Peer Review File

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Reviewer A

Comment 1: "The quality, size and clarity of Fig 1 and Fig 2 require improvement. In Fig 1, please clearly label CXCR4, BSP, DDR 1 in blood vessel on the right side of the figure, like it was done in circulation part of the figure. The legends in Fig 2 are too small to read in its current form. Fig 2 is hard to follow with different colors of arrows and solid vs dashed lines"

Reply 1: We thank the reviewer for this suggestion. Figure 1, now contains labels as suggested. We also increased the size of the figure. For Figure 2, we increased the size of the legend and font. Additionally, we added a solid black arrow to the legend for "Expressess" to improve clarity and removed one of the dashed lines from the figure. We also increased the size of the symbols and font size.

Changes in text: Changes to figure 1 and 2 as above.

Comment 2: "The mechanism of denosumab was briefly discussed in the article and it's important to include the immunomodulatory effect of denosumab. DENIVOS clinical trial is underway to study denosumab and nivolumab combination therapy in NSCLC with bone metastases"

Reply 2: We agree with the reviewer's comment. We now discuss this in the "response to immunotherapy" and "Denosumab" sections of the manuscript. We also include a reference to the DENIVOS trial.

Changes in the text:

-P15-16, Lines 339-340 with "Denosumab may have an additional…and the bone microenvironment"

-P24, Lines 522 - 524 with "One such trial….and is ongoing."

Reviewer B:

Comment 1: "1. The Narrative Review Checklist requires that rationale and objectives be included in Introduction. While this is review is comprehensive, it is unclear what unmet needs the authors are trying to address."

Reply 1: The rationale for our review is now highlighted in the introduction as well as the abstract section. While prior reviews on this topic have been published, our review highlights recent publications and addresses response to chemo- and immunotherapy, as well as the discussion regarding predicting development of and outcomes in patients with bone metastases.

Changes in the text: adjusted wording on P3, Line 63 to include "the objectives"

Comment 2: "For use of appropriate imaging, the authors should refer major NSCLC guidelines. One clinical question would be whether clinicians should routinely screen for bone metastasis at diagnosis of NSCLC, especially when FDG-PET scans are not readily available."

Reply 2: We referenced NCCN guidelines on P7, Line 180. However, we have now

added text regarding imaging when PET is not available - with citations from the American College of Radiology appropriateness criteria and American College of Chest physicians included. The NCCN and American College of Chest Physician guidelines both recommend evaluation of distant metastases at diagnosis (not specific to bone). Routine screening for bone metastases has not been recommended in the guidelines, but the recommendation for general evaluation of distant metastases may detect bone metastases.
Changes in the text: Added citations regarding guideline recommendations and included a sentence on alternative staging if PET-CT is not available: P9, Lines 200 – 202

Comment 3: "The authors repeatedly mention that NSCLC patients with bone metastases have poor prognosis, citing several publications. However, this could be due to publication bias. It could also bias due to searching for papers with the keyword bone metastases, which would likely return papers that show patients with bone metastases have poor prognosis. The authors need to show data that patients have poorer prognosis compared with other stage 4 patients, e.g., brain or liver metastases. In addition, survival after diagnosis of bone metastases will be longer in patients who receive routine screening for bone metastases compared with those who do not."
Reply 3: We agree with the reviewer's insightful comment regarding including data on bone metastases versus other metastases. We reviewed the literature and found varied results. These have now been summarized in the manuscript.
Changes in the text: We included a line with multiple citations addressing the reviewer's comments on P18-19, Lines 405-408

Comment 4: ""Factors predicting development of bone metastases" should be written before "Treatment of bone metastases.""
Reply 4: Changed per reviewer recommendation.
Changes in the text: Moved P11, line 279 – Page 13, line 340 to start at P10, line 210

Comment 5: "P. 3, line 63: "bony metastasis" -> "bone metastasis""
Reply 5: changed per recommendation
Changes in the text: P. 3, line 63: changed "bony metastasis" -> "bone metastasis"

Comment 6: "P. 4, line 94: The authors should specify which integrins preferentially interact with BSP. It is also of interest whether integrins that are abarrently expressed by tumor cells are associated with bone metastases."
Reply 6: We could not find a study specific to integrins and BSP in NSCLC, but we did add a citation from an in vitro breast cancer study regarding the preferential integrins. Similarly, we found studies associating integrin expression with increased invasiveness and migration (e.g. <Fong, Yi-Chin, et al. "Transforming growth factor-β1 increases cell migration and β1 integrin up-regulation in

human lung cancer cells." *Lung cancer* 64.1 (2009): 13-21.> and < Kwakwa, Kristin A., and Julie A. Sterling. "Integrin αvβ3 signaling in tumor-induced bone disease." *Cancers* 9.7 (2017): 84.> and < Navab, R., et al. "Integrin α11β1 regulates cancer stromal stiffness and promotes tumorigenicity and metastasis in non-small cell lung cancer." *Oncogene* 35.15 (2016): 1899-1908.>) but these were not specific to bone metastases in NSCLC.
Changes in the text: Added a line regarding this on P5, lines 96-97