JNCI J Natl Cancer Inst (2015) 107(2): dju413

doi:10.1093/jnci/dju413
First published online January 31, 2015
Article

ARTICLE

nab-Paclitaxel Plus Gemcitabine for Metastatic Pancreatic Cancer: Long-Term Survival From a Phase III Trial

David Goldstein, Robert Hassan El-Maraghi, Pascal Hammel, Volker Heinemann, Volker Kunzmann, Javier Sastre, Werner Scheithauer, Salvatore Siena, Josep Tabernero, Luis Teixeira, Giampaolo Tortora, Jean-Luc Van Laethem, Rosemary Young, Darryl Neil Penenberg, Brian Lu, Alfredo Romano, Daniel D. Von Hoff

Affiliations of authors: Prince of Wales Hospital, University of New South Wales, Sydney, NSW, Australia (DG); Royal Victoria Regional Health Centre, Barrie, ON, Canada (RHEM); Hôpital Beaujon, Clichy, France (PH); Klinikum Grosshadern, University of Munich, Munich, Germany (VH); Universitätsklinikum Würzburg, Würzburg, Germany (VK); Hospital Clinico San Carlos, Madrid, Spain (JS); Medizinische Universität Wien, Wien, Austria (WS); Ospedale Niguarda Ca' Granda, Milan, Italy (SS); Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Universitat Autònoma de Barcelona, Barcelona, Spain (JT); Hôpital Saint Antoine, Paris, France (LT); Azienda Ospedaliera Universitaria Integrata and University of Verona, Verona, Italy (GT); Hôpital Erasme, Brussels, Belgium (JLVL); Royal Hobart Hospital, Hobart, Australia (RY); Celgene Corporation, Summit, NJ (DNP); Celgene Corporation, Summit, NJ (BL); Celgene Corporation, Boudry, Switzerland (AR); Virginia G. Piper Cancer Center at Scottsdale Healthcare/TGen, Scottsdale, AZ (DDVH).

Correspondence to: David Goldstein, MD, Prince of Wales Hospital, Department of Oncology, University of New South Wales, South Eastern Sydney Illawarra, NSW Health, Barker Street, Randwick, New South Wales, 2031, Sydney, Australia (e-mail: david.goldstein@sesiahs.health.nsw.gov.au).

Abstract

Background: Positive findings from the phase III MPACT trial led to the regulatory approval of *nab*-paclitaxel plus gemcitabine as a treatment option for patients with metastatic pancreatic cancer. This report is an update of overall survival (OS) based on longer follow-up.

Methods: Patients (n = 861) with metastatic pancreatic cancer and a Karnofsky performance status of 70 or greater were randomly assigned one to one to receive *nab*-paclitaxel + gemcitabine or gemcitabine alone. Efficacy data for this post hoc analysis were collected through May 9, 2013. Exploratory analyses of carbohydrate antigen 19-9 (CA19-9) and neutrophil-to-lymphocyte ratio (NLR) were conducted. The primary efficacy endpoint was OS, which was analyzed for all randomly assigned patients by the Kaplan-Meier method. All statistical tests were two-sided.

Results: The median OS was statistically significantly longer for *nab*-paclitaxel plus gemcitabine vs gemcitabine alone (8.7 vs 6.6 months, hazard ratio [HR] = 0.72, 95% confidence interval [CI] = 0.62 to 0.83, $P < .001$). Long-term (>three-year) survivors were identified in the *nab*-paclitaxel plus gemcitabine arm only (4%). In pooled treatment arm analyses, higher CA19-9 level and NLR at baseline were statistically significantly associated with worse OS. There appeared to be a treatment effect for OS favoring *nab*-paclitaxel plus gemcitabine over gemcitabine alone in poor-prognosis subgroups defined by these factors (HR = 0.612, $P < .001$ for CA19-9 level ≥ median and HR = 0.81, $P = .079$ for NLR > 5).

Conclusions: These data confirm and extend the primary report of OS, supporting the superior efficacy of *nab*-paclitaxel plus gemcitabine over gemcitabine alone. Subgroup analyses support the relevance of CA 19-9 and NLR as prognostic markers in metastatic pancreatic cancer.

Received: March 31, 2014; **Revised:** September 9, 2014; **Accepted:** November 11, 2014

Pancreatic cancer is one of the deadliest tumor types, accounting for approximately 7% of all cancer deaths in the United States (1). Among all cancer types, pancreatic cancer ranks 11th in incidence but fourth in mortality (1). Gemcitabine monotherapy became a standard first-line treatment option for metastatic pancreatic cancer after it demonstrated superior clinical benefit over 5-fluorouracil (2–4). Median overall survival (OS) for patients who received gemcitabine monotherapy for advanced pancreatic cancer in key trials has ranged from 5.7 to 6.8 months (2,5,6). Experimental treatment arms have failed to statistically significantly improve OS over gemcitabine in numerous phase III trials (7–13). In fact, until recently, only two trials had demonstrated statistically significant improvements in OS over gemcitabine for patients with this disease: a phase III study that showed a modest benefit for patients receiving gemcitabine plus erlotinib (median = 6.24 vs 5.91 months, hazard ratio [HR] = 0.82, $P = .038$, 12-month OS rates of 23% vs 17%) and a phase II/III trial that found a statistically significant OS benefit for leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX, median = 11.1 vs 6.8 months, HR = 0.57, $P < .001$), although FOLFIRINOX was also associated with a marked potential for toxicity (5,6).

nab-Paclitaxel ([Abraxane], Celgene Corporation, Summit, NJ) is an albumin-based formulation of paclitaxel that has demonstrated clinical benefit over solvent-based paclitaxel in patients with metastatic breast cancer (14) and non–small cell lung cancer (15). A 2011 report revealed encouraging initial findings for patients with metastatic pancreatic adenocarcinoma treated at the maximum tolerated dose of *nab*-paclitaxel plus gemcitabine in a phase I/II trial: a median OS of 12.2 months, an overall response rate by Response Evaluation Criteria In Solid Tumors (RECIST) of 48%, and a median progression-free survival of 7.9 months (16).

These results led to an international phase III trial (MPACT, ClinicalTrials.gov, trial number NCT00844649) in which 861 patients with metastatic pancreatic cancer were randomly assigned to receive *nab*-paclitaxel plus gemcitabine at the recommended doses from the phase I/II study (*nab*-paclitaxel 125 mg/m^2 plus gemcitabine 1000 mg/m^2 on days 1, 8, and 15 of each 28-day cycle) or gemcitabine alone (17). Treatment with *nab*-paclitaxel plus gemcitabine demonstrated statistically significant improvements across all endpoints vs gemcitabine alone, including OS (primary endpoint, median = 8.5 vs 6.7 months, HR = 0.72, 95% confidence interval [CI] = 0.62 to 0.83, $P < .001$), progression-free survival (median = 5.5 vs 3.7 months, HR = 0.69, 95% CI = 0.58 to 0.82, $P < .001$), and independently reviewed overall response rate (23% vs 7%, response rate ratio = 3.19, 95% CI = 2.18 to 4.66, $P < .001$). The most common grade 3 or higher adverse events with *nab*-paclitaxel plus gemcitabine were neutropenia, leukopenia, fatigue, and peripheral neuropathy.

Examination of prognostic markers at baseline may aid in designing more effective treatment plans for patients with metastatic pancreatic cancer (18). Carbohydrate antigen 19-9 (CA19-9) is a prognostic marker that has proven useful 18-21). However, not all patients secrete Lewis antigens such as CA19-9, and only 80% to 85% of patients can possibly demonstrate an elevated CA19-9 level (19,21). Furthermore, an elevated CA19-9 level could lead to a false-positive cancer diagnosis, suggesting that additional markers are needed. Retrospective studies suggest that neutrophil-to-lymphocyte ratio (NLR), a marker of systemic inflammatory response, may provide valuable prognostic information in many malignancies, including pancreatic cancer (22–27).

The initial publication of the MPACT trial reported an OS analysis in which 80% of patients had died (17). This report describes an updated analysis of OS from MPACT with an extended data cutoff (eight months longer) at the time the trial was closed. At that time, 90% of patients in the intent-to-treat (ITT) population had died. Additional analyses include the prognostic impacts of baseline CA19-9 levels and NLR on OS and evaluations of treatment effect in patient subgroups defined by these factors.

Methods

The study design and patient characteristics have been described previously (17). Key parameters are described below. The independent ethics committee at each participating institution approved the study. All patients provided written informed consent before the initiation of the study.

Patients

A total of 861 adults (≥18 years of age) with a Karnofsky performance status (KPS) score of 70 or higher and histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas were enrolled. Disease was required to be measurable by RECIST version 1.0 (28). Additional eligibility criteria included adequate hepatic, hematologic, and renal function (including a bilirubin level ≤ the upper limit of the normal range, an absolute neutrophil count ≥ 1.5×10^9/L, and a hemoglobin level ≥ 9 g/dL). Treatment with fluorouracil or gemcitabine as a radiation sensitizer in the adjuvant setting was allowed if given at least six months prior to random assignment.

Previous chemotherapy for metastatic disease was an exclusion criterion for this study. Patients with islet cell neoplasms or locally advanced adenocarcinoma were also excluded, as were patients who had received cytotoxic doses of any systemic chemotherapy, including gemcitabine, in the adjuvant setting.

Study Design and Treatment

This was an international, multicenter, open-label, phase III study conducted at 151 sites. Patients were randomly assigned in a one to one ratio to receive a 30- to 40-minute intravenous infusion of *nab*-paclitaxel 125 mg/m^2, followed by an infusion of gemcitabine 1000 mg/m^2 on days 1, 8, 15, 29, 36, and 43, or gemcitabine alone 1000 mg/m^2 weekly for seven of eight weeks (cycle 1). Patients received treatment on days 1, 8, and 15 every four weeks in subsequent cycles. Patient random assignment was stratified by geographic region, performance status, and liver metastases. Treatment continued until either disease progression or unacceptable toxicity.

Assessments

Tumor response was evaluated every eight weeks by spiral computed tomography or magnetic resonance imaging. Scans were evaluated by investigators and by an independent radiological evaluation using RECIST version 1.0. CA19-9 level was assessed at baseline and every eight weeks thereafter. NLR was evaluated at baseline; subgroup analyses were based on a cutoff ratio of five, per a previous publication in advanced pancreatic cancer (22).

Investigators monitored treatment-related adverse events and serious adverse events, weekly central laboratory testing, and the rates of dose reductions, dose interruptions, and premature discontinuations of the study drug. Treatment-related adverse events were graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf) and coded to correspond with the preferred terms in the

ARTICLE

Medical Dictionary for Regulatory Activities version 15.0. The safety data reported here are updated from the original publication (17).

Statistical Analysis

All efficacy analyses were performed on the ITT population, which was composed of all enrolled patients. The primary efficacy endpoint was OS, which was analyzed for all randomly assigned patients by the Kaplan-Meier method. Per the study protocol, the treatment effect on OS was assessed for statistical significance by a log-rank test stratified by the prespecified random assignment stratification criteria of geographic region (North America vs other), baseline KPS (70 to 80 vs 90 to 100), and presence of liver metastases (yes vs no). Survival data for patients who were lost to follow-up were censored at the last date at which they were known to be alive. A patient population of 842 patients with 608 events allowed 90% power to detect a hazard ratio of 0.769 at a two-sided α level of 0.049 for death with *nab*-paclitaxel plus gemcitabine vs gemcitabine alone. The data cutoff for the original OS analysis was September 17, 2012. The data cutoff for this updated analysis was May 9, 2013, which corresponded to the date the trial was closed following complete analysis of the post-study 120-day safety evaluation conducted as part of the standard regulatory process. The secondary endpoints were progression-free survival and overall response rate (not updated in this analysis because they were not likely to have changed with extended follow-up).

A multivariable survival analysis for OS was carried out using a Cox proportional hazards model that included the complete set of prespecified baseline factors: treatment group, age, sex, KPS, geographic region, primary tumor location within the pancreas, presence of biliary stent, previous Whipple procedure, presence of liver metastasis, presence of lung metastasis, peritoneal carcinomatosis, stage at diagnosis, number of metastatic sites, and CA19-9 level. Baseline NLR was added to the model for a post hoc exploratory analysis. The OS analyses reported in this study did not require tests for homogeneity because they were based on proportional hazard models rather than linear models. Factors with a *P* value under .10 were considered significant and allowed to remain in the model per the study protocol. Baseline CA19-9 level was analyzed as a continuous variable, and the hazard ratio was based on EXP (CA19-9 coefficient), where EXP is the exponential function. To address the statistical issue of multiple comparisons, we performed a Bonferroni correction on the multivariable model of OS, using α/k, in which α represents the statistical level of significance used to test the variables in the mode (α = .05) and k is the total number of independent variables tested (k = 6).

A descriptive evaluation of baseline characteristics based on survival durations was performed within each treatment arm. This evaluation was qualitative and not subject to statistical analysis.

All statistical tests were two-sided and performed using Statistical Analysis Software (SAS) version 9.2. All *P* values were derived from Wald χ^2 tests, except for the comparison of OS (described previously).

Results

A total of 431 patients were assigned to the *nab*-paclitaxel plus gemcitabine arm, and 430 were assigned to the gemcitabine-alone arm (ITT population) (Figure 1). All demographic and clinical characteristics at baseline were well balanced between the two groups (Table 1). Most patients (84%) had metastasis to the liver, and more than 50% of patients had baseline CA19-9 levels greater than or equal to 59 × the upper limit of normal. CA19-9 level at baseline was not produced by 13% of patients.

Overall Survival in the ITT Population

The median follow-up for this updated survival analysis was 13.9 months. The data were based on 774 deaths (90% of patients), including 380 in the *nab*-paclitaxel plus gemcitabine group (88%) and 394 in the gemcitabine-alone group (92%). The median OS for patients who received *nab*-paclitaxel plus gemcitabine (8.7 months, 95% CI = 7.89 to 9.69) was statistically significantly longer than for those who received gemcitabine alone (6.6 months, 95% CI = 6.01 to 7.20, HR = 0.72, 95% CI = 0.62 to 0.83, $P < .001$) (Figure 2A). The time point at which 25% of the patients were alive was later for *nab*-paclitaxel plus gemcitabine than for gemcitabine alone (14.8 months [95% CI = 13.93 to 15.64] vs 11.1 months [95% CI = 10.12 to 12.39]). A previous sensitivity analysis in which data were censored at the time of secondary therapy confirmed the findings of the OS analysis (17). Extended follow-up also identified patients who survived longer than 24 months in the *nab*-paclitaxel plus gemcitabine treatment arm (Table 2), including 4% of patients who survived at least 36 months and 3% of patients who survived at least 42 months. No patients survived for 36 months in the gemcitabine-alone treatment group. The treatment effect favoring *nab*-paclitaxel plus gemcitabine over gemcitabine alone remained statistically significant across most patient subgroups (Figure 2B).

A Cox multivariable analysis model of the 643 patients for whom data on all factors tested were available found that treatment group, presence of liver metastases, KPS, age, and baseline

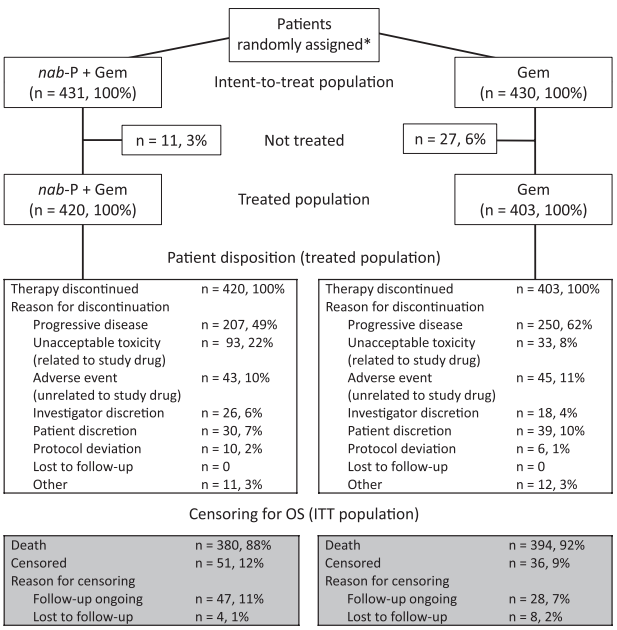


Figure 1. Updated Consolidated Standards of Reporting Trials diagram as of May 9, 2013. *One patient was randomly assigned to gemcitabine (Gem) but was treated with *nab*-paclitaxel + Gem. In the intent-to-treat analysis, this patient was analyzed as randomly assigned. In all analyses of the treated population, the patient was analyzed as treated. CONSORT = Consolidated Standards of Reporting Trials; Gem = gemcitabine; ITT = intent-to-treat; *nab*-P = *nab*-paclitaxel; OS = overall survival.

Table 1. Baseline patient characteristics (17)

Variable	*nab*-P + Gem (n = 431)	Gem (n = 430)	All patients (n = 861)
Age			
Median years (range), y	62 (27-86)	63 (32-88)	63 (27-88)
< 65 y, %	59	56	58
≥ 65 y, %	41	44	42
Sex, %			
Male	57	60	58
Race, %			
Asian	2	2	2
Black	4	4	4
White	88	87	87
Hispanic	6	6	6
Other	1	1	1
KPS, %			
100	16	16	16
90	42	46	44
80	35	30	32
70	7	8	7
60	<1*	0	<1
Pancreatic primary tumor location, %			
Head	44	42	43
Body	31	32	31
Tail	24	26	25
Unknown	1	1	1
Current site(s) of metastasis, %			
Liver	85	84	84
Lung	35	43	39
Peritoneum	4	2	3
No. of metastatic sites, %			
1	8	5	6
2	47	48	47
3	32	33	32
> 3	14	15	14
CA19-9 level†			
Median, U/mL	2294	2759	2470
Normal, %	16	15	15
ULN to < 59 × ULN, %	32	32	32
≥ 59 × ULN, %	52	53	52
Previous therapy, %			
Radiation	4	3	3
Chemotherapy	5	3	4
Whipple procedure	7	7	7
Biliary stent	19	16	17

* Two patients had a Karnofsky performance status (KPS) of 70 at screening but a KPS of 60 at baseline on day 1 of cycle 1. CA19-9 = carbohydrate antigen 19-9; Gem = gemcitabine; KPS = Karnofsky performance status; *nab*-P = *nab*-paclitaxel; ULN = upper limit of normal.

† Not all patients have Lewis antigens and thus cannot secrete CA19-9. The evaluable n for CA19-9 was 379 patients in the *nab*-P + Gem group and 371 patients in the Gem-alone group.

NLR were all independent predictors of survival (Table 3); however, the number of metastatic sites did not reach statistical significance ($P = .105$) in this model. The baseline characteristics of the patients included in the multivariable analysis were similar to those of the ITT population (Supplementary Table 1, available online). In a Bonferroni-corrected model, the cutoff for statistical significance was 0.008, and the factors that remained significant were treatment (HR = 0.68, 95% CI = 0.57 to 0.80, $P < .001$), liver metastasis (HR = 1.65, 95% CI = 1.28 to 2.12, $P < .001$), KPS (HR = 1.47, 95% CI = 1.24 to 1.74, $P < .001$), and NLR (HR = 0.57, 95% CI = 0.48 to 0.68, $P < .001$).

In a further effort to understand which baseline characteristics may have influenced survival, patients within each treatment arm were divided into subgroups based on survival duration, and the baseline characteristics of each survival subgroup were evaluated (Table 4). Baseline characteristics of long-term (≥two-year) survivors were similar between the two groups, with the exception of sex (48% male in the *nab*-paclitaxel plus gemcitabine group vs 64% male in the gemcitabine-alone group) and baseline CA19-9 levels. A higher proportion of patients with elevated baseline CA19-9 levels (≥ 59 × the upper limit of normal) were alive for two years or longer with *nab*-paclitaxel plus gemcitabine treatment than with gemcitabine alone (55% vs 15%).

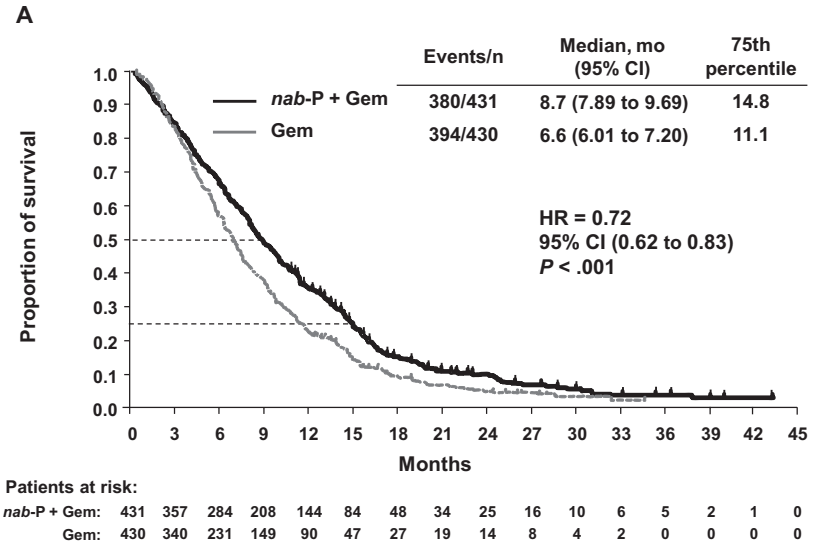
Subgroup Analyses

The median baseline CA19-9 level for all patients was 2470 U/mL (range = 0.3-12 207 654). Among patients with a baseline CA19-9 level greater than or equal to the median, OS was statistically significantly longer for those who received *nab*-paclitaxel plus gemcitabine than for those who received gemcitabine alone (HR = 0.612, 95% CI = 0.49 to 0.76, $P < .001$) (Figure 3). Among patients with a baseline CA19-9 level less than the median, there was a trend toward a treatment effect on OS favoring *nab*-paclitaxel plus gemcitabine (HR = 0.833, 95% CI = 0.67 to 1.04, $P = .113$). Notably, the OS for patients treated with *nab*-paclitaxel plus gemcitabine was similar regardless of whether baseline CA19-9 levels were less than the median or greater than or equal to the median (HR = 0.983, 95% CI = 0.79 to 1.23, $P = .470$). However, in the gemcitabine-alone arm, OS was statistically significantly longer in patients with baseline CA19-9 levels less than the median compared with patients whose baseline CA19-9 levels were greater than or equal to the median (HR = 0.773, 95% CI = 0.62 to 0.97, $P = .001$).

A pooled treatment arm analysis of the updated OS data revealed that patients with an NLR of less than or equal to five (n = 543) had a statistically significantly better OS compared with patients whose NLR was greater than five (n = 309, median = 9.1 vs 5.0 months, HR = 1.839, $P < .001$) (Figure 4). *nab*-Paclitaxel plus gemcitabine (n = 266) resulted in a statistically significantly longer OS vs gemcitabine alone (n = 277) in patients with an NLR of less than or equal to five (median = 10.9 vs 7.9 months, HR = 0.67, $P < .001$). A similar trend favoring *nab*-paclitaxel plus gemcitabine (n = 160) vs gemcitabine alone (n = 149) was observed in the NLR over five group, although this difference did not reach statistical significance (median = 5.6 vs 4.3 months, HR = 0.81, $P = .079$).

Consistent with the results for the overall population, a treatment benefit favoring *nab*-paclitaxel plus gemcitabine over gemcitabine alone was noted in subgroups based on performance status ($P < .001$ for KPS 70-80 and $P = .005$ for KPS 90-100) and the presence ($P < .001$) or absence ($P = .111$) of liver metastases. Within each treatment arm, these factors remained prognostic of survival. Patients with a KPS of 90 to 100 had a better OS than patients with a KPS of 70 to 80 in both the *nab*-paclitaxel plus gemcitabine arm (9.7 vs 7.6 months, HR = 0.76, $P = .009$) and the gemcitabine-alone arm (7.9 vs 4.3 months, HR = 0.57, $P < .001$). Similarly, the absence of liver metastases was associated with a better OS than the presence of liver metastases in the *nab*-paclitaxel plus gemcitabine arm (11.1 vs 8.3 months, HR = 0.58, $P = .001$) and the gemcitabine-alone arm (10.2 vs 5.9 months, HR = 0.58, $P < .001$).

ARTICLE



B

Group	nab-P + Gem Events/n	nab-P + Gem Median OS, mo	Gem Events/n	Gem Median OS, mo	HR	P Value
All patients	380/431	8.7	394/430	6.6	0.72	< .001
Age < 65 years	220/254	9.6	222/242	6.8	0.65	< .001
Age ≥ 65 years	160/177	7.7	172/188	6.5	0.80	.048
Female	157/186	9.7	156/173	7.1	0.71	.004
Male	223/245	8.1	238/257	6.2	0.74	.002
KPS 70 - 80	156/179	7.6	153/161	4.3	0.59	< .001
KPS 90 - 100	220/248	9.7	240/268	7.9	0.77	.005
Primary tumor location: head	167/191	9.5	170/180	6.4	0.59	< .001
Primary tumor location: other	210/237	8.1	221/246	6.9	0.79	.017
Liver metastases	331/365	8.3	331/360	5.9	0.71	< .001
No liver metastases	49/66	11.1	63/70	10.2	0.73	.111
1 metastatic site	25/33	12.9	20/21	9.0	0.47	.038
2 metastatic sites	184/202	8.6	185/206	6.9	0.77	.016
3 metastatic sites	117/136	7.9	129/140	5.9	0.79	.069
> 3 metastatic sites	54/60	8.7	60/63	5.0	0.51	.001
Normal CA 19-9	50/60	9.3	49/56	7.0	0.90	.640
CA 19-9 ULN to < 59 × ULN	108/122	8.8	109/120	7.3	0.80	.111
CA 19-9 ≥ 59 × ULN	177/197	8.4	184/195	5.7	0.61	< .001
Australia	52/61	9.4	57/59	6.7	0.59	.010
Eastern Europe	63/64	7.7	60/62	5.9	0.84	.372
Western Europe	28/38	10.7	27/38	6.9	0.82	.471
North America	237/268	8.8	250/271	6.6	0.69	< .001

Figure 2. Updated overall survival (intent-to-treat population). **A)** Kaplan-Meier overall survival (OS) curve. *P* value from stratified log-rank test. **B)** Forest plot of the hazard ratios for OS in patient subgroups. *P* values from Wald χ^2 tests. All statistical tests were two-sided. CI = confidence interval; Gem = gemcitabine, HR = hazard ratio; KPS = Karnofsky performance status; *nab*-P = *nab*-paclitaxel; OS = overall survival; ULN = upper limit of normal.

Safety

The most common grade 3 or higher adverse events were previously reported (17). Briefly, *nab*-paclitaxel plus gemcitabine appeared to increase the rates of any-grade neutropenia, leukopenia, fatigue, peripheral neuropathy, and diarrhea (Table 5). The addition of *nab*-paclitaxel did not appear to substantially increase the rates of any-grade anemia or thrombocytopenia. The number of patients who experienced at least one grade 3 or higher treatment-related, treatment-emergent adverse event was 326 (77%) in the *nab*-paclitaxel plus gemcitabine arm and 205 (51%) in the gemcitabine-alone arm. The frequency and severity of adverse events was not influenced by baseline performance status, as demonstrated by the similar rates of adverse events between patients with KPS 70 to 80 and KPS 90 to 100 (Table 5). Grade 3 peripheral neuropathy occurred in 71 patients (17%) in the *nab*-paclitaxel plus gemcitabine arm. Of these 71 patients, 31 (44%) experienced an improvement to grade 1 or less after dose delay. The median time to improvement to grade 1 or less neuropathy was 29 days, and 44% of patients were able to resume treatment with *nab*-paclitaxel.

Discussion

This updated analysis of the phase III MPACT trial confirmed the treatment effect in favor of *nab*-paclitaxel plus gemcitabine vs gemcitabine alone for OS (more than a two-month difference at the median, $P < .001$), including at the tail of the survival curve. The extended data cutoff allowed an OS analysis of mature data from 90% of the patients in the study. This led to the identification of long-term (≥three-year) survivors in the *nab*-paclitaxel plus gemcitabine arm (4%) and an evaluation of baseline characteristics shared by long-term survivors vs the ITT population.

In a new multivariable analysis, visceral metastases and KPS were found to be statistically significant independent predictors

of survival, as was age (Table 3). In this unadjusted multivariable model of the extended analysis, NLR at baseline was also a significant predictor of OS ($P \leq .001$) (Table 3). Adjustment by Bonferroni correction eliminated age as an independent predictor of survival.

This follow-up study also yielded interesting findings regarding subgroup treatment effects based on CA19-9 levels and NLR, two known markers of prognosis. CA19-9 level is elevated in approximately 60% to 80% of patients with advanced pancreatic cancer, and it has been used as an aid in assessing the extent of disease and as a marker of tumor response (18,29). Studies have indicated that higher baseline CA19-9 levels are generally associated with poorer clinical outcomes, including one report specific to patients who received gemcitabine therapy (18–20). Patients treated with *nab*-paclitaxel plus gemcitabine demonstrated similar OS regardless of whether baseline CA19-9 levels were less than the median or greater than or equal to the median (Figure 3), whereas in the gemcitabine-alone arm, OS was statistically significantly longer for patients with baseline CA19-9 levels less than the median vs greater than or equal to the median ($P = .001$) (Figure 3). In addition, among patients with a baseline

Table 2. Overall survival rates: update as of May 9, 2013*

	Survival rate, %	
Time point	*nab*-P + Gem (n = 431)	Gem (n = 430)
6 months	66	55
12 months	35	22
24 months	10	5
36 months	4	0
40 months	3	0
42 months	3	0

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

Table 3. Multivariable analysis of overall survival based on updated data as of May 9, 2013*

	Updated analysis	
Covariable	HR (95% CI)	P†
Treatment *nab*-P + Gem vs Gem	0.68 (0.57 to 0.80)	<.001
Presence of liver metastases Yes vs no	1.65 (1.28 to 2.12)	<.001
KPS 70-80 vs 90-100	1.47 (1.24 to 1.74)	<.001
NLR ≤ 5 vs > 5	0.57 (0.48 to 0.68)	<.001
Age < 65 vs ≥ 65 years	0.81 (0.69 to 0.96)	.016
Geographic region Eastern Europe vs North America	1.19 (0.99 to 1.43)	.063

* Gem = gemcitabine, HR = hazard ratio; KPS = Karnofsky performance status; *nab*-P = *nab*-paclitaxel; NLR = neutrophil-to-lymphocyte ratio.
† *P* values from two-sided Wald χ^2 tests.

Table 4. Baseline characteristics in subgroups divided by overall survival duration*

	All patients (17)		1- to 2-year survivors		>2-year survivors	
Variable	*nab*-P + Gem (n = 431)	Gem (n = 430)	*nab*-P + Gem (n = 119)	Gem (n = 76)	*nab*-P + Gem (n = 25)	Gem (n = 14)
Median age, y (range)	62 (27-86)	63 (32-88)	62 (27-80)	63 (41-85)	61 (46-78)	64 (50-83)
≥ 65 years, %	41	44	36	47	28	36
Male, %	57	60	55	49	48	64
Race, %						
Asian	2	2	1	0	8	14
Black	4	4	3	3	8	0
White	88	87	89	89	80	79
Hispanic	6	6	5	8	4	7
Other	1	1	2	0	0	0
Region, %						
Australia	14	14	13	11	20	14
Eastern Europe	15	14	11	11	8	21
North America	62	63	66	67	72	64
Western Europe	9	9	9	12	0	0
KPS, %						
100	16	16	20	26	32	50
90	42	46	39	53	48	36
80	35	30	39	17	20	14
70	7	8	2	4	0	0
60	<1	0	0	0	0	0
Liver metastases, %	85	84	84	74	56	57
CA19-9 level, %						
Normal	16	15	14	15	15	38
ULN to < 59 × ULN	32	32	34	42	30	46
≥ 59 × ULN	52	53	51	43	55	15
≤ Median	51	49	51	60	45	85
> Median	49	51	49	40	55	15

*CA19-9 = carbohydrate antigen 19-9; Gem = gemcitabine; KPS = Karnofsky performance status; *nab*-P = *nab*-paclitaxel; ULN = upper limit of normal.

ARTICLE

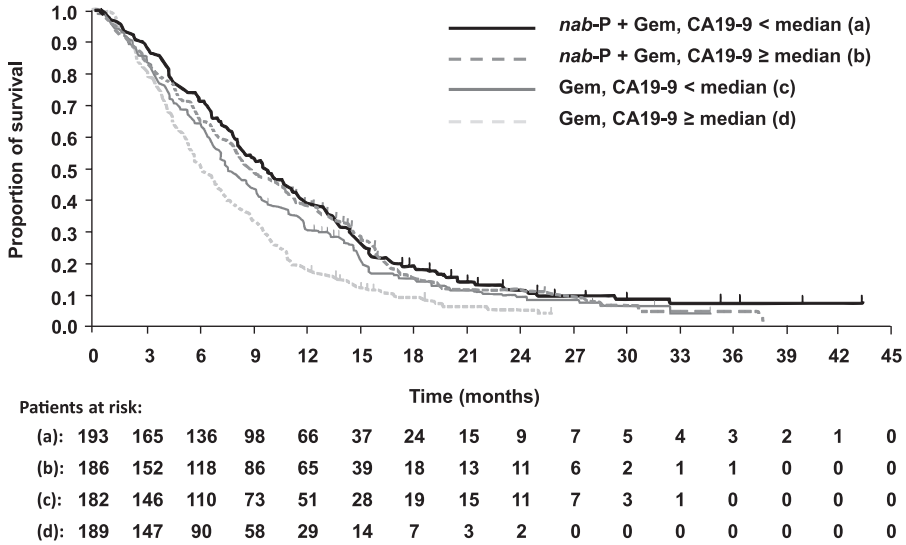


Figure 3. Overall survival by treatment and baseline CA19-9 level. Kaplan-Meier survival curve of subgroups divided by treatment arm and baseline CA19-9 level (less than or greater than or equal to the median). Gem = gemcitabine; *nab*-P = *nab*-paclitaxel; OS = overall survival.

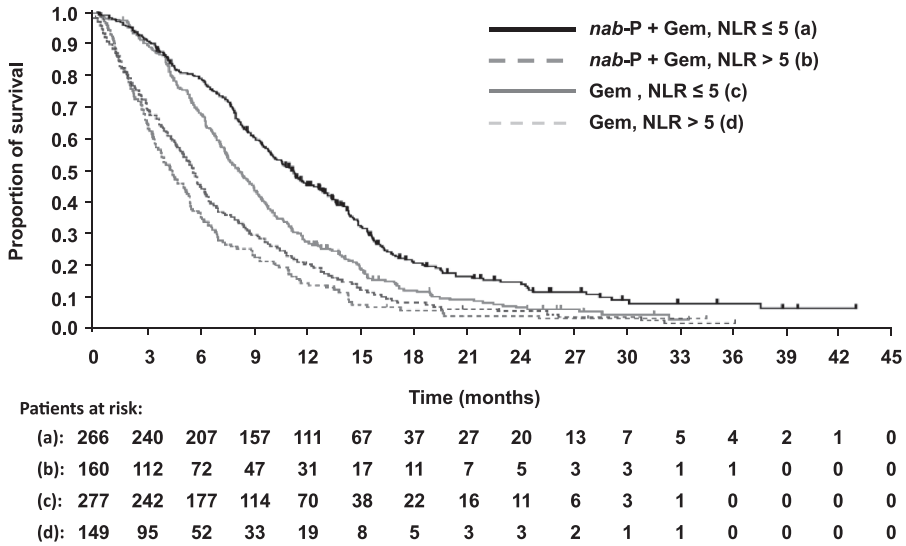


Figure 4. Overall survival by treatment and baseline neutrophil-to-lymphocyte ratio (NLR). Kaplan-Meier survival curve of subgroups divided by treatment arm and baseline NLR (less than or equal to or greater than five). Gem = gemcitabine; *nab*-P = *nab*-paclitaxel; OS = overall survival.

ARTICLE

CA19-9 level greater than or equal to the median, OS was statistically significantly longer for those who received *nab*-paclitaxel plus gemcitabine vs those who received gemcitabine alone ($P < .001$) (Figure 3). These results suggest that *nab*-paclitaxel was able to reduce or overcome the effect of baseline CA19-9 level as a prognostic factor, whereas treatment with gemcitabine alone was not. This may reflect an improved response rate, reducing the impact of a higher tumor burden, or it may reflect that the combination acts on metabolic pathways not amenable to blockade by gemcitabine alone (30).

Although it has not yet been as thoroughly evaluated in pancreatic cancer, NLR—a marker of systemic inflammatory response—is an important prognostic factor for a number of malignancies, including colorectal cancer and non–small cell lung cancer (31–33). This inflammatory response appears to promote the microenvironment to facilitate tumor progression and metastasis (34). Recently, elevated baseline NLR was shown to predict shorter OS in a retrospective analysis of patients who were treated with gemcitabine-based chemotherapy for advanced pancreatic cancer (median = 2.4 months for patients with an NLR > 5 vs 7.7 months for patients with an NLR ≤ 5, HR = 5.77, $P < .001$) (22). However, similar analyses in prospective clinical trials have been lacking. The multivariable analysis in this follow-up report confirmed the prognostic significance of NLR, and the median OS for patients with an NLR of less than or equal to vs greater than five was 9.1 vs 5.0 months, respectively. Among patients with an NLR greater than five, the hazard ratio of 0.81 and *P* value of 0.079 suggest a trend toward a treatment effect favoring *nab*-paclitaxel plus gemcitabine. The observed association of neutrophilia with angiogenesis suggests that this patient subset may benefit from the addition of antiangiogenic therapy, despite its lack of benefit in unstratified trials (8,23,35).

The utility of this regimen may be further refined once the results of additional potentially predictive molecular studies

Table 5. Safety

Select adverse events	*nab*-P + Gem					Gem				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic, n (%)										
All treated			n = 405*					n = 388		
KPS 90-100			n = 241					n = 241		
KPS 70-80			n = 164†					n = 146		
Neutropenia										
All treated	297 (73)	43 (11)	101 (25)	107 (26)	46 (11)	225 (58)	35 (9)	86 (22)	83 (21)	21 (5)
KPS 90-100	185 (77)	22 (9)	65 (27)	67 (28)	31 (13)	156 (65)	20 (8)	60 (25)	60 (25)	16 (7)
KPS 70-80	112 (68)	21 (13)	36 (22)	40 (24)	15 (9)	68 (47)	15 (10)	25 (17)	23 (16)	5 (3)
Leukopenia										
All treated	357 (88)	100 (25)	130 (32)	116 (29)	11 (3)	298 (77)	116 (30)	119 (31)	59 (15)	4 (1)
KPS 90-100	220 (91)	56 (23)	83 (34)	72 (30)	9 (4)	200 (83)	72 (30)	86 (36)	39 (16)	3 (1)
KPS 70-80	137 (84)	44 (27)	47 (29)	44 (27)	2 (1)	97 (66)	44 (30)	32 (22)	20 (14)	1 (1)
Thrombocytopenia										
All treated	302 (75)	169 (42)	81 (20)	43 (11)	9 (2)	272 (70)	162 (42)	73 (19)	29 (7)	8 (2)
KPS 90-100	191 (79)	105 (44)	50 (21)	28 (12)	8 (3)	179 (74)	108 (45)	49 (20)	19 (8)	3 (1)
KPS 70-80	111 (68)	64 (39)	31 (19)	15 (9)	1 (1)	93 (64)	54 (37)	24 (16)	10 (7)	5 (3)
Anemia										
All treated	393 (97)	104 (26)	233 (58)	52 (13)	4 (1)	374 (96)	136 (35)	189 (49)	43 (11)	6 (2)
KPS 90-100	236 (98)	69 (29)	139 (58)	25 (10)	3 (1)	235 (98)	93 (39)	109 (45)	30 (12)	3 (1)
KPS 70 - 80	157 (96)	35 (21)	94 (57)	27 (16)	1 (1)	139 (95)	43 (29)	80 (55)	13 (9)	3 (2)
Receipt of growth factors, n/N (%)										
ITT			110/431 (26)					63/430 (15)		
KPS 90-100			72/248 (29)					43/268 (16)		
KPS 70-80			38/179 (21)					20/161 (12)		
Nonhematologic, n (%)										
All treated			n = 421					n = 402[c]		
KPS 90-100			n = 246					n = 248		
KPS 70-80			n = 174					n = 153		
Fatigue										
All treated	228 (54)	51 (12)	104 (25)	72 (17)	1 (<1)	147 (37)	53 (13)	67 (17)	26 (6)	1 (<1)
KPS 90-100	139 (57)	34 (14)	72 (29)	33 (13)	0	94 (38)	42 (17)	38 (15)	14 (6)	0
KPS 70-80	89 (51)	17 (10)	32 (18)	39 (22)	1 (1)	53 (35)	11 (7)	29 (19)	12 (8)	1 (1)
Peripheral neuropathy‡										
All treated	221 (52)	94 (22)	56 (13)	71 (17)	0	21 (5)	18 (4)	2 (<1)	1 (<1)	0
KPS 90-100	142 (58)	58 (24)	36 (15)	48 (20)	0	13 (5)	12 (5)	1 (<1)	0	0
KPS 70-80	79 (45)	36 (21)	20 (11)	23 (13)	0	8 (5)	6 (4)	1 (1)	1 (1)	0
Diarrhea										
All treated	157 (37)	82 (19)	51 (12)	24 (6)	0	53 (13)	34 (8)	16 (4)	3 (1)	0
KPS 90-100	99 (40)	54 (22)	30 (12)	15 (6)	0	32 (13)	19 (8)	10 (4)	3 (1)	0
KPS 70-80	58 (33)	28 (16)	21 (12)	9 (5)	0	21 (14)	15 (10)	6 (4)	0	0

* n = 404 for thrombocytopenia in all treated patients. Gem = gemcitabine; ITT = intent-to-treat; KPS = Karnofsky performance status; *nab*-P = *nab*-paclitaxel.
† n = 163 for thrombocytopenia for patients with a KPS of 70 to 80.
‡ Peripheral neuropathy was reported on the basis of preferred terms defined by the standardized queries in the *Medical Dictionary for Regulatory Activities* version 15.0.

are completed. Initial data on secreted protein acidic and rich in cysteine (SPARC) expression in the phase I/II trial suggested enhanced efficacy in tumors that expressed higher vs lower levels of SPARC (17). SPARC analyses from the MPACT trial are currently ongoing and will be the subject of future publications.

This study is likely to be broadly representative of the population of patients with metastatic disease. Limitations of our study include the lack of a quality-of-life analysis and the addition of post hoc analyses and multiple comparisons that were not prespecified in the study's statistical plan. Like all post hoc subgroup analyses, the comparisons of OS in subsets defined by NLR and CA 19-9 were susceptible to the possibility of spurious findings.

In conclusion, these updated results confirm and expand on the longer-term benefits of the previously reported treatment effect favoring *nab*-paclitaxel plus gemcitabine for OS. They further support the use of this combination therapy as a new standard option for patients with advanced pancreatic cancer, including those with higher-risk baseline features, such as those with a KPS of 70 to 80 in whom no increases in grade 3 or higher adverse events were observed. In addition, *nab*-paclitaxel plus gemcitabine may be an excellent comparator for future studies. Finally, *nab*-paclitaxel plus gemcitabine may serve as a backbone on which to add other therapies for patients with this disease.

Funding

This work was supported by the Celgene Corporation.

Notes

We thank all the patients and their families who participated in this phase III study: Amanda Johnson, Heidi Marks, and Tammy Davis of the Celgene Corporation for coordination of the clinical trial sites, Desmond McGovern and Stefano Ferrara of Celgene

Corporation for medical monitoring, Hui Liu of the Celgene Corporation for biostatistical support, and John McGuire of MediTech Media for medical writing assistance.

References

1. American Cancer Society. *Cancer facts & figures 2014*. Atlanta, Georgia: American Cancer Society; 2014. http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf. Accessed March 28, 2014.
2. Burris HA, III, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15(6):2403–2413.
3. The National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. V1.2014. http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed March 28, 2014.
4. Seufferlein T, Bachet JB, Van Cutsem E, Rougier P. ESMO Guidelines Working Group. Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23(Suppl 7):vii33–vii40.
5. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817–1825.
6. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 2007;25(15):1960–1966.
7. Colucci G, Labianca R, Di Costanzo F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol*. 2010;28(10):1645–1651.
8. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol*. 2010;28(22):3617–3622.
9. Goncalves A, Gilabert M, Francois E, et al. BAYPAN study: a double-blind phase III randomized trial comparing gemcitabine plus sorafenib and gemcitabine plus placebo in patients with advanced pancreatic cancer. *Ann Oncol*. 2012;23(11):2799–2805.
10. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol*. 2009;27(33):5513–5518.
11. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2009;27(23):3778–3785.
12. Abou-Alfa GK, Letourneau R, Harker G, et al. Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. *J Clin Oncol*. 2006;24(27):4441–4447.
13. Stathopoulos GP, Syrigos K, Aravantinos G, et al. A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. *Br J Cancer*. 2006;95(5):587–592.
14. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil–based paclitaxel in women with breast cancer. *J Clin Oncol*. 2005;23(31):7794–7803.
15. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non–small-cell lung cancer: final results of a phase III trial. *J Clin Oncol*. 2012;30(17):2055–2062.
16. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol*. 2011;29(34):4548–4554.
17. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369(18):1691–1703.
18. Boeck S, Stieber P, Holdenrieder S, Wilkowski R, Heinemann V. Prognostic and therapeutic significance of carbohydrate antigen 19-9 as tumor marker in patients with pancreatic cancer. *Oncology*. 2006;70(4):255–264.
19. Bauer TM, El-Rayes BF, Li X, et al. Carbohydrate antigen 19-9 is a prognostic and predictive biomarker in patients with advanced pancreatic cancer who receive gemcitabine-containing chemotherapy: a pooled analysis of 6 prospective trials. *Cancer*. 2013;119(2):285–292.
20. Hess V, Glimelius B, Grawe P, et al. CA 19-9 tumour-marker response to chemotherapy in patients with advanced pancreatic cancer enrolled in a randomised controlled trial. *Lancet Oncol*. 2008;9(2):132–138.
21. Tempero MA, Uchida E, Takasaki H, Burnett DA, Steplewski Z, Pour PM. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. *Cancer Res*. 1987;47(20):5501–5503.
22. An X, Ding PR, Li YH, et al. Elevated neutrophil to lymphocyte ratio predicts survival in advanced pancreatic cancer. *Biomarkers*. 2010;15(6):516–522.
23. Proctor MJ, McMillan DC, Morrison DS, Fletcher CD, Horgan PG, Clarke SJ. A derived neutrophil to lymphocyte ratio predicts survival in patients with cancer. *Br J Cancer*. 2012;107(4):695–699.
24. Xue P, Kanai M, Mori Y, et al. Neutrophil-to-lymphocyte ratio for predicting palliative chemotherapy outcomes in advanced pancreatic cancer patients. *Cancer Med*. 2014; In press.
25. Stotz M, Gerger A, Eisner F, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. *Br J Cancer*. 2013;109(2):416–421.
26. Teo M, Mohd Sharial MS, McDonnell F, Conlon KC, Ridgway PF, McDermott RS. Prognostic role of neutrophil-to-lymphocyte ratio in advanced pancreatic ductal adenocarcinoma: impact of baseline fluctuation and changes during chemotherapy. *Tumori*. 2013;99(4):516–522.
27. Wang DS, Luo HY, Qiu MZ, et al. Comparison of the prognostic values of various inflammation based factors in patients with pancreatic cancer. *Med Oncol*. 2012;29(5):3092–3100.
28. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92(3):205–216.
29. Koprowski H, Herlyn M, Steplewski Z, Sears HF. Specific antigen in serum of patients with colon carcinoma. *Science*. 1981;212(4490):53–55.
30. Frese KK, Neesse A, Cook N, et al. Nab-paclitaxel potentiates gemcitabine activity by reducing cytidine deaminase levels in a mouse model of pancreatic cancer. *Cancer Discov*. 2012;2(3):260–269.
31. Halazun KJ, Aldoori A, Malik HZ, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts survival following

ARTICLE

hepatic resection for colorectal liver metastases. *Eur J Surg Oncol*. 2008;34(1):55–60.
32. Kishi Y, Kopetz S, Chun YS, Palavecino M, Abdalla EK, Vauthey JN. Blood neutrophil-to-lymphocyte ratio predicts survival in patients with colorectal liver metastases treated with systemic chemotherapy. *Ann Surg Oncol*. 2009;16(3):614–622.
33. Sarraf KM, Belcher E, Raevsky E, Nicholson AG, Goldstraw P, Lim E. Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2009;137(2):425–428.
34. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. *Cell*. 2011;144(5):646–674.
35. Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol*. 2009;27(13):2231–2237.