

Peer Review File

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Reviewer A

Comment 1:

This is nice review of role of CTC in MIBC.

I agree with the way that they have presented the data.

It would be important for authors however to look into at least colo rectal cancer early stage where ctDNA concept started from and used even more and the performance or it in that subgroup so as to show that it is one of the tool to revolutionise the treatment,

Reply 1: We thank the reviewer for this suggestion. We have added an additional citation on colorectal cancer to the introductory section (Kotani et al, Nature Medicine, 2023; GALAXY: the observational arm of the ongoing CIRCULATE-Japan study) and refer to the finalized DYNAMIC trial (Tie et al, NEJM, 2022) in the following section. As this is a commentary on the Powles et al. study published in European Urology in 2023, we prefer not to go into too much detail on where the ctDNA concept started but suggest to keep the main focus on ctDNA in bladder cancer and the ongoing ctDNA-guided intervention trials.

Changes in the text: We now write the following:

“Multiple studies have documented the potential biomarker value of ctDNA for detection of minimal residual disease in multiple cancer types (1–3) - including bladder cancer (4).” (Page 1, line 1-18)

“In colon cancer, results from the randomized DYNAMIC trial have demonstrated that ctDNA-guided management of patients with stage II colon cancer reduced the number of patients receiving adjuvant chemotherapy without compromising RFS (6).” (Page 1, line 23-26)

Reviewer B

Comment 2:

This review is focused in the present role of ctDNA analysis in the decision-making process in patients with MIBC. The manuscript is well written and the references are corrent. As my only comment, I would suggest that the authors add some more figures to describe in more detail the design of the studies (MODERN, TOMBOLA, IMVIGOR 011)that are currently underway regarding the role of ctDNA as a predictive biomarker

Reply 2: We thank the reviewer for the suggestion and we have now added a table of the overall details of the MODERN, TOMBOLA and IMVIGOR011 trials (Table 1).

Reviewer C

Comment 3:

General comments: this is a commentary referring to the use of ctDNA in bladder cancer

Specific comments:

1. line 54 should state “sparing” rather than “sparring”

Reply 3: We have now modified the text.

Changes in the text: We now write “sparing” instead (Page 3, line 76).

Comment 4:

2. Perhaps adding on the authors' perspectives on the practical application/value of ctDNA in practice for bladder cancer patients even as the studies have not yet read out

Reply 4: We thank the reviewer for this suggestion, which is of high importance. However, we think that the clinical perspectives of ctDNA testing in bladder cancer are already highlighted throughout the commentary. On page 3, line 82-87 we mention the potential benefit of using ctDNA in clinical practice, but that these potential benefits still need to be demonstrated in clinical trials. The section on page 4-5, line 126-142 describes the clinical potential application of ctDNA besides guiding adjuvant treatment, including guiding neoadjuvant treatment, bladder preservation and monitoring of response to systemic treatment. Furthermore, we conclude the commentary by stating that *“Based on current data, we believe that ctDNA analyses will revolutionize cancer treatment to better administer the right treatments to the right patients.”* We think that adding more specific examples of use may be premature, as we need the trial read out results, and we prefer not to include additional details on this.

Changes in the text: No changes in the text.