**SUPPLEMENTARY APPENDIX**

# Tempero MA, Pelzer U, O'Reilly EM, et al. Adjuvant *nab*-Paclitaxel Plus Gemcitabine in Resected Pancreatic Cancer: Results From A Randomized, Open label, Phase 3 Trial

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**Appendix 2.** Complete inclusion and exclusion criteria.

*Inclusion criteria*

1. Histologically confirmed resected PDAC with macroscopic complete resection (R0 and R1). Patients with neuroendocrine (and mixed type) tumors were excluded

2. Pancreatic ductal adenocarcinoma (PDAC) staging: T1-3, N0-1, M0

3. Patient should be able to start treatment no later than 12 weeks postsurgery

4. Male or nonpregnant, nonlactating females who are ≥18 years of age at the time of signing the informed consent form

5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1

6. Acceptable hematology parameters:

- Absolute neutrophil count (ANC) ≥1500 cell/$mm^3$
- Platelet count ≥100,000/$mm^3$
- Hemoglobin ≥9 g/dL

7. Acceptable blood chemistry levels:

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit of normal range (ULN)
- Total bilirubin ≤ULN (patients with Gilbert syndrome could have bilirubin of up to 1.5 × ULN)
- Alkaline phosphatase ≤2.5 × ULN
- Serum creatinine within ULNs or calculated clearance ≥50 mL/min/1.73 $m^2$. If using creatinine clearance, actual body weight should be used for calculating creatinine clearance (e.g., using the Cockroft-Gault formula). For patients with a body mass index >30 kg/$m^2$, lean body weight should be used instead

8. Carbohydrate antigen 19-9 (CA19-9) <100 U/mL assessed within 14 days of randomization

9. Acceptable coagulation studies (e.g., prothrombin time or international normalized ratio and partial thromboplastin time within normal limits (WNLs), ±15%)

10. Females of child-bearing potential (defined as a sexually mature woman who has not undergone hysterectomy [the surgical removal of the uterus] or bilateral oophorectomy [the surgical removal of both ovaries] or has not been naturally postmenopausal for at least 24 consecutive months [i.e., has had menses at any time during the preceding 24 consecutive months]) must:

- Agree to the use of two physician-approved contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intrauterine device; barrier contraceptive with spermicide; or vasectomized partner) while on study investigational product (IP); and for 3 months following the last dose of IP; and
- Has negative serum pregnancy test result at screening

11. Male patients must practice true abstinence (true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions, and for 6 months following IP discontinuation—even if he has undergone a successful vasectomy

12. Understand and voluntarily sign an informed consent form prior to any study-related assessments or procedures being conducted

13. Be able to adhere to the study visit schedule and other protocol requirements

*Exclusion criteria*

1. Prior neoadjuvant treatment, radiation therapy, or systemic therapy for pancreatic adenocarcinoma

2. Presence of or history of metastatic or locally recurrent PDAC

3. Any other malignancy within 5 years prior to randomization, with the exception of adequately treated in situ carcinoma of the cervix, uteri, or nonmelanomatous skin cancer (all treatment of which should have been completed 6 months prior to randomization)

4. Active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy—defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment

5. Known history of human immunodeficiency virus (HIV) infection or known history of active hepatitis B or C and are currently serologically positive with evidence of prior or signs of active chronic hepatitis

6. History of allergy or hypersensitivity to *nab*-paclitaxel or gemcitabine or any of their excipients

7. Serious medical risk factors involving any of the major organ systems or serious psychiatric disorders, which could compromise the patient's safety or the study data integrity. These include, but are not limited to:

- History of connective tissue disorders (e.g., lupus, scleroderma, arteritis nodosa)
- History of interstitial lung disease, slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis, or multiple allergies

- History of the following within 6 months prior to cycle 1 day 1: a myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association Class III-IV heart failure, uncontrolled hypertension, clinically significant cardiac dysrhythmia or electrocardiogram abnormality, cerebrovascular accident, transient ischemic attack, or seizure disorder
- Peripheral neuropathy grade ≥2
- Concomitant use of immunosuppressive or myelosuppressive medications that would, in the opinion of the investigator, increase the risk of serious neutropenic complications

8. Enrollment in any other clinical protocol or investigational study with an interventional agent or assessments that may interfere with study procedures

9. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from participating in the study

10. Any condition including the presence of laboratory abnormalities, which places the patient at unacceptable risk if he/she were to participate in the study

11. Any condition that confounds the ability to interpret data from the study

12. Unwillingness or inability to comply with study procedures

**Appendix 3.** Dose modifications.

Doses could be reduced for hematologic and other toxicities, based on the highest grade as defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0. For each drug, two levels of dose modifications were allowed, one level at a time, as described in Supplementary Table 1.

**Table S1.** Levels of dose modifications.

| **Dose Level** | ***nab*-Paclitaxel (mg/m$^2$)*** | **Gemcitabine (mg/m$^2$)*** |
|---|---|---|
| Study dose | 125 | 1000 |
| –1 | 100 | 800 |
| –2 | 75 | 600 |

***** Dose reductions may or may not be concomitant. If the dose was withheld due to hematologic toxicity on day 15, with either a held dose or no dose modification on day 8, patients were to be considered for either treatment at the next lower dose level and/or addition of white blood cell (WBC) growth factor support when the patient had adequate ANC and platelet counts to begin day 1 of the next cycle.

If dose modifications were required at the start of a cycle or within a cycle due to neutropenia and/or thrombocytopenia, doses of *nab*-paclitaxel and gemcitabine could be adjusted as detailed in **Table S2**. In the combination arm, the investigator could hold one agent while continuing the other and remain on study. The combination could be restarted at the discretion of the treating physician.

WBC growth factor could be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in patients with an ANC <500 cells/mm$^3$. Patients not experiencing resolution of neutropenia within 21 days, despite uninterrupted WBC growth factor treatment, had to discontinue study treatment. In addition, WBC growth factors could be administered as

supportive therapy to recover ANC adequately such that dosing levels were maintained. If a dose reduction was required due to neutropenia, a dose re-escalation could be considered with continued growth factor support. If a dose reduction was required for a reason other than neutropenia, a dose re-escalation could be permitted after discussion with the sponsor. If hematologic toxicity was restricted to platelet counts alone, dose modification of only gemcitabine could be considered after discussion with the sponsor. Dose modifications for other adverse drug reactions (ADRs) are provided in Supplementary Table 3.

**Table S2.** Dose modifications for neutropenia and/or thrombocytopenia.

| **Cycle Day** | **ANC (cells/mm$^3$)** | | **Platelet Count (cells/mm$^3$)** | ***nab*-Paclitaxel or gemcitabine dose** |
|---|---|---|---|---|
| **Day 1** | ≥1500 | AND | ≥100,000 | Treat on time at current dose levels |
| | <1500 | OR | <100,000 | Delay doses until recovery |
| **Day 8** | ≥1000 | AND | ≥75,000 | Treat on time at current dose levels |
| | ≥500 but <1000 | OR | ≥50,000 but <75,000 | Reduce doses one dose level |
| | <500 | OR | <50,000 | Withhold doses |
| **Day 15: if day 8 doses were given without modification:** | | | | |
| **Day 15** | ≥1000 | AND | ≥75,000 | Treat on time at current dose levels |
| | ≥500 but <1000 | OR | ≥50,000 but <75,000 | Reduce doses one dose level from day 8; consider following with WBC growth factors for support* |
| | <500 | OR | <50,000 | Withhold doses |
| **Day 15: if day 8 doses were reduced:** | | | | |
| **Day 15** | ≥1000 | AND | ≥75,000 | Treat with same doses as on day 8; consider following with WBC growth factors for support* |
| | ≥500 but <1000 | OR | ≥50,000 but <75,000 | Reduce doses one dose level from day 8; consider following with WBC growth factors for support* |
| | <500 | OR | <50,000 | Withhold doses |
| **Day 15: if day 8 doses were withheld:** | | | | |
| **Day 15** | ≥1000 | AND | ≥75,000 | Option A: maintain dose level from day 1 and follow with WBC growth factors for support*<br>OR<br>Option B: reduce doses one dose level from day 1 |
| | ≥500 but <1000 | OR | ≥50,000 but <75,000 | Option A: reduce one dose level from day 1 and follow with WBC growth factors for support*<br>OR<br>Option B: reduce doses two dose levels from day 1 |
| | <500 | OR | <50,000 | Withhold doses |

* The use of WBC growth factors was applicable only if the dose-limiting hematologic toxicity was limited to neutropenia or febrile neutropenia.

**Table S3.** Dose modifications for other ADRs.

| ADR | *nab*-Paclitaxel Dose | Gemcitabine Dose |
|---|---|---|
| Febrile neutropenia: grade 3 or 4* | Withhold doses until fever resolves and ANC is ≥1500; resume at next lower dose level[†] | |
| Peripheral neuropathy: grade 3 or 4 | Withhold dose until improvement to ≤grade 1; resume at next lower dose level[†] | Treat with same dose |
| Cutaneous toxicity: grade 2 or 3 | Reduce doses to next lower dose level[†]; discontinue treatment if ADR persists | |
| For all other nonhematologic toxicities (except nausea, vomiting, alopecia, and pulmonary embolism[‡]) of ≥grade 3 | Withhold dose of either or both agent(s) until improvement to ≤grade 1; resume at next lower dose level[†] | |

* WBC growth factor could be given according to institutional guidelines to treat neutropenic fever or infections associated with neutropenia and to prevent febrile neutropenia in patients with an ANC of <500 cells/mm$^3$.

[†] See Table S1.

[‡] To resume intraperitoneal drug administration in the event of a pulmonary embolism or deep-vein thrombosis, patients were required to be started on low-molecular-weight heparin or similar anticoagulation therapy. Grade 4 events must have been resolved to grade ≤3 within 21 days to continue intraperitoneal drug administration.

**Table S4.** Dose omissions, delays, and intensity.

| | ***nab*-Paclitaxel + Gemcitabine (n=429)** | | |
|---|---|---|---|
| | ***nab*-Paclitaxel** | **Gemcitabine** | **Gemcitabine (n=423)** |
| **Patients with ≥1 dose omission, n (%)** | 268 (62) | 234 (55) | 148 (35) |
| **Patients with no dose omission, n (%)** | 161 (38) | 195 (45) | 275 (65) |
| **Patients with dose omissions per cycle, n/N (%)*** | | | |
| Cycle 1 | 127/429 (30) | 126/429 (29) | 66/423 (16) |
| Cycle 2 | 73/408 (18) | 66/408 (16) | 43/412 (10) |
| Cycle 3 | 98/393 (25) | 80/393 (20) | 42/386 (11) |
| Cycle 4 | 106/364 (29) | 77/364 (21) | 44/366 (12) |
| Cycle 5 | 101/323 (31) | 67/323 (21) | 33/339 (10) |
| Cycle 6 | 69/298 (23) | 20/298 (7) | 19/317 (6) |
| **Number of dose omissions per patient, n (%)** | | | |
| 1 omission | 99 (37) | 114 (49) | 86 (58) |
| 2 omissions | 62 (23) | 66 (28) | 33 (22) |
| 3 omissions | 31 (12) | 25 (11) | 18 (12) |
| 4 omissions | 18 (7) | 17 (7) | 6 (4) |
| 5 omissions | 13 (5) | 8 (3) | 5 (3) |
| 6 omissions | 14 (5) | 4 (2) | 0 |
| 7 omissions | 9 (3) | 0 | 0 |
| 8 omissions | 6 (2) | 0 | 0 |
| 9 omissions | 9 (3) | 0 | 0 |
| 10 omissions | 2 (1) | 0 | 0 |
| 11 omissions | 1 (<1) | 0 | 0 |
| 12 omissions | 3 (1) | 0 | 0 |
| 15 omissions | 1 (<1) | 0 | 0 |
| **Patients with ≥1 dose delay, n (%)** | 218 (51) | 225 (52) | 142 (34) |
| **Patients with no dose delay, n (%)** | 211 (49) | 204 (48) | 281 (66) |
| **Patients with dose delays per cycle, n/N (%)†** | | | |
| Cycle 1 | 7/429 (2) | 7/429 (2) | 8/423 (2) |
| Cycle 2 | 98/406 (24) | 99/408 (24) | 43/412 (10) |
| Cycle 3 | 57/384 (15) | 60/393 (15) | 46/386 (12) |
| Cycle 4 | 67/348 (19) | 71/364 (20) | 31/366 (8) |
| Cycle 5 | 56/288 (19) | 64/323 (20) | 33/339 (10) |
| Cycle 6 | 54/254 (21) | 63/297 (21) | 42/317 (13) |
| **Number of dose delays per patient, n (%)** | | | |

| | ***nab*-Paclitaxel + Gemcitabine (n=429)** | | |
|---|---|---|---|
| | ***nab*-Paclitaxel** | **Gemcitabine** | **Gemcitabine (n=423)** |
| 1 delay | 132 (61) | 129 (57) | 96 (68) |
| 2 delays | 55 (25) | 60 (27) | 32 (23) |
| 3 delays | 20 (9) | 21 (9) | 11 (8) |
| 4 delays | 9 (4) | 13 (6) | 2 (1) |
| 5 delays | 2 (1) | 2 (1) | 1 (1) |
| **Dose intensity (mg/m²/week)‡** | | | |
| N | 429 | 429 | 423 |
| Mean | 70.0 | 594.9 | 652.0 |
| SD | 17.8 | 127.9 | 115.9 |
| Median | 70.4 | 600.0 | 683.7 |
| Min, Max | 10.4, 175.0 | 83.3, 1400.0 | 323.1, 1500.0 |

For 'Number of dose reductions/delays/omissions per patient', percentages are based on patients with dose reduction/delay/omission respectively.

* Percentage is calculated as number of patients with at least one dose omission within a cycle divided by the number of patients planned to be treated within corresponding cycle.

† Percentage is calculated as number of patients with at least one dose reduction/delay of a non-missing dose within a cycle divided by the number of patients treated within corresponding cycle.

‡ Dose intensity during the treatment is defined as the cumulative dose / treatment duration in weeks.

**Appendix 4.** Statistical Analyses.

*Patient populations*

The intent-to-treat (ITT) population consisted of all randomized patients regardless of whether the patient received any IP or had any efficacy assessment results collected. The treated population consisted of all randomized patients who received at least one dose of IP. The treatment groups for the safety analyses were based on the treatment as received if different from the assigned treatment by randomization. The per-protocol population consisted of all treated as randomized patients who met all eligibility criteria and had no radiological evidence of PDAC prior to randomization by independent review.

*Efficacy analyses*

All efficacy analyses were conducted based on the ITT population. The primary and secondary efficacy analyses were conducted based on the treated population and per-protocol population.

Primary efficacy analyses

The primary efficacy endpoint was disease-free survival (DFS), which was defined as the time from the date of randomization to the date of disease recurrence or death, whichever was earlier. Disease recurrence was determined by the independent radiological review of computed tomography or magnetic resonance imaging scans. The survival distribution of DFS was estimated using the Kaplan-Meier method: medians and two-sided 95% CIs were provided by treatment arms. DFS was compared between the two arms using a stratified log-rank test, with the stratification factors: resection status (R0 vs. R1) and nodal status (lymph node [LN]+ vs.

LN–). The associated hazard ratio (HR) and two-sided 95% CIs were provided using the stratified Cox proportional hazards model, adjusted for the same stratification factors as in the stratified log-rank test.

Censoring rules

If a patient died or had recurrence and had not received new anticancer therapy or surgery before death or recurrence, the date of death or recurrence was the DFS date. If a patient did not die or had no recurrence and had not received new anticancer therapy or cancer-related surgery, the last tumor assessment date with disease-free status was the DFS date. If a patient did not die or had no disease recurrence prior to the start of subsequent new anticancer therapy or cancer-related surgery, the last tumor assessment date with disease-free status prior to the start of new anticancer therapy or surgery was the DFS date.

Secondary efficacy analyses

The secondary efficacy endpoint was overall survival (OS), which was defined as the time from the date of randomization to the date of death. Patients who were alive were censored on the date last known to be alive. The survival distribution of OS was estimated using Kaplan-Meier methods: medians and two-sided 95% CIs are provided by treatment arm. The survival rates at different time points were provided. *P* values based on a stratified log-rank test were provided. The associated HRs and two-sided 95% CIs were provided using the stratified Cox proportional hazards model.

Subgroup analyses

Results of the primary analysis of DFS and OS were analyzed within the following subgroups:

1. Geographic region (North America, Europe, Australia, and Asia Pacific)
2. Age (<65 and ≥65 years)
3. Sex (male and female)
4. ECOG PS (0 and 1)
5. PDAC location (head and other)
6. Surgical staging
7. Tumor grade (well differentiated, moderately differentiated, poorly differentiated, and undifferentiated)
8. Resection status (R0 vs. R1)
9. Nodal status (LN+ vs. LN−)
10. Level of CA19-9 at baseline if indicated by the data (WNL, ULN <100 U/mL and ≥100 U/mL)
11. Microscopic distance from tumor to the closest margin (<1 and ≥1 mm)

Note that the geographic region, resection status (R0 vs. R1), and nodal status (LN+ vs. LN−) were based on the clinical data instead of Interactive Randomization Technology data. The number of patients in the surgical-staging subgroup was insufficient; per the statistical analysis plan, this subgroup analysis was not performed.

The methods described for the endpoints of DFS and OS were used for each subgroup. Resection status or nodal status was not included as a stratification factor for the resection status

or nodal status subgroup analysis, respectively, in the stratified Cox proportional hazards model or when estimating the stratified log-rank *P* value.

A forest plot was provided based on the stratified HRs for each subgroup.

A summary table of serum CA19-9 values and changes from baseline by cycle and treatment arm is provided. The subsequent anticancer therapies and clinically reviewed subsequent new anticancer therapies or cancer-related surgeries is summarized by treatment arm.

*Safety Analyses*

All safety analyses were conducted based on the treated population.

Adverse events

The safety population, which included all randomized patients who received at least one dose of IP, was the analysis population for all safety analyses. Adverse events (AEs) were analyzed in terms of treatment-emergent AEs (TEAEs)—defined to be any event that began or worsened in grade after the start of IP through 28 days after the last dose of IP. All events were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA). AEs were summarized by severity/grade based on the NCI CTCAE v4.0. If a patient experienced the same AE multiple times during the treatment, the event was counted only once and by the greatest severity.

TEAEs; grade ≥3 TEAEs; serious AEs; TEAEs leading to dose reduction, dose interruption, or treatment discontinuation; and TEAEs with an outcome of death were summarized per treatment arm by MedDRA system organ class and preferred terms. Adverse events of special interest of the *nab*-paclitaxel plus gemcitabine combination identified in previous trials in a similar population were summarized in the same manner.

Laboratory results

To investigate the maximal degree of myelosuppression, the NCI CTCAE v4.03 grades for ANC, WBC, platelet count, and hemoglobin were summarized for each treatment group by the most severe grade in each treatment cycle and by the most severe grade at any time during the treatment.

Hepatic and renal function were summarized for each treatment group using the most severe NCI CTCAE grade for ALT, AST, total bilirubin, and creatinine by cycle and at any time during the treatment.

**Appendix 5.** Schedule of assessments.

**Table S5.** Assessments performed on days 1, 8, and 15 of each cycle.

| Assessment | Day 1* | Days 8 and 15 |
|---|---|---|
| Physical examination† | Y | N |
| Weight | Y | N |
| Body surface area | Y | N |
| Concomitant medications | Y | Y |
| Concurrent procedures | Y | Y |
| Peripheral neuropathy | Y | N |
| Vital signs | Y | Y |
| ECOG PS | Y | Y |
| Clinical chemistry panel‡ | Y | N |
| Complete blood count§ | Y | Y |
| Quality-of-life questionnaire‖ | Y | N |
| Adverse events | Y | Y |

* Day 1 evaluations for cycle 1 could be omitted if screening evaluations were performed within 72 hours of cycle 1 day 1.
† Source documented only.
‡ Including but not limited to sodium, potassium, chloride, glucose, blood urea nitrogen, alkaline phosphatase, ALT, AST, serum albumin, total bilirubin, and creatinine.
§ Including differential blood count and platelet count.
‖ Prior to dosing; only in cycle 4.

**Table S6**. Reasons for screen failure.

| **Parameter, n (%)** | **All Screened Patients (N=1226)** |
|---|---|
| **Inclusion criteria failed** | |
| CA19-9 <100 U/mL* | 125 (10) |
| Acceptable blood chemistry† | 45 (4) |
| Pancreatic cancer surgical staging‡ | 37 (3) |
| Ability to adhere to study visit schedule and other protocol requirements | 13 (1) |
| Histologically confirmed PC with complete resection§ | 12 (1) |
| Acceptable hematology parameters‖ | 9 (1) |
| Patient ability to start treatment ≤12 weeks post-surgery | 7 (1) |
| ECOG PS ≤1 | 2 (<1) |
| Acceptable coagulation studies¶ | 2 (<1) |
| Understand and voluntarily sign informed consent | 2 (<1) |
| **Exclusion criteria met** | |
| Presence/history of MPC | 81 (7) |
| Unwillingness/inability to comply with study protocol | 28 (2) |
| Any significant medical condition, laboratory abnormality, or psychiatric illness | 11 (1) |
| Any other malignancy within 5 years of randomization** | 9 (1) |
| Serious medical risk factors involving any major organ system or serious psychiatric disorders | 9 (1) |
| Prior neoadjuvant treatment or radiation therapy or systemic therapy for PC | 2 (<1) |

| | |
|---|---|
| Active infections requiring systemic therapy | 2 (<1) |
| Enrollment in any other clinical protocol or investigational study with an interventional agent that may interfere with the study | 2 (<1) |
| Any condition that confounds the ability to interpret data | 2 (<1) |
| Known history of HIV infection or active hepatitis B or C[††] | 1 (<1) |
| Any condition, including the presence of laboratory abnormalities, that places the patient at unacceptable risk if they were to participate in the study | 1 (<1) |

MPC, metastatic pancreatic cancer; PC, pancreatic cancer.
* Assessed ≤14 days after randomization.
[†] Includes AST/ALT ≤2.5×ULN, total bilirubin ≤ULN, alkaline phosphatase ≤2.5×ULN, serum creatinine ≤ULN, or calculated clearance ≥50 mL/min/1.73 $m^2$.
[‡] Acceptable staging included T1-3, N0-1, M0.
[§] Complete resection defined as R0 or R1.
[‖] Includes ANC ≥1500/$mm^3$, platelet count ≥100,000/$mm^3$, and hemoglobin ≥9 g/dL.
[¶] Demonstrated by prothrombin time or international normalized ratio and partial thromboplastin time WNLs (±15%).
** Excludes adequately treated in situ carcinoma of the cervix, uterus, or nonmelanomatous skin cancer with treatments completed 6 months prior to this study.
[††] Includes patients who were currently serologically positive with evidence of prior or signs of active chronic hepatitis.

**Appendix 6.** Treatment exposure.

**Table S7.** Treatment exposure (treated population).

| **Parameter** | ***nab*-Paclitaxel plus gemcitabine (n=429)** | **Gemcitabine (n=423)** |
|---|---|---|
| Duration of treatment, median (IQR), weeks | 24.0 (19.0-24.9) | 24.0 (21.1-24.1) |
| Number of cycles administered, median (range) | 6.0 (1-6) | 6.0 (1-6) |
| Number of doses administered, median (range) | | |
| *nab*-Paclitaxel | 15.0 (1-18) | NA |
| Gemcitabine | 16.0 (1-18) | 17.0 (1-18) |
| Cumulative dose, median (range), mg/m$^2$* | | |
| *nab*-Paclitaxel | 1500.0 (125-2250) | NA |
| Gemcitabine | 13,200.0 (1000-18,000) | 15000.0 (1000-18,000) |
| Dose intensity, median (range), mg/m$^2$/week† | | |
| *nab*-Paclitaxel | 70.41 (10.4-175.0) | NA |
| Gemcitabine | 600.00 (83.3-1400.0) | 683.72 (323.1-1500.0) |
| Percentage of protocol dose, median (range), %‡ | | |
| *nab*-Paclitaxel | 75.11 (11.1-186.7) | NA |
| Gemcitabine | 80.00 (11.1-186.7) | 91.16 (43.1-200.0) |
| Patients with ≥1 dose reduction, n (%)§ | | |
| *nab*-Paclitaxel | 273 (63.6) | NA |
| Adverse event | 273 (100.0) | NA |
| Per protocol | 2 (0.7) | NA |

| Parameter | *nab*-Paclitaxel plus gemcitabine (n=429) | Gemcitabine (n=423) |
|---|---|---|
| Other | 3 (1.1) | NA |
| Gemcitabine | 266 (62.0) | 213 (50.4) |
| Adverse event | 265 (99.6) | 207 (97.2) |
| Per protocol | 2 (0.8) | 1 (0.5) |
| Other | 3 (1.1) | 6 (2.8) |
| Patients with ≥1 dose delay, n (%) | | |
| *nab*-Paclitaxel | 218 (50.8) | NA |
| Gemcitabine | 225 (52.4) | 142 (33.6) |
| Patients with ≥1 dose omission, n (%) | | |
| *nab*-Paclitaxel | 268 (62.5) | NA |
| Gemcitabine | 234 (54.5) | 148 (35.0) |

NA, not applicable.

* Defined as the sum of all doses taken across the treatment period.

† Defined as the cumulative dose divided by treatment duration weeks.

‡ Defined as 100×(dose intensity divided by protocol weekly dose). For *nab*-paclitaxel, the protocol weekly dose was 125×3/4 (93.75) mg/m²/week; for gemcitabine, the protocol weekly dose was 1000×3/4 (750) mg/m²/week.

§ A patient can have multiple reasons for dose reduction. Any patient who had multiple reasons within each category was presented once. For reasons for dose reduction, percentages are based on patients with dose reductions.

**Table S8**. Summary of censoring of DFS by independent radiological review.

| **Parameter** | ***nab*-Paclitaxel plus gemcitabine (n=432)** | **Gemcitabine (n=434)** |
|---|---|---|
| Number of patients with disease recurrence or death, n (%) | 226 (52) | 213 (49) |
| Disease recurrence | 204 (47) | 183 (42) |
| Death | 22 (5) | 30 (7) |
| Number of patients censored, n (%) | 206 (48) | 221 (51) |
| Reasons for censoring, n (%) | | |
| DFS follow-up ongoing | 100 (23) | 94 (22) |
| Scanning discontinued per disease recurrence by investigator assessment | 53 (12) | 63 (15) |
| New anticancer therapy or cancer-related surgery | 26 (6) | 31 (7) |
| Lost to follow-up | 14 (3) | 23 (5) |
| Residual or recurrent disease at baseline | 10 (2) | 9 (2) |
| No postbaseline assessment | 3 (1) | 0 |
| Not evaluable at baseline | 0 | 1 (<1) |
| DFS follow-up time for censored patients | | |
| n | 206 | 221 |
| Median (range), months | 22.2 (0.03-52.4) | 13.8 (0.03-48.3) |

**Appendix 7.** Subsequent therapies.

**Table S9.** Subsequent new anticancer therapies or cancer-related surgeries.

| **Parameter, n (%)** | ***nab*-Paclitaxel plus gemcitabine (n=432)** | **Gemcitabine (n=434)** |
|---|---|---|
| Patients with subsequent anticancer therapies or cancer-related surgery | 237 (55) | 245 (56) |
| Specific therapy used* | | |
| 5-FU based† | 112 (26) | 102 (24) |
| FOLFIRINOX | 89 (21) | 80 (18) |
| *nab*-Paclitaxel based | 36 (8) | 90 (21) |
| Gemcitabine based | 33 (8) | 20 (5) |
| Radiation | 28 (6) | 30 (7) |
| Chemoradiation | 25 (6) | 31 (7) |
| MM-398/liposomal irinotecan based | 25 (6) | 13 (3) |
| Experimental | 24 (6) | 19 (4) |
| Surgery | 16 (4) | 16 (4) |
| Other | 8 (2) | 13 (3) |

5-FU, 5-fluouracil.
* Arranged by descending order of incidence in the *nab*-paclitaxel plus gemcitabine group.
† 5-FU includes 5-FU, capecitabine, or titanium silicate-1 as monotherapy and/or in combination as long as it does not contain all the agents included in FOLFIRINOX.

**Appendix 8.** Efficacy data.

**Figure S1.** Forest plot subgroup analysis of investigator-assessed DFS (ITT population; based on the primary data cutoff date [December 31, 2018]).

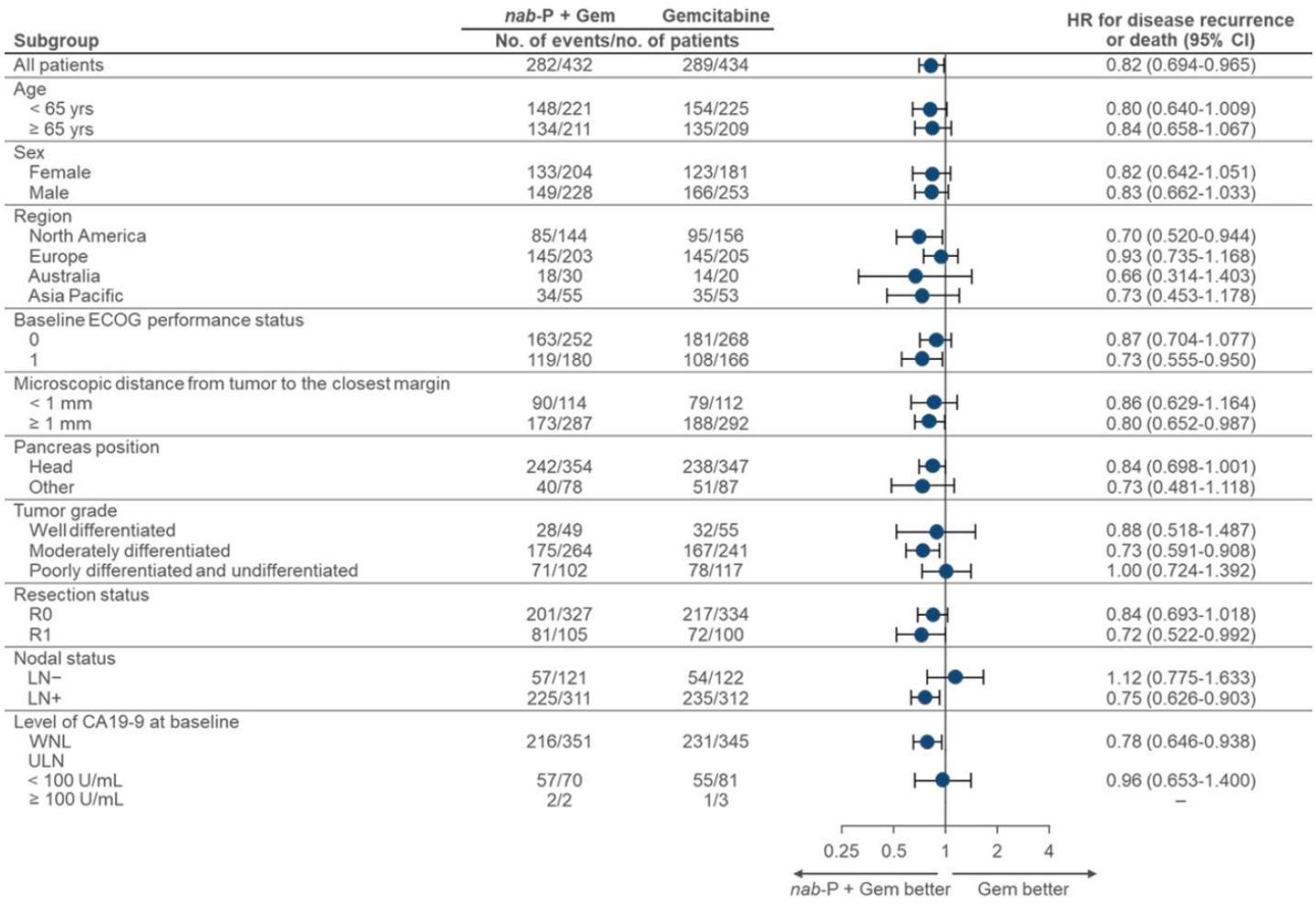

**Figure S2.** Forest plot subgroup analysis of OS (ITT population; based on the updated 5-year data cutoff date [April 9, 2021]).