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Letter to the Editor Re: Ahn DH, Krishna K, Blazer M, *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

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We read with interest the article on a recent retrospective analysis from The Ohio State University, which reported that a modified regimen of *nab*-paclitaxel plus gemcitabine (biweekly [q2w]) in patients with metastatic pancreatic cancer was associated with an acceptable toxicity profile and appeared to be relatively effective.[1] We would like to point out caveats that must be considered before comparing the retrospective, single-institution chart review study in the United States ($N = 79$) with the global MPACT trial ($N = 831$; conducted at 151 centers), in which patients received *nab*-paclitaxel plus gemcitabine weekly for the first 3 of 4 weeks (qw 3/4).[2] These caveats include, but are not limited to, the retrospective nature of the analysis (*versus* the prospective phase III MPACT trial), differences in methodology (e.g. patients seen every 2 weeks *versus* every week in MPACT), the lack of requirement for informed consent (requirement in both MPACT and our phase I/II study), differences in the rigor and completeness of the screening evaluation for inclusion in the study, and differences in patient populations (Table 1) and supportive care.[1–3] Additionally, our prospective phase I/II study,[3] conducted at four US centers ($n = 67$), should also be considered when interpreting efficacy and safety results of the relatively small retrospective analysis from The Ohio State University (Table 2).

Differences in efficacy and safety assessments and methodology

Overall survival (OS) and progression-free survival (PFS) in the retrospective analysis were assessed from the date of last clinic visit prior to starting therapy.[1] In our phase I/II study, both OS and PFS were assessed from first treatment, and in MPACT from the date of randomization, which occurred within 3 days of first treatment (median, 2 days).[2,3] However, the time from the last prior clinic visit to the start of therapy was not identified in the Ohio State retrospective analysis and could have been longer than 2 days, which has the potential to skew the reported OS and PFS results.

Toxicity was assessed 2 weeks after each dose in the retrospective analysis compared with 1 week after each dose in the phase I/II trial and MPACT (even during the week of rest, on day 21, patients were assessed for adverse events), which makes comparisons of safety data inappropriate.[1–3]

Furthermore, the order of the *nab*-paclitaxel and gemcitabine infusions was unclear from the article, which often described gemcitabine first.[1] Per the Abraxane prescribing information, the *nab*-paclitaxel infusion is immediately followed by gemcitabine,[4] which is supported by preclinical evidence, including a report by Frese and colleagues

Table 1. Comparison of Patient Populations

	Retrospective[1] *nab*-P 125 mg/m² + Gem 1000 mg/m² q2w *n* = 57 (MPC)	**Our phase I/II[3] *nab*-P 125 mg/m² + Gem 1000 mg/m² qw 3/4 *n* = 44**	**Phase III MPACT[2] *nab*-P 125 mg/m² + Gem 1000 mg/m² qw 3/4 *n* = 431**
ECOG PS, %			
0	Not specified	50	58[a]
1	(All pts were 0 or 1)	50	42[a]
2	0	0	<1[a]
Number of metastatic sites, %			
1–2	79	59	55
⩾3	21	41	45
Liver metastases, %	61	77	85
CA19-9			
Median, U/ml	Not reported	881	2294
Normal, %	18	16	16
Elevated, %	82	84	84
⩾59 × ULN, %	Not reported	Not reported	52

CA 19-9, carbohydrate antigen 19-9; ECOG-ACRIN, Eastern Cooperative Oncology Group - American College of Radiology Imaging Network; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; KPS, Karnofsky performance status; MPC, metastatic pancreatic cancer; nab-P, nab-Paclitaxel; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; qw 3/4, weekly for the first 3 of 4 weeks; q2w, every 2 weeks.
[a]MPACT assessed KPS; conversion to ECOG PS by table from the ECOG-ACRIN group.[6]

Table 2. Comparison of Efficacy

	Retrospective[1] *nab*-P 125 mg/m² + Gem 1000 mg/m² q2w *n* = 57 (MPC)	**Our phase I/II[3] *nab*-P 125 mg/m² + Gem 1000 mg/m² qw 3/4 *n* = 44**	**Phase III MPACT[2,7] *nab*-P 125 mg/m² + Gem 1000 mg/m² qw 3/4 *n* = 431**
OS, median, months	10.0	12.2	8.7
PFS, median, months	5.4	7.9	5.5
Investigator-assessed ORR, %	19	48	29
Number of cycles, median (standardized to 4-week cycles)	3.5	6.0	4.0[a]

[a]Note, the median number of cycles in MPACT was 3.0 in the *nab*-paclitaxel plus gemcitabine arm, but cycle 1 was 8 weeks; subsequent cycles were 4 weeks each.

that demonstrated that *nab*-paclitaxel administration elevated intratumoral gemcitabine levels.[5]

Differences in patient baseline characteristics

Table 1 outlines a number of differences among the patient populations in the three studies and suggests that patients in the retrospective analysis may have had lower tumor burden than those in our studies. Notably, in the retrospective analysis, the percentages of patients with Eastern Cooperative Oncology Group performance status 0 *versus* 1 were not reported separately, nor was the median CA19-9 level. Both performance status and CA19-9 levels are important prognostic

factors for survival in patients with metastatic pancreatic cancer, and these omissions make it difficult to interpret with confidence the survival results of the retrospective analysis.

Differences in efficacy and treatment exposure outcomes

The shorter treatment duration of the q2w schedule along with numerically inferior efficacy outcomes indicate that the lower dose intensity may place patients at a disadvantage compared with administration of the approved dosing schedule.

Our opinion is that practitioners should be reminded of the US Food and Drug Administration–approved dose and schedule for *nab*-paclitaxel plus gemcitabine and be mindful of the potential loss in clinical efficacy when considering a q2w *nab*-paclitaxel schedule as an initial treatment for patients with newly diagnosed disease. Even though the modified regimen may "appear to be relatively effective," as stated by the authors, noninferiority has not been demonstrated by any means, and one cannot draw the conclusion that the regimens are equivalent in efficacy.

Furthermore, the authors of the analysis at The Ohio State University suggested that prospective, randomized studies should be conducted to further evaluate the q2w *versus* the qw 3/4 schedule; however this type of prospective trial would be difficult to conduct. Based on results presented in the retrospective analysis and evaluating our own prospective data, we believe that, until such a trial is conducted and shows evidence otherwise, *nab*-paclitaxel plus gemcitabine given qw 3/4 is a more effective regimen.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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