Peer Review File

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Reviewer A

I want to start by thanking the authors for their effort in writing this interesting and informative editorial commentary.
Thanks very much.

I have a few comments which would enhance the flow of this article and make it even more informative:
1-For the paragraph discussing IGF-1R mechanism, I think it is better for it to be placed right after the introduction, before you start the discussion about the trial.
Understood. I have placed the IGF-1R paragraph right after the first paragraph, as the reviewer suggests. I have modified the text slightly, to make a better transition between the first and the second paragraphs. I have marked these changes in blue. I have added this text to the end of the first paragraph: "*In the absence of chemotherapeutic options for these patients, there is a need to develop new targeted therapies with biologic rationale*[6]." I have added this text at the beginning of the second paragraph: "*One of the pathways found deregulated in Ewing sarcoma was the insulin-like growth factor-1 receptor (IGF-1R), thus offering a new molecular target for treatment*[7]." References 6 and 7 are new, included after the revision.

2-You can as well cite this article which is a systematic review about biomarkers in ES and it discussed IGF-1R: Daher M, Zalaquett Z, Chalhoub R, Abi Farraj S, Abdo M, Sebaaly A, Kourie HR, Ghanem I. Molecular and biologic biomarkers of Ewing sarcoma: A systematic review. J Bone Oncol. 2023 Apr 26;40:100482. doi: 10.1016/j.jbo.2023.100482. PMID: 37180735; PMCID: PMC10173001.
Thanks. I have cited this paper at the end of the first paragraph (reference 6).

Reviewer B

Excellent and comprehensive review.

Agree anti-IGF-1R antibody alone is not sufficient for efficacy.

Perhaps in combination with a payload (e.g., Ac-225) may have higher clinical efficacy.

Thanks for these comments. I have not modified the manuscript in response to reviewer B.

Reviewer C

This is well written editorial primarily explaining lack of efficacy of ganitumab in a recent COG phase III trial as well as in previous studies of this insulin-like growth factor-1 receptor antibody in patients with Ewing sarcoma, concluding that future studies should be substantiated by strong preclinical data in a sufficient number of cancer models, and by preclinical studies of suitable biomarkers to enrich the population of patients likely to obtain a clinical benefit.

I have little to add and suggest to add to the title that this was a COG trial including the NCT#, since more than one trial is discussed (although not phase III). In addition, in the first paragraph it might help to give a range instead of just saying "more than 50% of these patients will relapse during the following five years". With this statement it is unclear whether 46 or 10% will stay in remission after 5 years. Taken together, I commend this thoroughly parsed editorial without restriction.

Thanks for these comments. In response to them, I have taken these actions:

1) I have modified the title to include reference to the Children's Oncology Group.

2) I have included the ClinicalTrials.gov identifier in the text.

3) I have changed the sentence of the first paragraph. The new sentence is: "*[...] a majority (around 80%) of patients diagnosed with metastatic disease experience relapse or progression during long term follow-up*".