

Dose modification and efficacy of *nab*-paclitaxel plus gemcitabine vs. gemcitabine for patients with metastatic pancreatic cancer: phase III MPACT trial

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Background: Dose modifications following adverse events (AEs) are an important part of the management of patients with pancreatic cancer treated with chemotherapy. While dose modifications are utilized to ensure patient safety, the subsequent influence of dose adjustments on treatment exposure and efficacy have not been reported in detail. This exploratory analysis examined the influence of dose modifications on treatment exposure and efficacy in the phase III MPACT trial, which demonstrated superior efficacy of *nab*-paclitaxel (*nab*-P) plus gemcitabine (Gem) to Gem alone for the treatment of metastatic pancreatic cancer.

Methods: Patients received either *nab*-P 125 mg/m² + Gem 1,000 mg/m² on days 1, 8, and 15 every 4 weeks or Gem 1,000 mg/m² weekly for the first 7 of 8 weeks (cycle 1) and then days 1, 8, and 15 every 4 weeks (cycle ≥2). The protocol allowed up to 2 dose reductions per agent. Dose delays were also used to manage toxicities.

Results: Toxicities that most commonly led to dose modifications were neutropenia, peripheral neuropathy, thrombocytopenia, and fatigue for *nab*-P and neutropenia, thrombocytopenia, and fatigue for Gem alone. Baseline characteristics were similar in patients with dose modifications and the intent-to-treat (ITT) population. Among the 421 treated patients in the *nab*-P + Gem arm, all patients initiated treatment at the per-protocol *nab*-P starting dose of 125 mg/m²; 172 (41%) had a *nab*-P dose reduction, and 300 (71%) had a *nab*-P dose delay during the study. Most dose modifications occurred after the first 3 months (2 cycles) of treatment. The majority of patients (104/172, 60%) required only 1 *nab*-P dose reduction, and over half of patients (163/300) had either 1 or 2 dose delays. Patients who underwent dose modifications of *nab*-P had greater treatment exposure than those who did not in terms of treatment duration, number of cycles administered, and cumulative dose of *nab*-P delivered. Overall survival (OS) was shorter in the *nab*-P + Gem arm for patients who did not vs. did undergo dose reduction [median, 6.9 vs. 11.4 months; hazard ratio (HR), 1.93; 95% CI, 1.53–2.44; P<0.0001] and for those who did not vs. did undergo a dose delay (median, 6.2 vs. 10.1, HR, 2.05; 95% CI, 1.60–2.63; P<0.0001). Progression-free survival (PFS) and overall response rate (ORR) were also improved in patients with dose modifications. Similar trends were observed in the Gem-alone arm. Multivariate analyses confirmed that both dose delay and dose reduction were significantly associated with OS.

Conclusions: This analysis suggests that although most doses of *nab*-P were given at the starting dose of 125 mg/m² the first 3 of 4 weeks, dose reductions and delays were effective when necessary to ameliorate toxicity allowing greater treatment exposure without compromising efficacy.

Keywords: Pancreatic cancer; *nab*-paclitaxel (*nab*-P); gemcitabine (Gem); dose reduction; dose delay

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Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States and Europe (1,2). Surgical resection is the only curative approach for pancreatic cancer (3), but because symptoms are subtle or absent in early stages, the large majority of patients present with advanced nonresectable disease (1). Historically, the prognosis for patients with metastatic disease has been particularly poor (1). For example, treatment with the long-time standard of care, gemcitabine (Gem) monotherapy, led to median overall survival (OS) values of approximately 5 to 7 months in multiple phase III trials of patients with metastatic pancreatic cancer (4-16). However, two phase III trials have demonstrated clinically meaningful survival advantages for an experimental regimen over Gem monotherapy: the PRODIGE ACCORD 11 trial of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) and the MPACT trial of *nab*-paclitaxel (*nab*-P) + Gem (17,18). To avoid toxicity with the per protocol FOLFIRINOX regimen, investigators have experimented with modification of starting components and doses; studies of modified FOLFIRINOX have demonstrated inconsistent efficacy results (19,20). The tolerability profile of *nab*-P + Gem allowed most doses of *nab*-P (71%) to be delivered at the per protocol level in the MPACT trial (18). However, little is known about how dose modifications may have affected treatment outcomes.

In the MPACT trial, *nab*-P + Gem demonstrated a longer OS [median, 8.5 *vs.* 6.7 months; hazard ratio (HR), 0.72; 95% CI, 0.62–0.83; *P*<0.001], a longer progression-free survival (PFS) (median, 5.5 *vs.* 3.7 months; HR, 0.69; 95% CI, 0.58–0.82; *P*<0.001) and a higher overall response rate (ORR) [23% *vs.* 7%; response rate ratio (RRR) 3.19; 95% CI, 2.18–4.66; *P*<0.001] than Gem alone (18). Furthermore, the OS benefit for *nab*-P + Gem over Gem alone was consistent across patient subgroups, and an updated analysis revealed a >2-month difference in OS at the median (8.7 *vs.* 6.6 months; HR, 0.72; 95% CI, 0.62–0.83; *P*<0.001) (21). Long-term survivors

(≥3 years) were also observed in the updated OS analysis, but only in the *nab*-P + Gem arm (4%). Treatment-related grade ≥3 neutropenia, leukopenia, peripheral neuropathy (no grade 4), and fatigue occurred more often in the *nab*-P + Gem arm than in the Gem-alone arm (18). These toxicities were effectively managed with dose reductions and delays.

Dose reductions and delays are standard methods to reduce the toxic effects of chemotherapy, particularly myelosuppressive chemotherapy. A correlation has been noted between dose intensity and efficacy in some clinical trials (22,23). However, in ovarian cancer and non-small cell lung cancer, dose modifications of specific treatments had no impact on clinical outcomes (24,25). A post hoc analysis of a phase II trial of *nab*-P monotherapy in metastatic breast cancer also revealed no association of dose reduction with OS (26). Management of adverse events (AEs) by dose modification is suspected to increase the likelihood that a patient with pancreatic cancer can remain on treatment and consequently experience greater treatment exposure. However, there are few data to support this directly. Despite higher rates of dose reductions in the *nab*-P + Gem arm *vs.* the Gem arm in the MPACT trial, patients receiving *nab*-P + Gem had a longer treatment duration than those in the Gem-alone arm (median, 3.9 *vs.* 2.8 months). The goal of this exploratory analysis was to fully characterize the use of dose reduction or delay to manage toxicities and the effect of that dose modification on efficacy in the MPACT trial.

Methods

Patients and methods of the MPACT trial have been described previously, including a previous publication of a CONSORT diagram (18).

Patients

Adults (≥18 years of age) with histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas and

Table 1 Dose modification for neutropenia or thrombocytopenia at day 8 or 15

Day 8			Day 15		
Blood counts ^a	<i>nab</i> -P	Gem	Blood counts ^a	<i>nab</i> -P	Gem
ANC >1,000 and platelets ≥75,000	100%	100%	ANC >1,000 and platelets ≥75,000	100%	100%
			ANC 500–1,000 or platelets 50,000–74,999	Full dose (treat on time) + G-CSF ^b	Full dose (treat on time) + G-CSF ^b
			ANC <500 or platelets <50,000	Hold + G-CSF ^b	Hold + G-CSF ^b
ANC 500–1,000 ^c or platelets 50,000–74,999	Decrease dose by 1 level (treat on time)	Decrease dose by 1 level (treat on time)	ANC >1,000 and platelets ≥75,000	Return to prior dose (treat on time) + G-CSF ^b	Return to prior dose (treat on time) + G-CSF ^b
			ANC 500–1,000 or platelets 50,000–74,999	Same dose (as day 8, treat on time) + G-CSF ^b	Same dose (as day 8, treat on time) + G-CSF ^b
			ANC <500 or platelets <50,000	Hold + G-CSF ^b	Hold + G-CSF ^b
ANC <500 ^c or platelets <50,000	Hold	Hold	ANC >1,000 and platelets ≥75,000	Decrease day 8 dose by 1 level (treat on time) + G-CSF ^b	Decrease day 8 dose by 1 level (treat on time) + G-CSF ^b
			ANC 500–1,000 or platelets 50,000–74,999	Decrease day 8 dose by 1 level (treat on time) + G-CSF ^b	Decrease day 8 dose by 1 level (treat on time) + G-CSF ^b
			ANC <500 or platelets <50,000	Hold + G-CSF ^b	Hold + G-CSF ^b

^a, units for cell counts all given as cells/mm³; ^b, G-CSF was optional for patients with low platelet levels only. To resume treatment after a dose being withheld, cell counts must have reached the specified levels at day 1, 8, or 15; ^c, patients who did not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, were discontinued from the study. ANC, absolute neutrophil count; G-CSF, granulocyte-colony stimulating factor; Gem, gemcitabine; *nab*-P, *nab*-paclitaxel.

a KPS score of ≥70 were enrolled. Measurable disease by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 was required (27). Additional eligibility criteria included adequate hepatic, hematologic, and renal function.

Study design and treatment

Patients were randomized 1:1 to receive a 30- to 40-minute intravenous infusion of *nab*-P 125 mg/m², followed by an infusion of Gem 1,000 mg/m² on days 1, 8, 15, 29, 36, and 43, or Gem alone 1,000 mg/m² weekly for 7 of 8 weeks (cycle 1). Patients were treated on days 1, 8, and 15 every 28 days in subsequent cycles. Patient randomization was stratified by Karnofsky performance status, geographic region, and the presence of liver metastases. Treatment continued until either disease progression by RECIST or unacceptable toxicity.

Assessments

Tumor response was assessed every 8 weeks, and scans were

evaluated by an independent radiology laboratory and by investigators using RECIST version 1.0.

Treatment-related AEs were graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (28). Hematologic AEs were assessed by central laboratory testing. All patients were evaluated on days 1, 8, and 15 of each 28-day cycle for AEs that would require dose modification. Per protocol, doses could be reduced up to 2 times per therapeutic agent (to 100 or 75 mg/m² for *nab*-P and to 800 or 600 mg/m² for Gem; dose reductions may or may not have been concomitant) in the event of unacceptable toxicity (Table 1, Table S1). Dose re-escalation was not allowed between cycles. Toxicities that required a delay of either drug for >21 days resulted in permanent discontinuation.

Investigators monitored treatment-related AEs and serious AEs, weekly central laboratory testing, and the rates of dose reductions, dose interruptions, and premature discontinuations of the study drug.

In all analyses, patients in the *nab*-P + Gem arm were

Table 2 Treatment exposure in the treated population

Variable	<i>nab</i> -P + Gem (n=421)		Gem (n=402)
	<i>nab</i> -P	Gem	
Per-protocol/total doses, n/n [%]	4,116/5,770 [71]	3,731/5,888 [63]	3,762/4,769 [79]
Patients with ≥ 1 dose delay, n [%]	300 [71]	295 [70]	230 [57]
AEs leading to dose delay, n [%]			
Neutropenia	68 [16]	75 [18]	43 [11]
Thrombocytopenia	50 [12]	57 [14]	36 [9]
Peripheral neuropathy	32 [8]	12 [3]	0
Fatigue	34 [8]	33 [8]	15 [4]
Patients with ≥ 1 dose reduction, n [%]	172 [41]	198 [47]	132 [33]
AEs leading to dose reduction, n [%]			
Neutropenia	44 [10]	81 [19]	54 [13]
Thrombocytopenia	15 [4]	36 [9]	35 [9]
Peripheral neuropathy	26 [6]	4 [1]	0
Fatigue	18 [4]	19 [5]	9 [2]

AE, adverse event; Gem, gemcitabine; *nab*-P, *nab*-paclitaxel.

designated as having had a dose reduction or delay based on modification of *nab*-P only. Doses not given within 2 days of the scheduled administration were considered dose delays. Reinitiation of treatment after a missed dose was required to be considered a delay.

Statistical analysis

All efficacy analyses were performed on the intent-to-treat (ITT) population, which was composed of all enrolled patients. The primary efficacy endpoint was OS, and the secondary endpoints were PFS and ORR. A multivariate analysis of OS was conducted that included the following covariates at baseline: age (<65 vs. ≥ 65 years), sex, KPS (70–80 vs. 90–100), geographic region (North America vs Eastern Europe, Western Europe, or Australia), pancreatic cancer primary location (head vs. other), presence of biliary stent, previous Whipple procedure, presence of liver metastases, presence of pulmonary metastases, peritoneal carcinomatosis, stage of diagnosis (IV vs. other), number of metastatic sites (1 vs. 2 vs. 3 vs. 4 vs. 5 vs. 6), and level of CA19-9 [$<$ upper limit of normal (ULN) vs. ULN to $59\times$ ULN vs. $>59\times$ ULN]. To assess the specific effect of each on OS, dose reduction (yes vs. no) and dose delay (yes vs. no) were added to the list of covariates, as was treatment group for the ITT analysis separately. Similar analyses were carried out within each treatment arm to account for the

finding that more dose modifications were required in the *nab*-P + Gem arm vs. the Gem arm. Otherwise, the effect of each factor (treatment arm and dose modification) could have been canceled by the other since they were related.

All statistical tests were 2-sided and performed using SAS 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Dose modifications

All patients initiated treatment at the per-protocol starting doses of *nab*-P 125 mg/m² + Gem 1,000 mg/m² or Gem alone at 1,000 mg/m². The median relative dose intensities were 81% for *nab*-P and 75% for Gem in the combination arm and 85% for Gem alone (18). The majority of patients with a *nab*-P dose reduction (104/172, 60%) required only 1 dose reduction; 33% had 2 dose reductions. Dose delays in the *nab*-P + Gem arm occurred in 71% of patients for *nab*-P and 70% for Gem (Table 2). The rate of dose delay in the Gem-alone arm was 57%. Most patients with a *nab*-P dose delay (163/300; 54%) had either 1 or 2 dose delays. Most *nab*-P dose reductions (155/257; 60%) and dose delays (679/946; 72%) occurred after the first 3 months (two cycles) of treatment.

The main reasons for dose reductions and delays of *nab*-P were similar and included neutropenia, peripheral neuropathy, thrombocytopenia, and fatigue. The AEs that

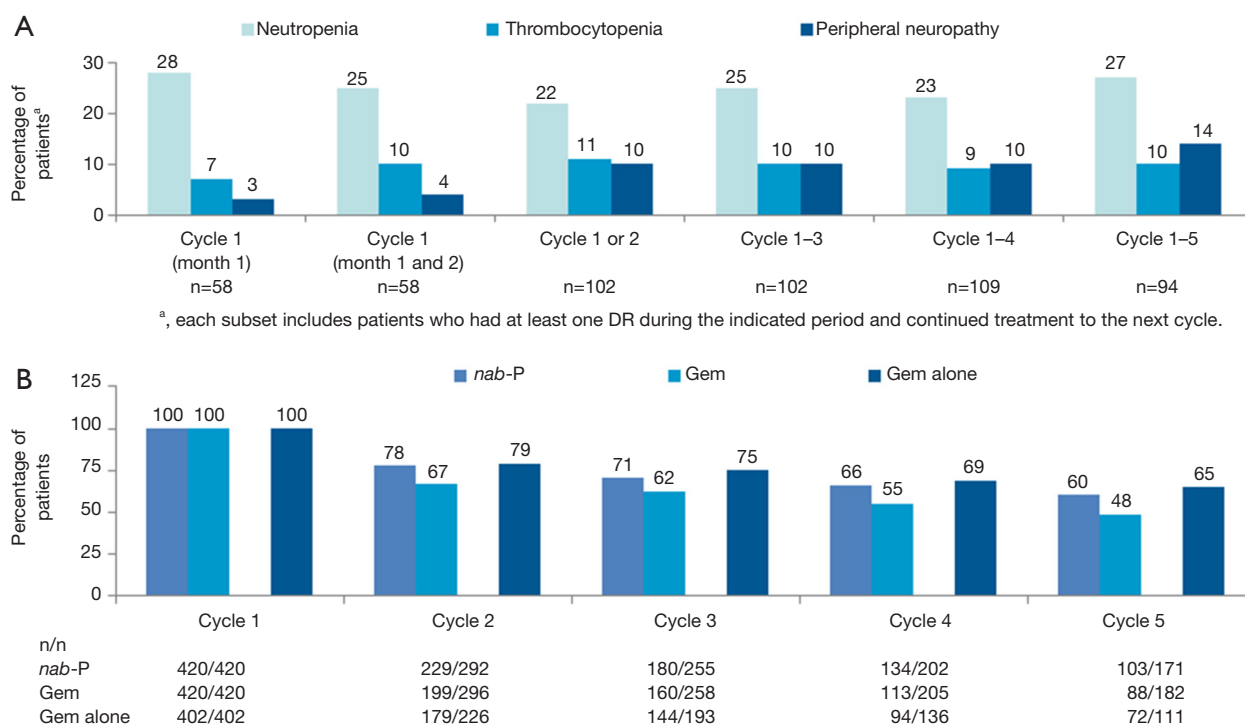


Figure 1 Summary of treatment related toxicities and percentage of patients receiving full-protocol dose by cycle. (A) The adverse events that led to *nab*-paclitaxel (*nab*-P) dose reduction by cycle are shown; (B) the percentages of patients who received full per-protocol doses are shown by cycle of treatment and treatment arm. DR, dose reduction; Gem, gemcitabine.

most often led to dose reductions or delays for Gem in each arm were neutropenia and thrombocytopenia (Table 2).

The AEs that led to dose reduction of *nab*-P by treatment cycle are represented in Figure 1A. Neutropenia was the AE that led to the highest rate of dose reduction throughout treatment. The percentages of dose reductions of *nab*-P due to neutropenia and thrombocytopenia were 25% and 10%, respectively, in cycle 1 and 27% and 10%, respectively, over cycles 1 to 5. The rates of dose reductions of *nab*-P due to peripheral neuropathy increased from 4% in cycle 1 to 14% over cycles 1 to 5. As expected, the percentages of patients in each treatment arm who received full doses of each drug decreased with increasing numbers of cycles (Figure 1B).

Treatment exposure based on dose modifications

To determine whether potential markers of frailty might associate with treatment exposure in this trial, the rates of dose reduction were examined in subsets of patients categorized by age and performance status. Neither of these factors appeared to influence the rate of dose reduction in either treatment arm (Table 3). In addition, the

baseline characteristics for each treatment arm appeared similar between the ITT population and the patients who underwent dose reductions or delays (Table S2).

In the *nab*-P + Gem arm, patients who underwent dose reductions or delays of *nab*-P had a greater extent of treatment exposure than those who did not in terms of treatment duration, number of cycles administered, and cumulative dose of *nab*-P delivered (Table 4). Similar trends were observed for Gem in the Gem-alone arm. Rates of subsequent therapies appeared to be similar for patients who did or did not undergo a dose modification (Table 4).

Effect of dose modification on efficacy

Patients were divided into subgroups based on whether they underwent at least one dose reduction or not, and the efficacy outcomes for each of these subgroups were compared within each treatment arm. Efficacy appeared to be better for patients who underwent dose modification than for those who did not in each arm. In the *nab*-P + Gem arm, the ORRs in patients who did not ($n=249$) vs. did ($n=172$) undergo a dose reduction were 16% vs. 34%, respectively

Table 3 Dose reductions in patients with markers of poor prognosis

Factor	<i>nab</i> -P + Gem			Gem	
	n	<i>nab</i> -P DR, %	Gem DR, %	n	DR, %
Age					
<65 years	246	40	45	225	32
≥65 years	175	42	50	177	33
Karnofsky performance status					
90-100	246	42	50	248	36
70-80	174	40	43	153	28

DR, dose reduction; Gem, gemcitabine; *nab*-P, *nab*-paclitaxel.**Table 4** Treatment exposure and subsequent therapies of patients with or without dose modifications

Parameter	<i>nab</i> -P + Gem (modifications of <i>nab</i> -P only)				Gem			
	Dose reduction		Dose delay		Dose reduction		Dose delay	
	Yes	No	Yes	No	Yes	No	Yes	No
Patients, n	172	249	300	121	132	270	230	172
Treatment duration, median, days	185.0	95.0	158.5	71.0	122.0	63.0	113.0	58.0
Cycles administered, median	6.0	2.0	5.0	1.0	4.0	1.0	3.0	1.0
Cumulative <i>nab</i> -P dose, median, mg/m ²	1,837.5	1,125.0	1,625.0	750.0	–	–	–	–
Cumulative Gem dose, median, mg/m ²	15,000.0	9,000.0	12,500.0	6,200.0	11,900.0	7,000.0	10,400.0	7,000.0
Patients with subsequent therapies, %	42	35	40	32	49	40	44	42

Gem, gemcitabine; *nab*-P, *nab*-paclitaxel.

(RRR, 0.49; 95% CI, 0.34–0.69; $P < 0.0001$). PFS was shorter for patients who did not undergo dose reductions *vs.* those who did (median, 3.8 *vs.* 8.8 months; HR, 2.62; 95% CI, 2.01–3.42; $P < 0.0001$), as was OS (*Figure 2A*). Better efficacy was also observed for patients who underwent dose reductions in the Gem-alone arm. The ORRs for patients who did not ($n=270$) *vs.* did ($n=132$) undergo a dose reduction were 4% *vs.* 14%, respectively (RRR, 0.31; 95% CI, 0.16–0.62; $P=0.0004$). As in the *nab*-P + Gem arm, PFS in the Gem arm was shorter for patients who did not undergo a dose reduction *vs.* those who did (median, 3.5 *vs.* 5.5 months; HR, 2.13; 95% CI, 1.61–2.83; $P < 0.0001$), as was OS (*Figure 2B*).

Similar efficacy trends favoring patients who underwent at least one dose delay were observed for patients who underwent at least one dose reduction. In the *nab*-P + Gem arm, patients who did not undergo a dose delay ($n=121$) had a lower ORR (10% *vs.* 29%; RRR, 0.34; 95% CI, 0.19–0.60; $P < 0.0001$), a shorter PFS (median 3.4 *vs.* 6.6 months; HR, 2.80; 95% CI, 2.13–3.69; $P < 0.0001$), and a shorter OS (*Figure 2C*) *vs.* those who did ($n=300$). In the Gem-alone arm, patients who

did not undergo a dose delay ($n=172$) also had a lower ORR (3% *vs.* 11%; RRR, 0.32; 95% CI, 0.14–0.77; $P=0.0061$), a shorter PFS (median, 3.4 *vs.* 5.0 months; HR, 1.70; 95% CI, 1.31–2.21; $P < 0.0001$), and a shorter OS (*Figure 2D*) *vs.* those who did ($n=230$), although the difference in OS did not reach statistical significance.

Additional analyses of dose modification and efficacy

A stepwise multivariate analysis of OS was performed, which included a number of baseline factors as well as treatment group, dose reduction, and dose delay. Both dose reduction (HR, 0.61; $P < 0.001$) and dose delay (HR, 0.77; $P=0.007$) were significantly associated with longer OS (*Table S3*). Treatment group, KPS, and presence of liver metastases were also significant predictors, as shown in a prior analysis (29), as was number of metastatic sites. Separate multivariate analyses were performed within each treatment arm to account for the statistical issue of higher rates of dose modifications in the *nab*-P + Gem arm (*Table S3*); dose reduction remained significantly associated with longer OS in each treatment

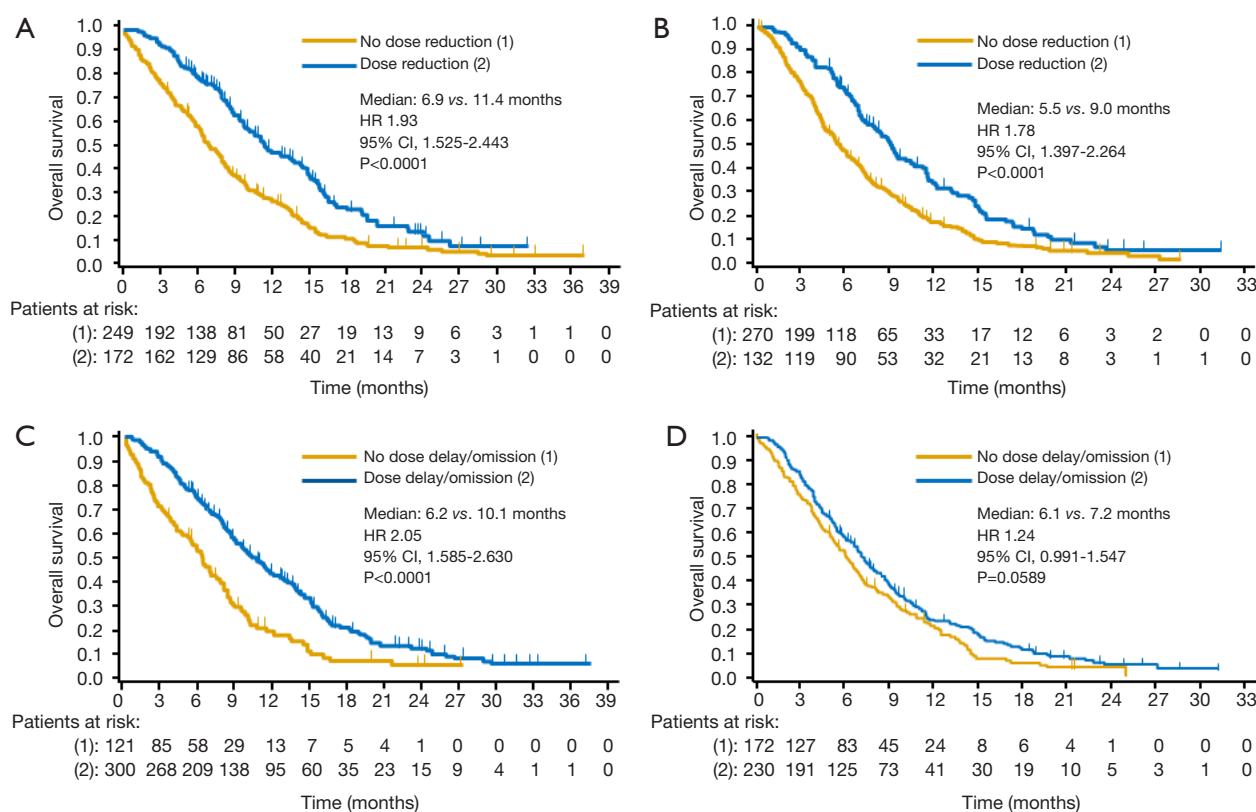


Figure 2 Kaplan-Meier curves of overall survival (OS) in patients who did or did not require dose reduction (A) of *nab*-paclitaxel (*nab*-P) in the *nab*-P + gemcitabine (Gem) arm and (B) in the Gem-alone arm, or patients who did or did not require dose delay (C) of *nab*-P in the *nab*-P + Gem arm and (D) in the Gem-alone arm.

arm, whereas dose delay was only significant in the *nab*-P + Gem arm (P=0.055 for the Gem arm).

OS was also assessed in an analysis that excluded patients who had disease progression before week 8 (cycle 1) to account for the possible influence of bias from the fact that early progression might have precluded dose modification (Table S4). Within each arm, patients with a dose reduction had a longer OS than patients who did not, and patients with a dose delay also had a longer OS than patients who did not.

To focus on patients with a presumed favorable biology, OS was assessed only in patients with a duration of tumor response above the median (median =6.03 months for the 130 patients who had a response). The Gem-only arm had only 11 patients with a duration of response above the median, which did not allow for statistical comparisons for dose reductions or delays. However, in the *nab*-P + Gem arm, which had 54 patients with a duration of response above the median, both dose reduction (HR, 0.24; P<0.001)

and dose delay (HR, 0.04; P<0.001) were significantly associated with longer OS.

Discussion

The MPACT trial established *nab*-P 125 mg/m² + Gem 1,000 mg/m² as a new standard therapy for advanced pancreatic cancer (3,18), but very little published information is available on the efficacy of the regimen after dose modification. In the *nab*-P + Gem arm, at least 1 *nab*-P dose modification was associated with longer OS and most dose modifications occurred after the second cycle (i.e., 3 months of treatment). Together, this suggests that the regimen with the starting dose of *nab*-P 125 mg/m² + Gem 1,000 mg/m² was feasible and dose modifications to alleviate toxicities were not detrimental. Most patients (60%) with a *nab*-P dose reduction had only 1 dose reduction, and 54% of patients with a *nab*-P dose delay had 1 or 2 dose delays during treatment. The longer median duration of treatment

in the *nab*-P + Gem *vs.* Gem arm (3.9 *vs.* 2.8 months) (18) likely reflects the improved efficacy of the combination and resulted in a higher proportion of patients in the *nab*-P + Gem arm requiring dose modification compared with the Gem-alone arm.

The AEs that led to the majority of dose modifications in the *nab*-P + Gem arm were neutropenia, thrombocytopenia, peripheral neuropathy, and fatigue. Although neutropenia and thrombocytopenia led to reductions of both drugs, peripheral neuropathy was responsible for *nab*-P reduction in 6% of patients and dose delay in 8% of patients in that arm but no dose reductions in the Gem-alone arm.

This analysis also evaluated associations between dose modifications and specific baseline characteristics and between dose modifications and efficacy. Older age and poorer performance status were not associated with a higher rate of dose modifications (Table 3). However, an interesting association was observed between dose modification and efficacy. In each treatment arm, patients with at least one dose reduction had a significantly higher ORR and longer OS and PFS than did patients without a dose reduction. Similar associations were observed for patients who did *vs.* did not undergo at least one dose delay, although in the Gem-alone arm the difference in OS for patients with *vs.* without a dose delay was not statistically significant ($P=0.0589$).

The reasons for the apparent link between efficacy and dose modification are not immediately clear. One possible explanation is that some patients may be inherently more sensitive to the drugs than others, potentially leading to increased efficacy, more prolonged exposure, and increased chance of experiencing a toxicity requiring dose modification. An alternative possibility is that dose modification in response to a toxicity may have allowed patients to receive greater treatment exposure (more cycles and higher cumulative dose) and that this greater exposure resulted in better clinical outcomes. Although the available data do not allow a definitive explanation for the association of dose modification with efficacy, a number of analyses presented here minimize the likelihood that the link is an artifact attributable to the presumed lower rate of dose modification among patients with early disease progression or death.

Although we are not aware of any studies in pancreatic cancer that have demonstrated a link between dose modification and better efficacy, associations have been observed between efficacy and the development of rash in patients treated with erlotinib for pancreatic cancer or

non-small cell lung cancer (30). In pancreatic cancer, the presence of grade ≥ 2 rash was significantly associated with longer OS (HR, 0.47; 95% CI, 0.34–0.64; $P<0.001$) and PFS (HR, 0.46; 95% CI, 0.33–0.65; $P<0.001$). Also, in the adjuvant treatment of stage III colon cancer, an association was reported between a capecitabine-specific adverse reaction and long-term efficacy (31). A post hoc analysis of data from the X-ACT trial demonstrated that capecitabine-treated patients who developed hand-foot syndrome had higher 5-year disease-free and OS rates compared with patients who did not develop the syndrome (61.3% *vs.* 55.5% and 73.8% *vs.* 66.3%, respectively).

The MPACT trial has firmly established *nab*-P 125 mg/m² + Gem 1,000 mg/m² the first 3 of 4 weeks as a novel, effective, and fairly well tolerated treatment option in patients with metastatic pancreatic cancer. Based on the present data investigating the use of dose reduction and/or delay of chemotherapeutic drugs to manage toxicities, as well as the effect of dose modification on efficacy, the following conclusions can be drawn: (I) there is a need to carefully monitor patients for neutropenia, thrombocytopenia, peripheral neuropathy, and fatigue; (II) the methods of dose modification outlined in the trial protocol were effective and should be followed in routine clinical practice; (III) these dose adjustments can be carried out with the knowledge that they do not reduce the efficacy of the established 125 mg/m² starting *nab*-P dose. Our data highlight the importance of titrating the dose of chemotherapeutic drugs to the individual patient, a strategy that, according to this exploratory analysis, seems to result in an optimal therapeutic outcome.

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Footnote

Conflicts of Interest: WS—reports grants, personal fees (for consultant, advisory board & invited speaker activities) and non-financial support (study medication drug supply) from Celgene Corporation, during the conduct of the study; RKR—reports grants and personal fees from Celgene Corporation, outside the submitted work; MM—reports grants from Celgene Corporation, during the conduct of

the study; personal fees from Celgene Corporation outside the submitted work; TG—nothing to disclose; DG—reports grants from Celgene Corporation, during the conduct of the study; grants from Pfizer, grants from Amgen, outside the submitted work; PH—reports consulting for Celgene Corporation during the conduct of the study; VK—reports honoraria for consulting and lectures by Celgene Corporation; HL—reports employment, stock ownership from Celgene Corporation; DM—reports employment, stock ownership from Celgene Corporation; AR—reports employment, stock ownership from Celgene Corporation; DDVH—reports consultant, honoraria, and research funding, Celgene Corporation.

Disclaimer: The authors were fully responsible for all content and editorial decisions for this manuscript.

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Supplementary

Table S1 Dose modification for other adverse events

Adverse event	<i>nab-P</i>	Gem
Grade 3 or 4 febrile neutropenia	Withhold until fever resolves and ANC $\geq 1,500 \text{ mm}^3$, resume at next lower dose level	
Grade 3 or 4 peripheral neuropathy	Withhold until improvement to grade ≤ 1 ; resume at next lower dose level	No dose reduction
Grade 2 or 3 cutaneous toxicity	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Grade 3 mucositis or diarrhea	Withhold until improvement to grade ≤ 1 ; resume at next lower dose level	

ANC, absolute neutrophil count; Gem, gemcitabine; *nab-P*, *nab*-paclitaxel.

Table S2 Baseline characteristics of patients with or without dose modifications

Variable	<i>nab</i> -P + Gem			Gem		
	ITT (n=431)	<i>nab</i> -P dose reduced (n=172)	<i>nab</i> -P dose delay (n=300)	ITT (n=431)	Dose reduced (n=132)	Dose delay (n=230)
Age						
Median years [range]	62 [27-86]	61 [27-83]	62 [27-83]	63 [32-88]	63 [38-88]	64 [38-88]
<65 years, %	59	58	58	56	55	56
≥65 years, %	41	42	42	44	45	44
Male, %	57	52	57	60	59	57
Race, %						
Asian	2	1	2	2	2	3
Black	4	3	4	4	5	3
White	88	88	86	87	89	88
Hispanic	6	6	6	6	5	6
Other	1	1	1	1	0	<1
KPS, %						
100	16	13	19	16	20	17
90	42	47	41	46	47	50
80	35	37	33	30	27	28
70	7	3	6	8	5	5
Pancreatic primary tumor location, %						
Head	44	44	46	42	39	44
Body	31	33	32	32	36	29
Tail	24	23	22	26	23	27
Unknown	1	1	1	1	1	<1
Current site(s) of metastasis, %						
Liver	85	85	85	84	78	82
Lung	35	40	35	43	42	43
Peritoneum	4	6	4	2	2	2
No. of metastatic sites, %						
1	8	6	7	5	6	3
2	47	45	50	48	48	48
3	32	31	29	33	36	35
>3	14	18	15	15	9	13
CA19-9 level ^a						
Median, U/mL	2,294	2,381	2,588	2,759	2,028	2,172
Normal, %	16	16	14	15	15	14
ULN to <59× ULN, %	32	27	27	32	30	32
≥59× ULN, %	52	47	49	53	45	47
Prior procedure, %						
Whipple procedure	7	6	6	7	10	6
Biliary stent	19	19	19	16	14	19

^a, not all patients have Lewis antigens and thus cannot secrete CA19-9. The evaluable n for CA19-9 for the ITT population was 379 patients in the *nab*-P + Gem group and 371 patients in the Gem-alone group. CA19-9, cancer antigen 19-9; Gem, gemcitabine; ITT, intent-to-treat; KPS, Karnofsky performance status; *nab*-P, *nab*-paclitaxel; ULN, upper limit of normal.

Table S3 Multivariate analyses of overall survival in ITT and treatment arms, including effect of dose modification

Covariate	Hazard ratio	95% CI	P value
Intent to treat (both arms)			
Treatment group (<i>nab</i> -P + Gem vs. Gem)	0.79	0.660–0.936	0.007
Age (<65 vs. ≥65 years)	0.84	0.712–1.002	0.052
KPS (70–80 vs. 90–100)	1.56	1.318–1.855	<0.001
Presence of liver metastases (yes vs. no)	1.78	1.385–2.297	<0.001
No. of metastatic sites (1 vs. 2 vs. 3 vs. 4 vs. 5 vs. 6)	1.11	1.015–1.222	0.023
Dose reduction (yes vs. no)	0.61	0.506–0.733	<0.001
Dose delay (yes vs. no)	0.77	0.642–0.931	0.007
<i>nab</i> -P + Gem arm only (including effect of dose reduction)			
Geographic region (Eastern Europe vs. North America)	1.76	1.281–2.410	<0.001
Age (<65 vs. ≥65 years)	0.77	0.606–0.980	0.034
KPS (70–80 vs. 90–100)	1.26	0.990–1.615	0.061
Presence of liver metastases (yes vs. no)	1.38	0.954–1.998	0.087
Previous Whipple procedure (yes vs. no)	0.61	0.386–0.970	0.037
Dose reduction (yes vs. no)	0.53	0.414–0.690	<0.001
<i>nab</i> -P + Gem arm only (including effect of dose delay)			
Geographic region (Eastern Europe vs. North America)	1.48	1.086–2.021	0.013
Age (<65 vs. ≥65 years)	0.75	0.588–0.952	0.018
KPS (70–80 vs. 90–100)	1.34	1.048–1.704	0.019
Presence of liver metastases (yes vs. no)	1.45	1.003–2.093	0.048
Previous Whipple procedure (yes vs. no)	0.60	0.379–0.958	0.032
Dose delay (yes vs. no)	0.51	0.390–0.672	<0.001
Gem arm only (including effect of dose reduction)			
KPS (70–80 vs. 90–100)	1.83	1.435–2.333	<0.001
Primary tumor location (head vs. other)	1.26	0.981–1.611	0.070
CA19-9 value at baseline (<ULN vs. ULN to 59× ULN vs. >59× ULN)	1.23	1.035–1.466	0.019
Presence of liver metastases (yes vs. no)	1.95	1.368–2.790	<0.001
No. of metastatic sites (1 vs. 2 vs. 3 vs. 4 vs. 5 vs. 6)	1.19	1.039–1.357	0.012
Dose reduction (yes vs. no)	0.61	0.466–0.789	<0.001
Gem arm only (including effect of dose delay)			
KPS (70–80 vs. 90–100)	1.84	1.439–2.346	<0.001
Primary tumor location (head vs. other)	1.30	1.016–1.674	0.037
CA19-9 value at baseline (<ULN vs. ULN to 59× ULN vs. >59× ULN)	1.25	1.055–1.490	0.010
Presence of liver metastases (yes vs. no)	2.08	1.457–2.972	<0.001
Peritoneal carcinomatosis (yes vs. no)	2.14	0.978–4.669	0.057
No. of metastatic sites (1 vs. 2 vs. 3 vs. 4 vs. 5 vs. 6)	1.14	0.997–1.309	0.055

Baseline factors examined for each model included age (<65 vs. ≥65 years), sex, KPS (70–80 vs. 90–100), geographic region [North America vs. each other region (Australia, Eastern Europe, Western Europe)], pancreatic cancer primary location (head vs. other), presence of biliary stent, previous Whipple procedure, presence of liver metastases, presence of pulmonary metastases, peritoneal carcinomatosis, stage of diagnosis (IV vs. other), number of metastatic sites (1 vs. 2 vs. 3 vs. 4 vs. 5 vs. 6), level of CA19-9 (<ULN vs. ULN to 59× ULN vs. >59× ULN). In the intent-to-treat analysis, both dose reduction (yes vs. no) and dose delay (yes vs. no) were added to the list of covariates, as was treatment group. In the individual treatment-arm analyses, dose reduction only or dose delay only was added. To remain in the multivariate model, a covariate was required to have a P value of <0.10; otherwise, that covariate would fall out of the model. cancer antigen 19-9; Gem, gemcitabine; ITT, intent-to-treat; CA19-9, KPS, Karnofsky performance status; *nab*-P, *nab*-paclitaxel; ULN, upper limit of normal.

Table S4 OS by dose modification in patients without progressive disease in the first 8 weeks

Variable	<i>nab</i> -P + Gem		Gem only	
	<i>nab</i> -P dose reduction	<i>nab</i> -P dose delay	Gem dose reduction	Gem dose delay
With dose modification				
OS, median, mo	11.5	10.7	9.2	7.7
n	165	281	119	202
Without dose modification				
OS, median, mo	7.6	6.1	5.9	6.3
n	225	109	232	149
HR (95% CI)	0.53 (0.412–0.671)	0.48 (0.371–0.629)	0.57 (0.441–0.739)	0.74 (0.583–0.946)
P value	<0.001	<0.001	<0.001	0.015

OS, overall survival; HR, hazard ratio; *nab*-P, *nab*-paclitaxel; Gem, gemcitabine.