

# Adjuvant *nab*-Paclitaxel + Gemcitabine in Resected Pancreatic Ductal Adenocarcinoma: Results From a Randomized, Open-Label, Phase III Trial

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**PURPOSE** This randomized, open-label trial compared the efficacy and safety of adjuvant *nab*-paclitaxel + gemcitabine with those of gemcitabine for resected pancreatic ductal adenocarcinoma (ClinicalTrials.gov identifier: [NCT01964430](https://clinicaltrials.gov/ct2/show/study/NCT01964430)).

**METHODS** We assigned 866 treatment-naive patients with pancreatic ductal adenocarcinoma to *nab*-paclitaxel (125 mg/m<sup>2</sup>) + gemcitabine (1,000 mg/m<sup>2</sup>) or gemcitabine alone to one 30-40 infusion on days 1, 8, and 15 of six 28-day cycles. The primary end point was independently assessed disease-free survival (DFS). Additional end points included investigator-assessed DFS, overall survival (OS), and safety.

**RESULTS** Two hundred eighty-seven of 432 patients and 310 of 434 patients completed *nab*-paclitaxel + gemcitabine and gemcitabine treatment, respectively. At primary data cutoff (December 31, 2018; median follow-up, 38.5 [interquartile range [IQR], 33.8-43 months), the median independently assessed DFS was 19.4 (*nab*-paclitaxel + gemcitabine) versus 18.8 months (gemcitabine; hazard ratio [HR], 0.88; 95% CI, 0.729 to 1.063; *P* = .18). The median investigator-assessed DFS was 16.6 (IQR, 8.4-47.0) and 13.7 (IQR, 8.3-44.1) months, respectively (HR, 0.82; 95% CI, 0.694 to 0.965; *P* = .02). The median OS (427 events; 68% mature) was 40.5 (IQR, 20.7 to not reached) and 36.2 (IQR, 17.7-53.3) months, respectively (HR, 0.82; 95% CI, 0.680 to 0.996; *P* = .045). At a 16-month follow-up (cutoff, April 3, 2020; median follow-up, 51.4 months [IQR, 47.0-57.0]), the median OS (511 events; 81% mature) was 41.8 (*nab*-paclitaxel + gemcitabine) versus 37.7 months (gemcitabine; HR, 0.82; 95% CI, 0.687 to 0.973; *P* = .0232). At the 5-year follow-up (cutoff, April 9, 2021; median follow-up, 63.2 months [IQR, 60.1-68.7]), the median OS (555 events; 88% mature) was 41.8 versus 37.7 months, respectively (HR, 0.80; 95% CI, 0.678 to 0.947; *P* = .0091). Eighty-six percent (*nab*-paclitaxel + gemcitabine) and 68% (gemcitabine) of patients experienced grade ≥ 3 treatment-emergent adverse events. Two patients per study arm died of treatment-emergent adverse events.

**CONCLUSION** The primary end point (independently assessed DFS) was not met despite favorable OS seen with *nab*-paclitaxel + gemcitabine.

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## INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer-related deaths.<sup>1-4</sup> Even with potentially curative surgery, the 5-year survival rate is approximately 20%.<sup>2,5</sup> Recent clinical trials in the adjuvant setting established survival benefits of gemcitabine + capecitabine and modified leucovorin

calcium (folinic acid), fluorouracil, irinotecan hydrochloride, oxaliplatin (FOLFIRINOX) over gemcitabine monotherapy in patients who initially presented with PDAC.<sup>6,7</sup> Therefore, gemcitabine + capecitabine and modified FOLFIRINOX are preferred category 1 recommendations for resected PDAC according to National Comprehensive Cancer Network Guidelines.<sup>8</sup>

## ASSOCIATED CONTENT

Appendix

Data Supplement  
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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## CONTEXT

### Key Objective

Pancreatic ductal adenocarcinoma has a poor prognosis even after surgical resection. This phase III study compared the efficacy and safety of adjuvant *nab*-paclitaxel + gemcitabine with gemcitabine in patients with surgically resected pancreatic ductal adenocarcinoma.

### Knowledge Generated

The primary end point of independently assessed disease-free survival was not met. However, overall survival favored *nab*-paclitaxel + gemcitabine versus gemcitabine (41.8 v 37.7 months) in the 5-year follow-up analysis.

### Relevance (G.K. Schwartz)

This negative randomized phase III study fails to change the standard of care for patients with resected pancreatic cancer. Five-year overall survival data from this study suggest the use of *nab*-paclitaxel + gemcitabine as a treatment alternative for selected patients who cannot receive modified FOLFIRINOX.\*

\*Relevance section written by JCO Associate Editor Gary K. Schwartz, MD.

The phase III MPACT trial demonstrated superiority of first-line *nab*-paclitaxel + gemcitabine versus gemcitabine monotherapy in metastatic PDAC.<sup>9,10</sup> The most common grade  $\geq 3$  adverse events (AEs) were neutropenia, leukopenia, fatigue, and peripheral neuropathy. *Nab*-paclitaxel + gemcitabine was hypothesized to extend disease-free survival (DFS) beyond the former gemcitabine standard in the adjuvant setting. The phase III AFACT trial investigated efficacy and safety of adjuvant *nab*-paclitaxel + gemcitabine compared with those of gemcitabine in patients who had undergone surgical resection for PDAC.

## METHODS

### Study Oversight

Steering committee members (Data Supplement, online only) and the sponsor designed this trial. Data were collected by investigators and analyzed by a sponsor-employed statistician. All aspects of the study were monitored by the sponsor.

### Patients

Patients were age  $\geq 18$  years, with histologically confirmed ductal PDAC with macroscopic complete resection, an Eastern Cooperative Oncology Group performance status  $\leq 1$ , and no history of metastatic or locally recurrent disease. Patients were required to have serum carbohydrate antigen 19-9  $< 100$  U/mL and no recurrent disease (per computed tomography or magnetic resonance imaging scans) at screening ( $\leq 14$  days of random assignment). Patients received no prior therapy (neoadjuvant, radiation, or systemic therapy) for PDAC. Patients were required to initiate adjuvant therapy  $\leq 12$  weeks of surgery (complete eligibility criteria, Data Supplement).

### Study Design

AFACT was a phase III, multicenter, open-label, randomized study conducted at 160 sites across 21 countries (EudraCT 2013-003398-91; ClinicalTrials.gov identifier: [NCT01964430](https://clinicaltrials.gov/ct2/show/study/NCT01964430)). Using a permuted-block random assignment method and interactive response technology, patients were randomly assigned 1:1 to receive *nab*-paclitaxel + gemcitabine or gemcitabine and stratified on the basis of resection status (R0 [tumor-free margin] v R1 [microscopically positive margin]), nodal status (lymph node–positive v lymph node–negative), and region (non-Asian regions [North America, Europe, and Australia] v Asia; a full list of countries, site names, and investigators can be found in Appendix [Table A1](#) [online only]).

The Protocol (online only) and informed consent forms were approved by each study site's independent ethics committee or institutional review board before study initiation. This study was conducted in accordance with Good Clinical Practice, as denoted in the International Council for Harmonisation E6 requirements, and with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained before any study-related procedure.

### Treatment

Patients received *nab*-paclitaxel 125 mg/m<sup>2</sup> followed by gemcitabine 1,000 mg/m<sup>2</sup> or gemcitabine 1,000 mg/m<sup>2</sup> alone as one intravenous infusion over 30-40 minutes on days 1, 8, and 15 of every 28-day cycle. Patients received six treatment cycles unless there was radiologic evidence of disease recurrence and unacceptable toxicity on the basis of the expert clinical judgment of the investigators or patient/physician decision otherwise. Supportive care could be administered per investigator's discretion. Two levels of dose modifications were permitted (Data Supplement).

## End Points and Assessments

The primary end point, independently assessed DFS, was defined as time from random assignment to disease recurrence or death. DFS values were not censored by the cause of death, so it is possible that not all deaths were due to PDAC. Independently assessed DFS was determined by radiologists blinded to the treatment assignment. Independent reviewers assessed disease recurrence on the basis of radiologic review (computed tomography or magnetic resonance imaging). Evaluation of new lesions followed RECIST version 1.1. After random assignment, disease recurrence was assessed every 8 weeks for the first 24 weeks and then every 12 weeks for the next 2.5 years until 3 years after random assignment. After 3 years, disease recurrence was assessed every 24 weeks up to 5.5 years after random assignment.

Secondary end points were overall survival (OS) and safety. AEs were coded using Medical Dictionary for Regulatory Activities v21.0 and graded for intensity according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. Investigators determined potential relationships between AEs and study treatments. Serious AEs were reported to the study sponsor's safety monitoring division.

Investigator-assessed DFS was evaluated in a prespecified sensitivity analysis; investigators determined recurrence using all available clinical information collected and evaluated using their expert judgment during the usual treatment of their patients. Independent review was not performed in real time or used to confirm investigator assessments (censoring rules provided in the Data Supplement). All patients were followed for survival. Initiation and types of new anticancer therapies were collected. Clinical assessments were made on days 1, 8, and 15 of each cycle (Data Supplement).

## Statistical Analyses

Original assumptions about DFS were based on historical outcomes of investigator-assessed median DFS with adjuvant gemcitabine (range, 13.4-14.3 months).<sup>11,12</sup> Contemporaneous phase III studies reported investigator-assessed median DFS with adjuvant gemcitabine ranging from 11.4 to 13.1 months.<sup>6,7,13</sup> On the basis of an independent assessment, to achieve the median DFS of 13.5 months (gemcitabine) and 18.5 months (*nab*-paclitaxel + gemcitabine; equivalent to a hazard ratio [HR], 0.73), approximately 438 DFS events were required to allow 90% power to detect a 27% reduction of risk in disease recurrence or death at a two-sided significance threshold of .05.

All efficacy analyses were conducted in the intent-to-treat population. Distribution of DFS was estimated using the Kaplan-Meier method; medians and two-sided 95% CIs were provided. DFS was compared between arms using the stratified log-rank test, with stratification factors of resection and lymph node status. The associated HR and two-sided 95% CI were provided using the stratified Cox proportional

hazards model. The same analyses were used for OS and investigator-assessed DFS. Percentage of protocol dose was calculated as percentage of dose intensity/protocol-specified weekly dose. All *P* values are descriptive and were not adjusted for multiplicity.

Concordance between independent and investigator review of disease recurrence was summarized. Patient data were censored in the independent review after the start of a new anticancer therapy or cancer-related surgery. Therefore, new lesions appearing afterward were not counted as recurrence. All statistical analyses were conducted using SAS v9.2 (SAS Institute, Cary, NC) or higher (Data Supplement).

## RESULTS

### Patients

One thousand two hundred twenty-six patients were screened, and 866 (71%) were enrolled between April 2014 and April 2016 in Europe (47%), North America (35%), Asia (12%), and Australia (6%), and randomly assigned to receive *nab*-paclitaxel + gemcitabine (*n* = 432) or gemcitabine (*n* = 434, Fig 1). Reasons for screen failure are given in the Data Supplement.

Demographic and baseline characteristics were balanced between arms (Table 1). The median age of patients was 64.0 years (interquartile range [IQR], 57.0-70.0). Most patients were men (56%) and had an Eastern Cooperative Oncology Group performance status of 0 (60%), R0 resection (76%), and lymph node involvement (72%).

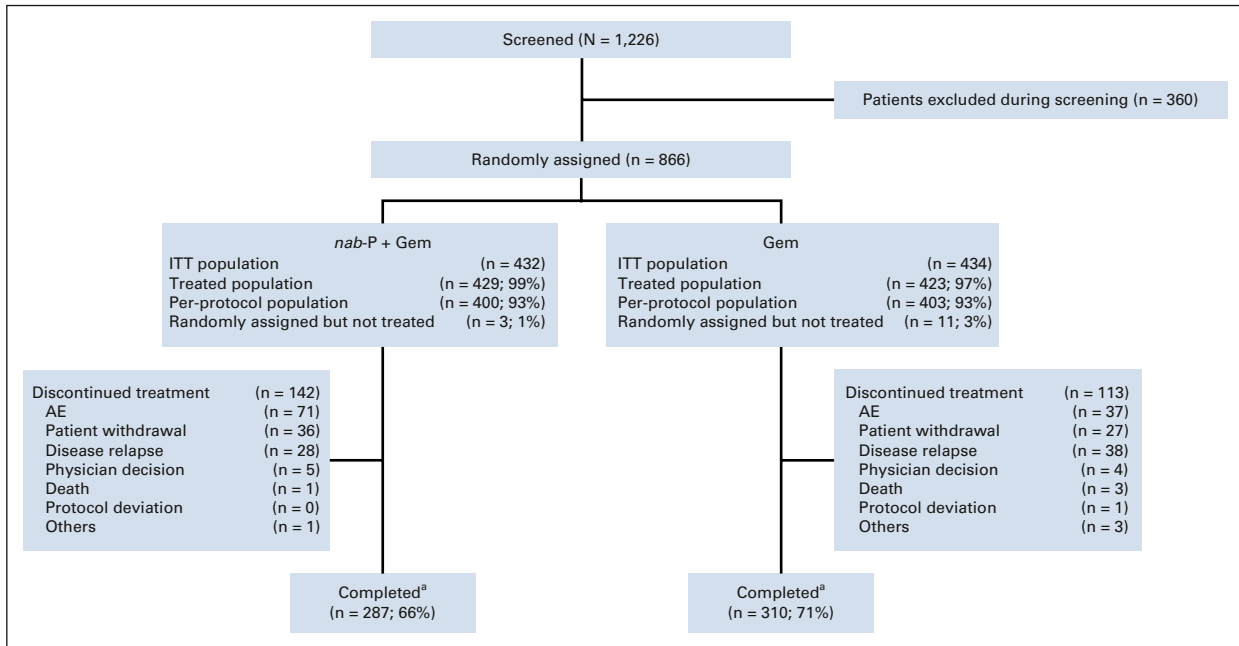
All analyses were conducted using data collected at the primary data cutoff (December 31, 2018) except for OS analyses, which were conducted at the primary data cutoff, the 16-month follow-up analysis cutoff (April 3, 2020), and the 5-year follow-up analysis cutoff (April 9, 2021).

### Treatment

One treatment cycle was defined as once-weekly administration of the study drug(s) for 3 weeks followed by 1 week without study treatment. In the treated population, six treatment cycles were administered to 69% (*nab*-paclitaxel + gemcitabine) and 75% (gemcitabine) of patients. The median treatment duration was 24 weeks in each arm (overall IQR, 20.1-24.3; Data Supplement). The median percentages of protocol dose that patients in the *nab*-paclitaxel + gemcitabine arm received were 75% (*nab*-paclitaxel) and 80% (gemcitabine) versus 91% with gemcitabine. In the *nab*-paclitaxel + gemcitabine arm, 64% of patients had  $\geq 1$  dose reduction; the corresponding rate in the gemcitabine arm was 50%. Dose omissions, delays, and intensity data are reported in the Data Supplement.

### Efficacy

At primary data cutoff (December 31, 2018), the median follow-up was 38.5 (IQR, 33.8-43.0) months. For the



**FIG 1.** CONSORT diagram. Flow diagram results between treatment arms after primary data cutoff (December 31, 2018). <sup>a</sup>Completed indicates patients who finished all six treatment cycles and received  $\geq 2$  doses of the study medication during cycle 6. AE, adverse event; Gem, gemcitabine; ITT, intent-to-treat; nab-P, nab-paclitaxel.

primary end point of independently assessed DFS, 439 of all treated patients (51%) had progressed or died. The median independently assessed DFS was 19.4 months (95% CI, 16.62 to 21.91) with nab-paclitaxel + gemcitabine versus 18.8 months (95% CI, 13.83 to 20.30) with gemcitabine. The difference between arms was not statistically significant (HR, 0.88; 95% CI, 0.729 to 1.063;  $P = .18$ ; Fig 2A).

For investigator-assessed DFS, 571 of all treated patients (66%) had experienced disease progression or died. The median investigator-assessed DFS was 16.6 months (95% CI, 14.55 to 19.29) with nab-paclitaxel + gemcitabine versus 13.7 months (95% CI, 11.24 to 16.00) with gemcitabine (HR, 0.82; 95% CI, 0.694 to 0.965;  $P = .02$ ; Fig 2B). The concordance between independent and investigator-assessed DFS was 77% (nab-paclitaxel + gemcitabine, 78%; gemcitabine, 76%). A summary of censoring is provided in the Data Supplement. Patients with recurrence per investigator assessment who started subsequent therapy ( $n = 26$  [nab-paclitaxel + gemcitabine] and  $n = 31$  [gemcitabine]) were censored for the independently assessed DFS analysis at initiation of subsequent anticancer therapy.

OS data at the primary data cutoff were 68% mature (427 of 630 target events); 48% (nab-paclitaxel + gemcitabine) and 51% (gemcitabine) of patients had died. The median OS was 40.5 months (IQR, 20.7 to not estimable) with nab-paclitaxel + gemcitabine compared with 36.2 (IQR, 17.7-53.3) months with gemcitabine (HR, 0.82; 95% CI, 0.680 to 0.996;  $P = .045$ ; Fig 2C).

A 16-month follow-up OS analysis was conducted (cutoff, April 3, 2020; median follow-up for survival, 51.4 [IQR, 47.0-57.0] months) on the basis of 511 events (81% mature); for nab-paclitaxel + gemcitabine versus gemcitabine, 57% versus 61% of patients had died. The median OS was 41.8 months (95% CI, 35.55 to 47.28) with nab-paclitaxel + gemcitabine versus 37.7 months (95% CI, 31.11 to 40.51) with gemcitabine (HR, 0.82; 95% CI, 0.687 to 0.973;  $P = .023$ ; Fig 2D).

A 5-year follow-up OS analysis was also conducted. At the cutoff (April 9, 2021), patients had been followed for  $\geq 5$  years or discontinued from the study. The overall median follow-up for OS was 63.2 (IQR, 60.1-68.7) months. A total of 268 and 287 events occurred in the nab-paclitaxel + gemcitabine and gemcitabine arms, respectively (88% mature); 62% versus 66% of patients had died. The median OS with nab-paclitaxel + gemcitabine was 41.8 months compared with 37.7 months with gemcitabine (HR, 0.80; 95% CI, 0.678 to 0.947;  $P = .0091$ ; Fig 2E). At a 5-year follow-up, the estimates of OS rates for  $\geq 5$  years were 38% with nab-paclitaxel + gemcitabine and 31% with gemcitabine.

### Subsequent Therapy

Overall, 55% (nab-paclitaxel + gemcitabine) and 56% (gemcitabine) of patients received a subsequent new anticancer therapy or cancer-related surgery (Data Supplement). Fluorouracil-based regimens (fluoropyrimidine monotherapy or a non-FOLFIRINOX combination; 26% [nab-paclitaxel + gemcitabine] versus 24% [gemcitabine])

**TABLE 1.** Demographic and Baseline Clinical Characteristics (intent-to-treat population)

Characteristic	<i>nab</i> -Paclitaxel + Gemcitabine (n = 432)	Gemcitabine (n = 434)	Total (n = 866)
Age, years			
Median (range)	64.0 (34-83)	64.0 (38-86)	64.0 (34-86)
< 65, No. (%)	221 (51)	225 (52)	446 (52)
≥ 65, No. (%)	211 (49)	209 (48)	420 (48)
< 75, No. (%)	382 (88)	399 (92)	781 (90)
≥ 75, No. (%)	50 (12)	35 (8)	85 (10)
Sex, No. (%)			
Female	204 (47)	181 (42)	385 (44)
Male	228 (53)	253 (58)	481 (56)
Race, No. (%)			
White	333 (77)	339 (78)	672 (78)
Asian	60 (14)	56 (13)	116 (13)
Black or African American	4 (1)	8 (2)	12 (1)
Others <sup>a</sup>	11 (3)	9 (2)	20 (2)
Not collected or reported	24 (6)	22 (5)	46 (5)
Region, No. (%)			
North America	144 (33)	156 (36)	300 (35)
Europe	203 (47)	205 (47)	408 (47)
Australia	30 (7)	20 (5)	50 (6)
Asia Pacific	55 (13)	53 (12)	108 (12)
ECOG PS, No. (%)			
0	252 (58)	268 (62)	520 (60)
1	180 (42)	166 (38)	346 (40)
Distance from tumor to the closest margin, mm, No. (%)			
< 1	114 (26)	112 (26)	226 (26)
≥ 1	287 (66)	292 (67)	579 (67)
Missing	31 (7)	30 (7)	61 (7)
Pancreatic cancer primary location, No. (%) <sup>b</sup>			
Head	354 (82)	347 (80)	701 (81)
Body	53 (12)	55 (13)	108 (12)
Tail	50 (12)	62 (14)	112 (13)
TNM classification, No. (%)			
T category			
T1	16 (4)	13 (3)	29 (3)
T2	38 (9)	37 (9)	75 (9)
T3	377 (87)	384 (88)	761 (88)
T4	1 (< 1)	0	1 (< 1)
N category			
N0	121 (28)	122 (28)	243 (28)
N1	311 (72)	312 (72)	623 (72)
M category			
M0	432 (100)	433 (> 99)	865 (> 99)
M1	0	1 (< 1)	1 (< 1)

(continued on following page)



**TABLE 1.** Demographic and Baseline Clinical Characteristics (intent-to-treat population) (continued)

Characteristic	<i>nab</i> -Paclitaxel + Gemcitabine (n = 432)	Gemcitabine (n = 434)	Total (n = 866)
Nodal status, No. (%)			
Lymph node–negative	121 (28)	122 (28)	243 (28)
Lymph node–positive	311 (72)	312 (72)	623 (72)
Resection status, No. (%)			
R0 (tumor-free margin)	327 (76)	334 (77)	661 (76)
R1 (microscopically positive margin)	105 (24)	100 (23)	205 (24)
Tumor grade, No. (%)			
Well differentiated	49 (11)	55 (13)	104 (12)
Moderately differentiated	264 (61)	241 (56)	505 (58)
Poorly differentiated	101 (23)	115 (26)	216 (25)
Undifferentiated	1 (< 1)	2 (< 1)	3 (< 1)
Unknown	9 (2)	5 (1)	14 (2)
Others	8 (2)	16 (4)	24 (3)
CA19-9			
No.	423	429	852
U/mL, median (IQR, Q1-Q3)	14.3 (6.9-27.4)	12.9 (5.9-27.6)	13.6 (6.3-27.5)
Level of CA19-9, No. (%)			
WNL	351 (81)	345 (80)	696 (80)
ULN < 100 U/mL	70 (16)	81 (19)	151 (17)
ULN ≥ 100 U/mL	2 (< 1)	3 (1)	5 (1)
Missing	9 (2)	5 (1)	14 (2)

Abbreviations: CA19-9, carbohydrate antigen 19-9; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; M, metastasis; N, node; Q1, quartile 1; Q3, quartile 3; R, resection; T, tumor; ULN, upper limit of normal; WNL, within normal limits.

<sup>a</sup>Includes patients who are Native Hawaiian or other Pacific Islander, American Indian, or Alaska Native.

<sup>b</sup>Patients could have multiple pancreas positions.

and FOLFIRINOX (21% v 18%) were most common. Eight percent of patients in the *nab*-paclitaxel + gemcitabine group and 21% in the gemcitabine arm received a new *nab*-paclitaxel–based subsequent therapy.

### Subgroup Efficacy Analyses

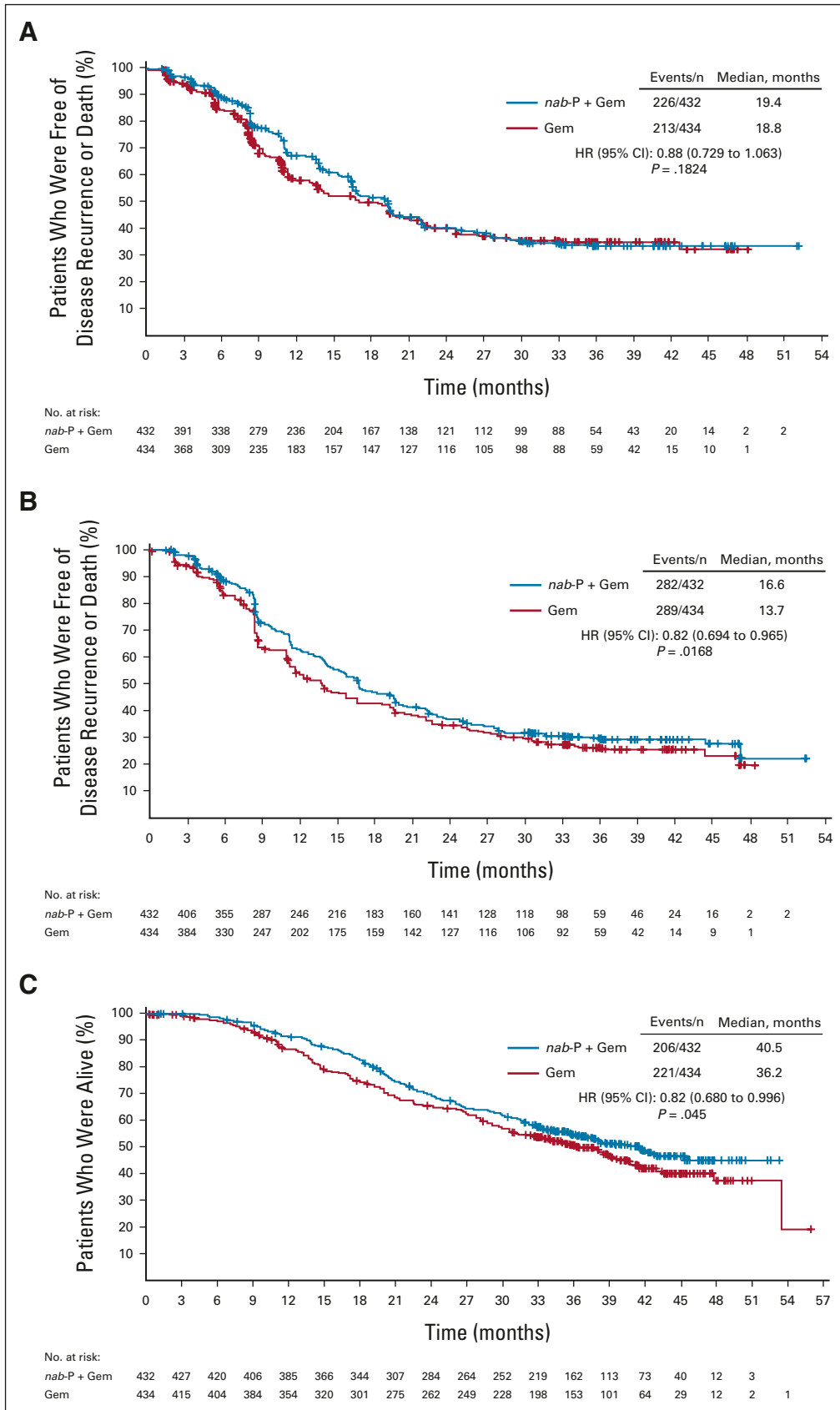
Results of the primary end point of independently assessed DFS in the primary analyses for prespecified subgroups are presented in [Figure 3A](#). Subgroup analyses of investigator-assessed DFS and OS were also performed (primary data cutoff, Data Supplement and [Fig 3B](#); 5-year follow-up data cutoff [OS only], Data Supplement). Patterns of independently assessed DFS ([Fig 3A](#)) and OS ([Fig 3B](#)) in the subgroups were generally consistent with observations from the intent-to-treat population.

### Safety

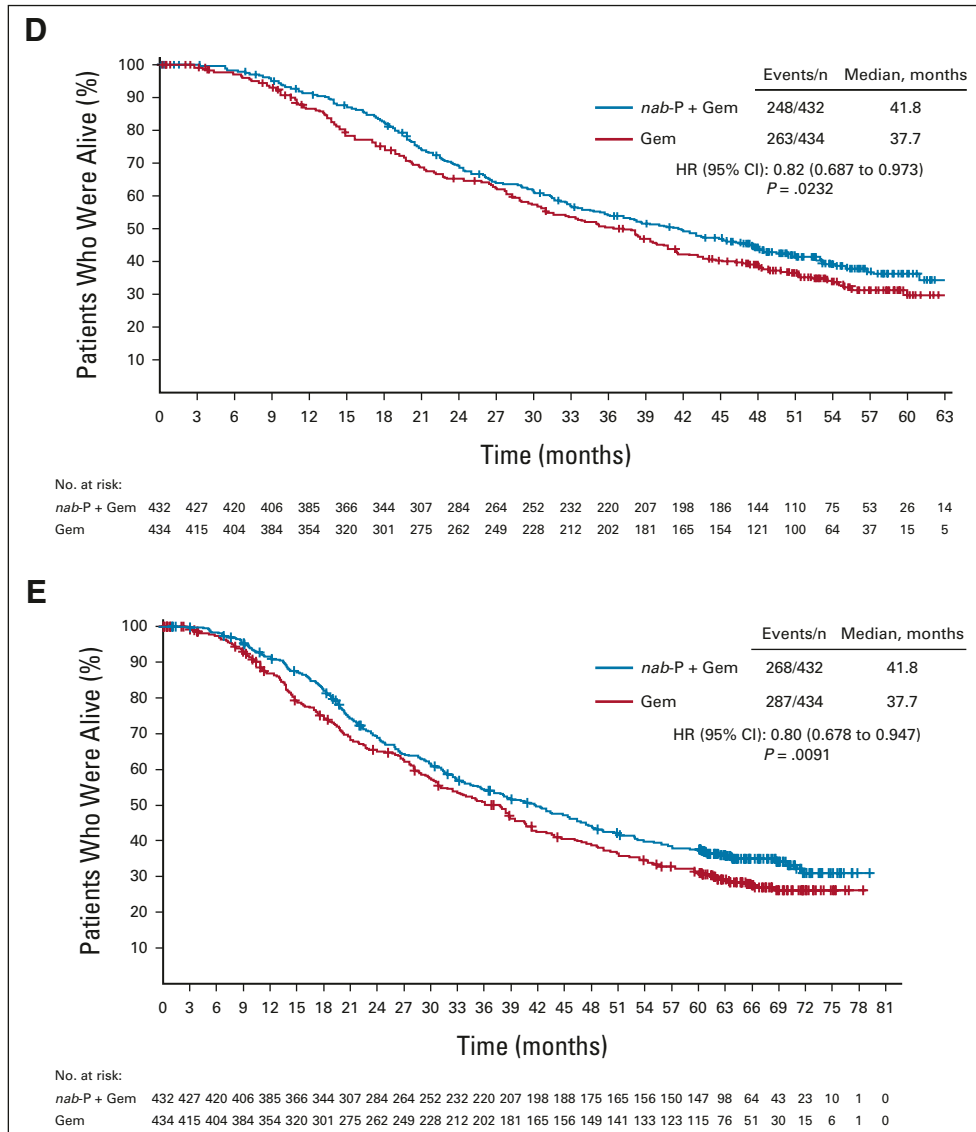
Treatment-emergent adverse event (TEAE) data reported herein are from the primary analysis (cutoff, December 31, 2018). All treated patients in the *nab*-paclitaxel + gemcitabine arm and 99% of those in the gemcitabine arm had ≥ 1 TEAE; grade ≥ 3 TEAEs were reported in 86% and 68% of patients,

respectively ([Table 2](#)). At least one serious TEAE occurred in 41% and 23% of patients, respectively. In the *nab*-paclitaxel + gemcitabine arm, 27% (*nab*-paclitaxel) and 17% (gemcitabine) of patients discontinued treatment because of TEAEs versus 10% in the gemcitabine arm. Two patients (< 1%) died in each arm because of TEAEs (*nab*-paclitaxel + gemcitabine arm: pneumonia and sepsis [n = 1 patient each]; gemcitabine arm: drug-induced liver injury and hepatic failure [n = 1] and capillary leak syndrome [n = 1]).

The most frequent grade ≥ 3 TEAEs with *nab*-paclitaxel + gemcitabine versus gemcitabine were neutropenia (49% v 43%), anemia (15% v 8%), and fatigue (10% v 3%). The incidence of grade ≥ 3 peripheral neuropathy was 15% (*nab*-paclitaxel + gemcitabine) versus 0% (gemcitabine). Among patients who experienced grade ≥ 3 peripheral neuropathy, 17% improved by ≥ 1 grade in a median of 195.0 days, whereas 16% improved to grade 1 or experienced resolution of peripheral neuropathy (median time to improvement, not reached). Of 77 treatment-emergent occurrences of grade ≥ 3 peripheral neuropathy observed among 64 patients, the majority (62%) commenced during cycle 4 or later. At the primary analysis



**FIG 2.** Kaplan-Meier curves of DFS and OS. Kaplan-Meier curves of DFS by (A) independent assessment and (B) investigator assessment (primary data cutoff, December 31, 2018). OS at data cutoffs (continued on following page)



**FIG 2.** (Continued). of the (C) primary analysis, (D) 16-month follow-up (April 3, 2020), and (E) 5-year follow-up (April 9, 2021). OS rates for  $\geq 5$  years were 38% with *nab*-paclitaxel + Gem and 31% with Gem. DFS, disease-free survival; Gem, gemcitabine; HR, hazard ratio; *nab*-P, *nab*-paclitaxel; OS, overall survival.

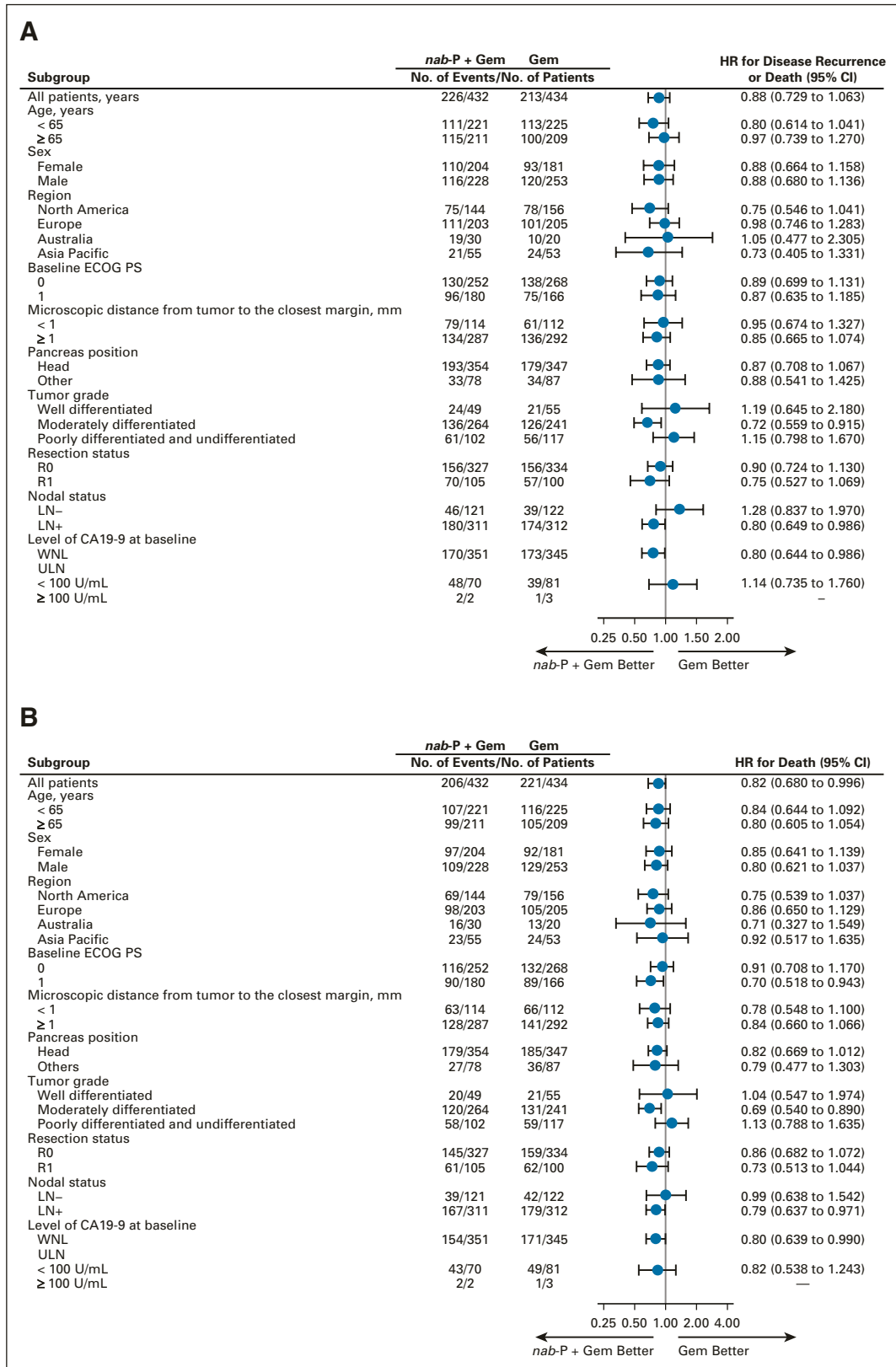
cutoff, 61% of all grade  $\geq 3$  peripheral neuropathy TEAEs were resolved. Additional grade  $\geq 3$  TEAEs of special interest included gastrointestinal events (10% v 2%), hepatic toxicity (6%, both arms), sepsis (5% v 2%), and febrile neutropenia (5% v 1%). White blood cell growth factor support was received by 153 (35%; *nab*-paclitaxel + gemcitabine) and 91 (21%; gemcitabine) patients.

**DISCUSSION**

The APACT trial did not meet the primary end point of independently assessed DFS. The prespecified sensitivity analysis of investigator-assessed DFS and the OS data suggested improved outcomes with

*nab*-paclitaxel + gemcitabine versus gemcitabine; however, since the primary end point was not met, comparisons are considered descriptive. The safety profile with adjuvant *nab*-paclitaxel + gemcitabine was generally consistent with data reported previously.<sup>9</sup> To our knowledge, APACT was the first trial of adjuvant treatment of PDAC to use blinded, centrally reviewed, independently assessed DFS as the primary end point, which was selected on the basis of an assumption that it would increase the scientific rigor of the trial and reduce possible unintentional investigator bias on survival outcomes. However, APACT was powered on the basis of investigator-assessed DFS data. This study offers a clinically important lesson for the field as radiographic





**FIG 3.** Forest plot subgroup analysis of DFS and OS. At the primary data cutoff (December 31, 2018), prespecified (A) blinded, independent, centrally reviewed DFS and (B) OS. CA19-9, carbohydrate antigen 19-9; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; HR, hazard ratio; LN, lymph node; *nab*-P, *nab*-paclitaxel; OS, overall survival; ULN, upper limit of normal; WNL, within normal limits.

postsurgical changes are sometimes difficult to distinguish from local recurrence.

A moderate concordance was observed between assessments of DFS. The discrepancy between the DFS analyses was likely due to the greater proportion of patients censored by independent assessments (48% [*nab*-paclitaxel + gemcitabine] and 51% [gemcitabine]) versus investigator assessments (35% [*nab*-paclitaxel + gemcitabine] and 33% [gemcitabine]) and the subsequent difference in number of DFS events (439 v 571 events, respectively). Per the investigator assessment, some patients were considered to have progressive disease and subsequent therapy was initiated. However, patients might not have met the formal radiologic criteria for progression; thus, their data were censored for central review at the time of initiation of subsequent therapy. Among patients who received gemcitabine monotherapy in AFACT, the independently assessed median DFS (18.8 months) was longer than the investigator-assessed DFS (13.7 months), a discrepancy similar to those with investigator assessments in the gemcitabine arms of previous trials, including ESPAC-4 (13.4 months) and PRODIGE-24 (12.8 months).<sup>6,7,11-13</sup> The results presented reflect complexities of accurately defining the recurrence time point. In addition, radiologic review in the absence of clinical context may be suboptimal for recurrence detection in resected PDAC, which represents a limitation of this study and could be considered in future trial designs in the adjuvant setting. Our findings suggest that radiologic data should be supported by clinical assessments (symptomatic deterioration, carbohydrate antigen 19-9 levels, pathology, and second-level diagnostic imaging such as positron-emission tomography). Furthermore, certain areas of recurrence,

such as in the surgical bed and mesenteric nodes, can be difficult to diagnose by imaging alone. These interpretations are consistent with an analysis of multiple ovarian cancer trials with similarly conflicting results.<sup>14</sup> Possible variations in the determination of resection status of patients represent a limitation in this study. Since AFACT enrolled patients globally, there was no central pathology review and there might have been regional differences in standards for defining R0 versus R1.

After the initiation of AFACT, capecitabine + gemcitabine and modified FOLFIRINOX became category 1–preferred regimens according to National Comprehensive Cancer Network Guidelines.<sup>8</sup> In the 16-month follow-up analysis, treatment with *nab*-paclitaxel + gemcitabine resulted in an effect on OS in AFACT (HR, 0.82) similar to capecitabine + gemcitabine in ESPAC-4 (HR, 0.82)<sup>6</sup> and a numerically higher 5-year survival rate (36% with *nab*-paclitaxel + gemcitabine in AFACT and 28% with gemcitabine-capecitabine in ESPAC-4<sup>15</sup>); however, these observations are not comparable because of differences in patient selection and subsequent therapy. Interestingly, the secondary end point of the phase II SWOG S1505 trial of perioperative *nab*-paclitaxel + gemcitabine versus modified FOLFIRINOX revealed a greater complete or major pathologic response rate and numerically longer DFS with *nab*-paclitaxel + gemcitabine specifically in patients undergoing resection.<sup>16</sup> Additional phase II data have suggested activity of perioperative *nab*-paclitaxel + gemcitabine.<sup>17-19</sup> Future studies investigating the impact of metastatic disease on patient response may elucidate the difference seen in DFS and OS.

The safety profile with adjuvant *nab*-paclitaxel + gemcitabine was generally consistent with that established by the phase III MPACT trial and revealed no unexpected AEs; however, some exceptions were noted. In both arms, grade  $\geq 3$  neutropenia was more frequent (49% with *nab*-paclitaxel + gemcitabine; 43% with gemcitabine) than in MPACT (38% with *nab*-paclitaxel + gemcitabine; 27% with gemcitabine). Although the 15% incidence of grade  $\geq 3$  peripheral neuropathy reported here was consistent with MPACT (17%), peripheral neuropathy in most patients in AFACT (84% of those who experienced grade  $\geq 3$  peripheral neuropathy) had not improved to grade  $\leq 1$  as of the data cutoff for the primary analysis, an unexpected finding. However, 61% of all grade  $\geq 3$  peripheral neuropathy events were resolved at the time of the primary analysis. Incidences of grade  $\geq 3$  leukopenia, thrombocytopenia, and fatigue in the *nab*-paclitaxel + gemcitabine arm were numerically lower than what was observed in MPACT.<sup>9</sup> The qualitative differences in safety outcomes may be the greater treatment exposure and duration of taxane-based therapy in AFACT compared with the metastatic setting in MPACT. The median duration of treatment in both the *nab*-paclitaxel + gemcitabine and gemcitabine groups was 24 weeks (approximately 6 months in both groups), whereas the median duration of treatment

**TABLE 2.** Safety (treated population)

Grade $\geq 3$ TEAE <sup>a</sup>	<i>nab</i> -Paclitaxel + Gemcitabine (n = 429), No. (%)	Gemcitabine (n = 423), No. (%)
Patients with $\geq 1$ grade $\geq 3$ TEAE	371 (86)	286 (68)
Hematologic		
Neutropenia	212 (49)	184 (43)
Anemia	63 (15)	33 (8)
Leukopenia	36 (8)	20 (5)
Febrile neutropenia	21 (5)	4 (1)
Nonhematologic		
Peripheral neuropathy (SMQ)	64 (15)	0
Fatigue	43 (10)	13 (3)
Asthenia	21 (5)	8 (2)
Diarrhea	22 (5)	4 (1)
Hypertension	17 (4)	27 (6)

Abbreviations: SMQ, Standardized Medical Dictionary for Regulatory Activities Queries; TEAE, treatment-emergent adverse event.

<sup>a</sup>Reported in  $\geq 5\%$  of patients in either treatment arm by system organ class and preferred term.

in the MPACT trial was 3.9 months in the *nab*-paclitaxel + gemcitabine group and 2.8 months in the gemcitabine group.<sup>9</sup> The median percentage of protocol doses of gemcitabine was 80% (*nab*-paclitaxel + gemcitabine arm) versus 91% (gemcitabine arm); despite the *nab*-paclitaxel + gemcitabine arm receiving fewer doses of gemcitabine, the investigator-assessed DFS and the OS data still supported improved outcomes with *nab*-paclitaxel + gemcitabine versus gemcitabine. This leaves two possible explanations: (1) the 11% difference had a negligible impact on outcomes and (2) the addition of *nab*-paclitaxel to gemcitabine might have compensated for any potential loss in efficacy from the 11% lower dose of gemcitabine in the combination arm.

The trial did not meet the primary end point; nonetheless, the median OS results in the 5-year follow-up analysis (April

9, 2021; 41.8 v 37.7 months [*nab*-paclitaxel + gemcitabine v gemcitabine, respectively]) provide valuable data pertinent to outcomes with adjuvant therapy in resected PDAC. Secondary analyses suggest that this regimen may provide insight when defining end points for future studies. Collectively, the data reflect the challenges of independent radiologic review without additional pertinent clinical data in this setting, particularly in a patient population highly selected for early-stage disease. Furthermore, *nab*-paclitaxel + gemcitabine represents an available treatment option for patients who cannot or prefer not to receive modified FOLFIRINOX or gemcitabine + capecitabine. Future analyses of the final OS, quality of life, and biomarker data may further inform management of patients with resected PDAC, particularly regarding the role of *nab*-paclitaxel + gemcitabine.

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Adjuvant nab-Paclitaxel + Gemcitabine in Resected Pancreatic Ductal Adenocarcinoma: Results From a Randomized, Open-Label, Phase III Trial**

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**Consulting or Advisory Role:** Bayer, Boehringer Ingelheim, Lilly, MSD, Merck Serono, Novartis, Sanofi, Taiho Pharmaceutical, Peptomyc, Chugai Pharma, Pfizer, Seattle Genetics, Array BioPharma, AstraZeneca, Genentech, Menarini, Servier, HaliuDx, F. Hoffmann LaRoche, Mirati Therapeutics, Pierre Fabre, Tessa Therapeutics, TheraMyx, Daiichi Sankyo, Samsung Bioepis, IQvia, Ikena Oncology, Merus, NeoPhore, Orion Biotechnology, Hutchison MediPharma, Scandion Oncology, Ona Therapeutics, SOTIO, Inspirna, Scorpion Therapeutics

**Other Relationship:** Medscape, MJH Life Sciences, PeerView, Physicians' Education Resource, Imedex/HMP

**Mingyu Li**

**Employment:** Ascentage Pharma

**Stock and Other Ownership Interests:** Bristol Myers Squibb/Celgene, Ascentage Pharma

**Stefano Ferrara**

**Employment:** SOTIO, BeiGene AG, Bristol Myers Squibb/Celgene/Juno (I)

**Stock and Other Ownership Interests:** BeiGene

**George Zhang**

**Employment:** Bristol Myers Squibb/Celgene

**Stock and Other Ownership Interests:** Bristol Myers Squibb/Celgene

**Brian Lu**

**Employment:** Bristol Myers Squibb/Celgene

**Stock and Other Ownership Interests:** Bristol Myers Squibb/Celgene

**Andrew V. Biankin**

**Employment:** AstraZeneca/MedImmune, BMSi

**Leadership:** Cambridge Cancer Genomics, Concr, Wollemia Oncology, Gabriel Precision Oncology, Cumulus Oncology

**Stock and Other Ownership Interests:** Cumulus Oncology, Modulus Oncology, Wollemia Oncology, Concur, Cambridge Cancer Genomics, Gabriel Precision Oncology, Humans.ai

**Honoraria:** Havas Lynx Group

**Consulting or Advisory Role:** AstraZeneca/MedImmune

**Speakers' Bureau:** Celgene

**Research Funding:** Celgene (Inst), AstraZeneca/MedImmune (Inst)

**Patents, Royalties, Other Intellectual Property:** Agilent Technologies—Royalty payments to Institute (University of Glasgow)

**Michele Reni**

**Consulting or Advisory Role:** Celgene, Lilly, AstraZeneca, Panavance Therapeutics, Viatrix, SOTIO, Servier, MSD/AstraZeneca

**Research Funding:** Celgene (Inst), AstraZeneca (Inst)

**Travel, Accommodations, Expenses:** Celgene

**Other Relationship:** Celgene, AstraZeneca

No other potential conflicts of interest were reported.

## APPENDIX

TABLE A1. List of AFACT Investigators and Sites

Country	Site Name	Principal Investigator
Australia	Prince of Wales Hospital	David Goldstein
	St Vincent's Hospital Sydney	Richard Epstein
	Icon Cancer Care South Brisbane	Paul Vasey
	Cabrini Hospital Malvern	Jeremy Shapiro
	Royal Brisbane & Women's Hospital	Matthew Burge
	The Canberra Hospital	Yu Jo Chua
	Monash Medical Center—Moorabbin Campus	Marion Harris
	Northern Cancer Institute, St Leonards	Nick Pavlakis
	St John of God Hospital Subiaco	Andrew Dean
	Austin Hospital	Niall Tebbutt
Austria	Medizinische Universität Wien	Gerald Prager
	Kaiser-Franz-Josef Spital	Christian Dittrich
	Landeskrankenhaus Wiener Neustadt	Friedrich Längle
	Universitätskrankenhaus Innsbruck	Kathrin Philipp-Abbrederis
	Salzburg Cancer Research Institute	Richard Greil
	Medizinische Universität Graz	Herbert Stöger
	A O Krankenhaus der Elisabethinen	Michael Girschikofsky
	Klinikum Wels-Grieskirchen GmbH	Thomas Kuehr
Belgium	UZ Leuven	Eric Van Cutsem
	Hôpital Erasme	Jean-Luc Van Laethem
	UZ Gent	Stéphanie Laurent
Canada	Princess Margaret Hospital	Neesha Dhani
	Sunnybrook Health Sciences Center Odette Cancer Centre	Yoo Joung Ko
	Tom Baker Cancer Centre	Scot Dowden
	Sir Mortimer B Davis Jewish General Hospital	Petr Kavan
	CHUM—Pavillon Asselin	Mustapha Édouard Tehfe
	Princess Margaret Hospital	Malcolm Moore
Czech Republic	Fakultni nemocnice Hradec Kralove	Eugen Kubala
	Krajska nemocnice T. Bati a.s.	Milan Kohoutek
Denmark	Odense Universitetshospital	Per Pfeiffer
	Aalborg Universitetshospital	Mette Yilmaz
	Herlev Hospital	Vibeke Parner
Finland	Tampereen Yliopistollinen Sairaala	Tapio Salminen
	Helsingin Yliopistollinen Keskussairaala	Leena-Maija Soveri
	Turun Yliopistollinen Keskussairaala	Eija Korkeila
	Temper University Hospital; Karolinska Institutet/University Hospital	Pia Osterlund

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TABLE A1. List of AFACT Investigators and Sites (continued)

Country	Site Name	Principal Investigator	
France	Hôpital Européen Georges Pompidou	Julien Taieb	
	CHRU de Poitiers La Miletie	David Tougeron	
	Hopital prive Jean Mermoz	Pascal Artru	
	CHU Angers	François Xavier Caroli-Bosc	
	Hôpital de Rangueil—PPDS	Rosine Guimbaud	
	CHRU Lille	Antony Turpin	
	Groupement Hospitalier Edouard Herriot	Thomas Walter	
	Groupe Hospitalier Pitié Salpêtrière	Jean Baptiste Bachet	
	Germany	Universitätskrankenhaus Würzburg	Volker Kunzmann
		Universitätskrankenhaus Tübingen	Florian Kreth
Charité—Universitätsmedizin Berlin		Uwe Pelzer	
Universitätskrankenhaus Hamburg Eppendorf		Andreas Block	
Universitätsklinikum Magdeburg		Marino Venerito	
Praxis für Innere Medizin Droettle Helmut		Helmut Oettle	
Klinikum Neuperlach		Meinolf Karthaus	
Universitätskrankenhaus Frankfurt		Jörg Trojan	
Universitätskrankenhaus Carl Gustav Carus an der TU Dresden		Gunnar Folprecht	
Universitätsmedizin Greifswald		Markus Lerch	
Klinikum Weiden		Frank Kullmann	
Praxis Internistischer Onkologie und Hämatologie Köln		Marcel Reiser	
LMU Klinikum der Universität München		Volker Heinemann	
Universitätsmedizin der Johannes Gutenberg—Universität Mainz		Marcus-Alexander Wörns	
Praxis Internistischer Onkologie und Hämatologie Frechen	Holger Schulz		
Charité-Universitätsmedizin Berlin	Hanno Riess		
Otto von Guericke University	Benjamin Garlipp		
Hong Kong	Queen Mary Hospital	Thomas Yau	
	Prince of Wales Hospital	Lam Stephen Chan	
Hungary	Debreceni Egyetem Klinikai Központ	Balazs Juhasz	
	Uzsoki Utcai Kórház	László Landherr	
	Petz Aladár Megyei Oktató Kórház	Tamas Pinter	
	Del-pesti Centrumkorház—Országos Hematológiai és Infektológiai Intezet	György Bodoky	
	Szegedi Tudományegyetem Szent-Györgyi Albert Klinikai Központ	Zsuzsanna Kahán	
Ireland	St Vincent's University Hospital	Raymond McDermott	
	Cork University Hospital—PIN	Derek Power	

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**TABLE A1.** List of AFACT Investigators and Sites (continued)

Country	Site Name	Principal Investigator
Italy	Azienda Ospedaliera Universitaria Integrata Di Verona	Giampaolo Tortora
	Ospedale San Raffaele S.r.l.—PPDS	Luca Gianni
	ASST Grande Ospedale Metropolitano Niguarda—Presidio Ospedaliero Ospedale Niguarda Ca' Granda	Salvatore Siena
	Istituto Nazionale Tumori Regina Elena	Michele Milella
	Azienda Ospedaliera Universitaria Pisana	Alfredo Falcone
	Azienda Ospedaliera Universitaria Ospedali Riuniti Umberto I-G.M. Lancisi-G. Salesi	Rossana Berardi
	Istituto Clinico Humanitas	Armando Santoro
	Fondazione Policlinico Universitario A Gemelli	Cinzia Bagalà
	Azienda Ospedaliera Universitaria Careggi	Francesco Di Costanzo
	Azienda Ospedaliera S Maria Di Terni	Fausto Roila
	Azienda Ospedaliera Universitaria Di Bologna—Policlinico S Orsola Malpighi	Andrea Arduzzoni
	Istituto Scientifico Romagnolo Per Lo Studio E La Cura Dei Tumori IRST	Giovanni Luca Frassinetti
	Ospedale Casa Sollievo Della Sofferenza IRCCS	Evaristo Maiello
	Arcispedale Santa Maria Nuova	Silvia Fanello
IRCCS Ospedale San Raffaele	Michele Reni	
Republic of Korea	Asan Medical Center—PPDS	Heung-Moon Chang
	Seoul National University Hospital	Do-Youn Oh
	Samsung Medical Center, Sungkyunkwan University School of Medicine—PPDS	Joon Oh Park
The Netherlands	Academisch Medisch Centrum Amsterdam	Johanna Wilmink
	Isala Klinieken	Jan Willem de Groot
	Catharina Hospital	Geert Creemers
Portugal	Centro Hospitalar de Lisboa Central	Eduardo Barroso
	Hospital da Luz	Tânia Rodrigues
	Centro Hospitalar de Sao Joao EPE	Cristina Sarmento
Singapore	National University Hospital	Cheng Ean Chee
	National Cancer Centre	David Tai
Spain	Hospital Universitario Vall d'Hebron—PPDS	Teresa Macarulla Mercade
	Hospital Universitario HM Sanchinarro—CIOCC	Manuel Hidalgo Medina
	Hospital Universitario Ramon y Cajal	Alfredo Carrato Mena
	Hospital Clinic de Barcelona	Joan Maurel Santasusana

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**TABLE A1.** List of AFACT Investigators and Sites (continued)

Country	Site Name	Principal Investigator	
	Hospital Universitario Virgen del Rocio	Maria Jose Flor Oncala	
	Hospital Universitario 12 de Octubre	Carlos Gomez Martin	
	CHUS – H. Clinico U. de Santiago	Rafael Lopez	
	Hospital General Universitario Gregorio Marañon	Andres Muñoz	
	Complejo Hospitalario de Navarra	Ruth Vera Garcia	
	Hospital Regional Universitario de Malaga—Hospital General	Inmaculada Ales	
	ICO l'Hospitalet—Hospital Duran i Reynals	Berta Laquente Sáez	
	Hospital Universitario Marques de Valdecilla	Fernando Rivera	
	Hospital Clinico San Carlos	Javier Sastre	
	Vall d'Hebron University Hospital and Institute of Oncology (VHIO)	Josep Tabernero	
	Taiwan	Taichung Veterans General Hospital	Cheng-Chung Wu
		National Taiwan University Hospital	Yu-Wen Tien
Tri-Service General Hospital		De-Chuan Chan	
Taipei Veterans General Hospital		Chung-Pin Li	
Chang Gung Memorial Hospital, Linkou		Tsann-Long Hwang	
National Cheng Kung University Hospital		Yan-Shen Shan	
United Kingdom	University of Glasgow—PPDS	Jeffry Evans	
	Weston Park Hospital	Jonathan Wadsley	
	Addenbrooke's Hospital	Pippa Corrie	
	University of Glasgow	Andrew Biankin	
United States	University of California San Francisco	Andrew Ko	
	Vanderbilt University Medical Center	Dana Cardin	
	Seattle Cancer Care Alliance	Elena Chiorean	
	SCRI Tennessee Oncology Nashville	Johanna Bendell	
	Ohio State University Comprehensive Cancer Center	Anne Noonan	
	University of Chicago	Hedy Kindler	
	Northside Hospital	Nishan Fernando	
	Memorial Sloan Kettering Cancer Center	Eileen M. O'Reilly	
	Karmanos Cancer Institute	Philip Philip	
	University of Texas Southwestern Medical Center	Muhammad Beg	
	University of Florida	Thomas George	
	University of Rochester Medical Center	Marcus Noel	
	University of Wisconsin	Noelle LoConte	
	NYU Langone Medical Center	Francis Arena	
	Thomas Jefferson University	James Posey	

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**TABLE A1.** List of AFACT Investigators and Sites (continued)

Country	Site Name	Principal Investigator
	Thomas Jefferson University	Jordan Winter
	Illinois Cancer Specialists (Niles)—USOR	Rajat Malhotra
	Oregon Health and Science University	Charles Lopez
	Cleveland Clinic	Davendra Sohal
	Mayo Clinic—PPDS	Robert McWilliams
	Lynn Cancer Institute	Warren Brenner
	SCRI Tennessee Oncology Chattanooga	Mark Womack
	State University of New York Upstate Medical Center (SUNY)	Rahul Seth
	Roswell Park Cancer Institute	Renuka Iyer
	UPMC Cancer Pavillion	Nathan Bahary
	NorthShore University HealthSystem Research Institute	Robert Marsh
	Ochsner Cancer Institute	Robert Ramirez
	Oncology Hematology Care Inc	Cynthia Chua
	SCRI Florida Cancer Specialists South	James Reeves
	Columbia University Medical Center	Gulam Manji
	University of Southern California	Anthony El-Khoueiry
	SCRI Florida Cancer Specialists South	Robert Weaver
	University of Michigan	Vaibhav Sahai
	University of Colorado	Wells Messersmith
	University of Virginia	Robert Dreicer
	Florida Hospital Cancer Institute	Ahmed Zakari
	Beth Israel Deaconess Medical Center	Andrea Bullock

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**TABLE A1.** List of AFACT Investigators and Sites (continued)

Country	Site Name	Principal Investigator
	Baylor College of Medicine	Benjamin Musher
	Mayo Clinic Arizona—PPDS	Mitesh Borad
	The Regents of the University of California	Edward Kim
	Case Western University	David Bajor
	Methodist Cancer Center	Tim Huyck
	University of Oklahoma Peggy and Charles Stephenson Cancer Center	Hassan Hatoum
	The Center for Cancer and Blood Disorders	Henry Xiong
	Wake Forest University School of Medicine	Boris Pasche
	Yale University School of Medicine	Jill Lacy
	University of Cincinnati	Olugbenga Olowokure
	Rocky Mountain Cancer Centers (Williams)—USOR	Allen Cohn
	Texas Oncology (Loop)—USOR	Donald Richards
	University of Louisville	Robert Martin
	Baylor Sammons Cancer Center	Andrew Paulson
	University of California San Diego	Paul Fanta
	University of California, San Francisco; Helen Diller Comprehensive Cancer Center	Margaret A. Tempero
	Mayo Clinic Cancer Center	Tanios Bekaii-Saab
	Vanderbilt-Ingram Cancer Center	Jordan Berlin
	Cleveland Clinic	Smitha Krishnamurthi
	Columbia University Medical Center	Paul Oberstein
	Ochsner Clinic Foundation	Jyotsna Fuloria