Response to Drs Von Hoff and Renschler

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Reply to Von Hoff and Renschler's Letter to the Editor re: Ahn *et al.* A modified regimen of biweekly gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer is both tolerable and effective: a retrospective analysis. *Ther Adv Med Oncol* https://doi.org/10.1177/1758834016676011

We have reviewed with great interest the letter by Von Hoff and Renschler.[1] We disagree with many of the points raised, whereas on some we agree while emphasizing the fact that many were already discussed in our paper as limitations of our analysis. We previously discussed the multiple considerations that factored into the choice of a modified regimen of gemcitabine and nab-paclitaxel, and we refer the authors to the original manuscript for that purpose.[2]

There is no evidence that dose reductions or delays affect efficacy

We first note that biweekly regimens have been shown, in a number of settings, including pancreatic and colorectal cancer, to improve tolerability with no adverse impact on outcome.[3–7]

In the MPACT trial, the combination of weekly gemcitabine and nab-paclitaxel required a large proportion of patients to undergo a dose reduction (47% for gemcitabine dose and 41% for nab-paclitaxel dose).[8] Additionally, a recent exploratory analysis by Von Hoff and colleagues from the MPACT trial indicated that dose reductions and delays were effective at improving tolerability and did not seem to compromise treatment efficacy.[9] In fact, the results of this analysis indicated that patients who underwent dose reductions or delays had an improved overall outcome.

Our study *versus* historic controls

We acknowledge that a retrospective analysis has significant limitations and is closer to a real-world observation than following the restrictive eligibility criteria of clinical trials. Early-phase trials tend to be even more restrictive and selective compared with phase III trials, which may explain the different results between the two studies listed by the authors in their letter. Additionally, in our setting, as in many large academic practices, 'best patients' are preferentially selected for either a clinical trial or a triplet regimen. As such, we believe that patients included in our retrospective analysis are more comparable with those in the MPACT trial. Supporting this further is a recent study from the British Columbia Cancer Agency showing that the majority of patients diagnosed with metastatic pancreatic cancer would never be candidates for either nab-paclitaxel/gemcitabine or FOLFIRINOX if the restrictive eligibility requirements of MPACT or PRODIGE were applied.[10] This reinforces the high likelihood that our patient population reflects more closely the one included in the MPACT trial, especially given the historic similarity of the respective results. Additionally, the results from our experience with the modified biweekly gemcitabine and nab-paclitaxel regimen appear to be similar to the results of the weekly regimen, as shown in more recent studies.[11]

In an era of value-based care, biweekly gemcitabine and nab-paclitaxel should be considered for comparative analysis *versus* the weekly regimen

Finally, we would like to emphasize the fact that, in this palliative setting, and despite the confirmed clinical benefit from the addition of nab-paclitaxel to gemcitabine, pancreatic cancer remains a disease with a dismal outcome; the combination provided an incremental median survival benefit of only 1.8 months.[12] In this palliative setting, in addition to cost, the impact of treatment-related toxicities on patient quality of life needs to be taken into strong consideration.

We do agree with Von Hoff and Renschler that randomized trials are required to establish standards. However, and although we understand the overall reluctance to spend additional resources to study the biweekly regimen, we disagree for all the reasons stated above that a weekly regimen would provide a superior outcome. We remain confident that the results of our study provide a very promising signal that should be considered for comparative analysis, given the cost and toxicity implications confounding the weekly regimen, especially in an era of value-based care. Additionally, biweekly regimens provide more favorable backbones on which to build in clinical trials, with the aim of continuing to improve on the modest gains observed with gemcitabine and nab-paclitaxel.

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Conflict of interest statement

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