- specified.

Changes in the text: no changes in text were done

Comment 3: 3. Consider commenting on the genes included in the definition of negative hyperselection. There is currently more data for the use of negative-selection with respect to KRAS, NRAS, BRAF, and HER2 amplification, than there is for the other genes included in the definition of negative hyperselection. Further, alterations in PIK3CA or PTEN can co-occur with KRAS or BRAF mutations, or can occur on their own without these MAPK pathway co-alterations. Should patients with alterations in PIK3CA, AKT1, or PTEN genes (in the absence of KRAS, NRAS, BRAF mutations, or HER2 amplification) be excluded from receiving anti-EGFR therapy?

Reply 3: Thanks for your comments. We consider that data publish in the literature in this matter is equivocal in different trials. Therefore, we consider that we don't have enough robust evidence to discuss this issue properly in this editorial.

Changes in the text: no changes in text were done

4. In the closing sentence the author calls for prospective validation of the study findings. Consider proposing how this could be ethically done as it would be unethical to prospectively give anti-EGFR therapy to KRAS/NRAS/BRAF V600E mutated patients.

Reply 4: Thanks for the comments.
As Stahler & Co mention in their own publication on Clin Cancer Res. 2024 Apr 1;30(7):1256-1263, there are some limitations in the analysis and therefore the results should be interpreted with caution. This is why they consider that prospective trial should be considered. We agree with their opinion. Furthermore, we consider that this should be mentioned in the editorial. On the other hand, in our opinion, how this prospective trial must be designed and the limitations of conducting such trials, are beyond the scope of this editorial. Investigators and collaborative groups are those who may evaluate and answer, how and when these prospective trials may be developed.

Changes in the text: no changes in text were done

Minor
5. On line 63, correct the abbreviation for EGFR, which is currently written as "EFGR"

Reply 5: we have modified our text as advised
Changes in the text: we modified our text to EGFR, as indicated (see Line 73, page 02)

6. On line 73, add a space to "with162".
Reply 6: We have modified our text as advised
Changes in the text: we add space to with 162 (see Line 86, page 02)

Reviewer C

I would like to congratulate the authors on their work. However, I have a few comments on the article:

1. The second paragraph is too short and needs to be expanded. Please add a description of the previous use of other anti-EGFR agents in the treatment of colorectal cancer. In fact, the use of bevacizumab has revolutionized this type of treatment. Please read these articles and add their references:
- Aquino de Moraes FC, Dantas Leite Pessôa FD, Duarte de Castro Ribeiro CH, Rodrigues Fernandes M, Rodríguez Burbano RM, Carneiro Dos Santos NP. Trifluridine-tipiracil plus bevacizumab versus trifluridine-tipiracil monotherapy for chemorefractory metastatic colorectal cancer: a systematic review and meta-analysis. BMC Cancer. 2024 Jun 3;24(1):674. doi: 10.1186/s12885-024-12447-8. PMID: 38825703; PMCID: PMC11145814. https://pubmed.ncbi.nlm.nih.gov/38825703/
- Otsu S, Hironaka S. Current Status of Angiogenesis Inhibitors as Second-Line Treatment for Unresectable Colorectal Cancer. Cancers (Basel). 2023 Sep 14;15(18):4564. doi: 10.3390/cancers15184564. PMID: 37760533; PMCID: PMC10526327. https://pubmed.ncbi.nlm.nih.gov/37760533/

Reply 1: We expanded second paragraph and added references. (see Line 18, page 01)

Changes in the text:
The choice of second-line treatment depends on the first-line therapy and biomarker status, including RAS and BRAF mutations, and also mismatch repair (MMR) and HER2 status. Second-line treatment usually includes chemotherapy combined with anti-VEGF antibody, such as aflibercept, bevacizumab or ramucirumab, or an anti-EGFR antibody. Moreover, the combination of encorafenib and cetuximab is recommended for BRAF V600E-mutated mCRC patients as the preferred treatment option in second line setting. Immunotherapy is advised for deficient mismatch repair tumors. In the third line setting, trifluridine-tipiracil plus bevacizumab is an effective treatment option for patients with refractory mCRC [3,4,5,6].

Reference added:
Aquino de Moraes FC, Dantas Leite Pessôa FD, Duarte de Castro Ribeiro CH, Rodrigues Fernandes M, Rodríguez Burbano RM, Carneiro Dos Santos NP. Trifluridine-tipiracil plus bevacizumab versus trifluridine-tipiracil monotherapy for chemorefractory metastatic colorectal cancer: a systematic review and meta-analysis. BMC Cancer. 2024 Jun 3;24(1):674. doi: 10.1186/s12885-024-12447-8. PMID: 38825703; PMCID: PMC11145814.
(see Line 147, page 03)

Reference added:
Otsu S, Hironaka S. Current Status of Angiogenesis Inhibitors as Second-Line Treatment for Unresectable Colorectal Cancer. Cancers (Basel). 2023 Sep 14;15(18):4564. doi: 10.3390/cancers15184564. PMID: 37760533; PMCID: PMC10526327.
(see Line 142, page 03)

2. On line 30, please provide the complete association measure (HR), including the confidence interval given in the study.

Reply 2: We have modified our text as advised

Changes in the text: (HR 0.82; 95% CI, 0.68-0.99; p = 0.03) (see Line 34, page 01)

3. Line 62: Please expand this paragraph by briefly describing the role of liquid biopsy in guiding the treatment of metastatic colorectal cancer using EGFR inhibitors. Read this article and add its reference:
- Mauri G, Vitiello PP, Sogari A, Crisafulli G, Sartore-Bianchi A, Marsoni S, Siena S, Bardelli A. Liquid biopsies to monitor and direct cancer treatment in colorectal cancer. Br J Cancer. 2022 Aug;127(3):394-407. doi: 10.1038/s41416-022-01769-8. Epub 2022 Mar 9. PMID: 35264786; PMCID: PMC9346106. https://pubmed.ncbi.nlm.nih.gov/35264786/

Reply 3: We expanded this paragraph and added references (see Line 66, page 02)

Changes in the text:
The collection of tumor-derived biomarkers from blood or other body fluids, known as liquid biopsy, allows for ctDNA analysis and enables the assessment of real-time tumor- associated genomic changes. Additionally, ctDNA monitoring can guide treatment selection in mCRC. The CHRONOS prospective clinical trial demonstrated that ctDNA-analysis is an effective strategy for identifying patients who could benefit from rechallenge with an anti-EGFR targeted agent. Furthermore, ctDNA analysis helps to identify rare genomic alterations [15].

Reference added:
Mauri G, Vitiello PP, Sogari A, Crisafulli G, Sartore-Bianchi A, Marsoni S, Siena S, Bardelli A. Liquid biopsies to monitor and direct cancer treatment in colorectal cancer. Br J Cancer. 2022 Aug;127(3):394-407. doi: 10.1038/s41416-022-01769-8. Epub 2022 Mar 9. PMID: 35264786; PMCID: PMC9346106
(see Line 188, page 04)

4. Lines 99 and 100: replace "+" with "plus" (panitumumab plus mFOLFOX6).

Reply 4: we have modified our text as indicated

Changes in the text: panitumumab plus mFOLFOX6 (see Line 111, page 03)

5. Lines 101 and 103: please add the p-value for the association measures (HR).
Reply 5: we have modified our text as advised, added p values

Changes in the text:
HR, 0.76; 95% CI, 0.61–0.95; p = 0.171
(see Line 113, page 03)

HR, 0.82; 95% CI, 0.50–1.35; p = 0.145
(see Line 115, page 03)

Reviewer D
This is a well written editorial piece referencing appropriate guidelines and making a synthesis and analysis of the PANAMA data

NO requests were indicated