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CA19-9 decrease at 8 weeks as a predictor of overall survival in a randomized phase III trial (MPACT) of weekly *nab*-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic pancreatic cancer

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Background: A phase I/II study and subsequent phase III study (MPACT) reported significant correlations between CA19-9 decreases and prolonged overall survival (OS) with *nab*-paclitaxel plus gemcitabine (*nab*-P + Gem) treatment for metastatic pancreatic cancer (MPC). CA19-9 changes at week 8 and potential associations with efficacy were investigated as part of an exploratory analysis in the MPACT trial.

Patients and methods: Untreated patients with MPC ($N = 861$) received *nab*-P + Gem or Gem alone. CA19-9 was evaluated at baseline and every 8 weeks.

Results: Patients with baseline and week-8 CA19-9 measurements were analyzed (*nab*-P + Gem: 252; Gem: 202). In an analysis pooling the treatments, patients with any CA19-9 decline (80%) versus those without (20%) had improved OS (median 11.1 versus 8.0 months; $P = 0.005$). In the *nab*-P + Gem arm, patients with ($n = 206$) versus without ($n = 46$) any CA19-9 decrease at week 8 had a confirmed overall response rate (ORR) of 40% versus 13%, and a median OS of 13.2 versus 8.3 months ($P = 0.001$), respectively. In the Gem-alone arm, patients with ($n = 159$) versus without ($n = 43$) CA19-9 decrease at week 8 had a confirmed ORR of 15% versus 5%, and a median OS of 9.4 versus 7.1 months ($P = 0.404$), respectively. In the *nab*-P + Gem and Gem-alone arms, by week 8, 16% (40/252) and 6% (13/202) of patients, respectively, had an unconfirmed radiologic response (median OS 13.7 and 14.7 months, respectively), and 79% and 84% of patients, respectively, had stable disease (SD) (median OS 11.1 and 9 months, respectively). Patients with SD and any CA19-9 decrease (158/199 and 133/170) had a median OS of 13.2 and 9.4 months, respectively.

Conclusion: This analysis demonstrated that, in patients with MPC, any CA19-9 decrease at week 8 can be an early marker for chemotherapy efficacy, including in those patients with SD. CA19-9 decrease identified more patients with survival benefit than radiologic response by week 8.

Key words: CA19-9, pancreatic cancer, chemotherapy, *nab*-paclitaxel, MPACT

introduction

Metastatic pancreatic adenocarcinoma is one of the most aggressive cancers, with <25% of patients alive 1 year after diagnosis [1]. Carbohydrate antigen 19-9 (CA19-9), a Lewis blood group antigen, is one of the most widely studied tumor markers in patients with advanced pancreatic cancer [2–5] due to its utility in determining prognosis and response to treatment [5–12]. In general, higher versus lower CA19-9 levels at baseline and increasing versus decreasing CA19-9 levels during therapy are associated with worse prognosis [5, 6]. However, the predictive value of decreasing CA19-9 levels during treatment for assessment of response and survival has not been clearly defined [6, 13]. In a pooled analysis of six phase II trials of patients with advanced pancreatic cancer

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treated with gemcitabine (Gem)-containing chemotherapy, after two cycles of treatment, ≤5% CA19-9 increase versus >5% increase from baseline was predictive of improved outcome [median overall survival (OS) 10.3 versus 5.2 months; $P = 0.002$] [6]. *nab*-Paclitaxel plus gemcitabine (*nab*-P + Gem), a new standard treatment option for patients with advanced pancreatic cancer, demonstrated superiority over Gem alone across all efficacy end points in a phase III trial, MPACT [14–16]. The phase I/II study of *nab*-P + Gem that preceded MPACT reported a significant correlation between decreases in CA19-9 levels of ≥50% versus <50% from baseline and improved survival (13.6 versus 6.5 months; $P = 0.004$) [16]. In a stepwise multivariate analysis, baseline CA19-9 level was not an independent predictor of survival in MPACT [17]; thus, an assessment to understand the dynamics of CA19-9 changes during treatment was warranted. Here, we report a detailed evaluation of the prespecified MPACT exploratory end points of changes in CA19-9 levels and correlations with OS, progression-free survival (PFS), and overall response rate (ORR).

methods

MPACT study design

The patients enrolled in and methods of the MPACT trial have been described previously [14]. Key parameters and methods specific to this subanalysis are described below. CA19-9 was evaluated at baseline and every 8 weeks up to week 40 per schedule. Patients could have had unscheduled CA19-9 measurements.

patient population

For analyses that examined the change from baseline to nadir in CA19-9, all patients who had a baseline and at least one postbaseline measurement were included. For analyses that examined the change from baseline to week 8, only patients who had a baseline and a week-8 measurement of CA19-9 were included.

end points and statistical methods

reduction in CA19-9 from baseline at nadir. The proportions of patients who achieved any, ≥20%, ≥60%, or ≥90% reduction from baseline at nadir during the study were compared between the two treatment groups using a χ^2 test for each level of reduction.

predictive value of CA19-9 at week 8 (landmark) for OS, PFS, and ORR. Patients who had a baseline and a week-8 measurement of CA19-9 were included in the analyses to assess the predictive/prognostic value of the percent change in ORR, PFS, and OS. The ORR, PFS, and OS outcomes for various categories of changes in CA19-9 levels were evaluated (including all patients with any increase, any decrease, and decreases ≥20%, ≥40%, ≥60%, or ≥90%). Treatment comparisons were conducted using a stratified log-rank test for OS and PFS and a stratified Cox model for hazard ratio (HR) based on geographic region (North America versus other), Karnofsky performance status (70–80 versus 90–100), and the presence of liver metastases (yes versus no). The stratification was not applied when there were fewer than 50 patients in either treatment group. The treatment comparisons for ORR outcomes were performed using a χ^2 test. Summaries of survival statistics (e.g. median months of survival) were calculated using the Kaplan–Meier method.

Per protocol, radiologic response by Response Evaluation Criteria In Solid Tumors (RECIST v1.0) [18] was required to be confirmed at an assessment at least 4 weeks after the initial finding. A RECIST-defined response at week 8 only, without a confirmatory radiologic finding, was noted as 'unconfirmed'.

kinetics of CA19-9 over time. The rate of decrease per week (i.e. velocity slope) of CA19-9 during the first 8 weeks of treatment was estimated for each patient using a mixed-effects model (PROC MIXED in SAS 9.2), with treatment as the fixed effect and patient as the random effect. All observations available from baseline to the end of cycle 1 (week 8) were included in the model. Approximately 9% of the patients had at least one additional CA19-9 measurement between baseline and week 8. Given the large variability and the skewness in the distribution of the CA19-9 values, log transformation was applied to the CA19-9 measurements for this analysis.

results

characterization of CA19-9 decreases from baseline

CA19-9 levels at baseline and at least one time point postbaseline were available for 512 patients (281 in the *nab*-P + Gem arm and 231 in the Gem-alone arm); the change in CA19-9 from baseline to nadir is described in supplementary Table S1, available at *Annals of Oncology* online.

Baseline and week-8 CA19-9 measurements were available for 454 patients (252 in the *nab*-P + Gem arm and 202 in the Gem-alone arm); 82% and 79%, respectively, had any decrease in CA19-9 at week 8 (Table 1). Baseline characteristics of patients with week-8 CA19-9 values were balanced between treatment arms and representative of the MPACT study population (supplementary Table S2, available at *Annals of Oncology* online) [14].

pooled analysis: correlation between decrease in CA19-9 levels from baseline to week 8 and OS

In a pooled analysis of all patients from the two treatment arms, patients who had any (>0%) reduction in CA19-9 from baseline to week 8 had a significant improvement in OS compared with those who did not have a reduction in CA19-9 (median OS 11.1 versus 8.0 months; $P = 0.005$; Table 2). Similar results were demonstrated with ≥20%, ≥60%, and ≥90% reductions in CA19-9 from baseline.

predictive and prognostic value of CA19-9 response at week 8: landmark analysis

At week 8, improved efficacy outcomes were observed in each arm for any decrease in CA19-9 levels and at all cutoff levels of CA19-9 decrease versus no change/any increase, with a statistically significant benefit in favor of *nab*-P + Gem versus Gem alone (Table 3; Figure 1). In general, compared with patients who met the individual cutoff values of any (>0%), ≥20%, ≥60%, or ≥90% decrease in CA19-9, patients who had no change or any increase or a <20%, <60%, or <90% decrease in CA19-9 at week 8 had lower confirmed ORR, PFS, and OS (Table 3). For example, in the *nab*-P + Gem arm, patients with any CA19-9 decrease had longer OS than patients with no change/any increase {median 13.2 versus 8.3 months; HR 0.53 [95% confidence interval (CI) 0.36–0.78]; $P = 0.001$}. A similar trend was observed in the Gem-alone arm, although it did not reach statistical significance [median 9.4 versus 7.1 months; HR 0.84 (95% CI 0.56–1.27); $P = 0.404$].

Table 1. Summary of baseline CA19-9 levels and change in CA19-9 levels from baseline at week 8

CA19-9 variables	*nab*-P + Gem ($N = 431$)[a]	Gem ($N = 430$)[a]
Patients with a baseline measurement, *n*	379	371
Baseline median, U/ml (min, max)	2294 (2, 6 159 233)	2759 (0, 12 207 654)
≥200 U/ml at baseline, *n* (%)	282 (74)	275 (74)
≥1000 U/ml at baseline, *n* (%)	228 (60)	220 (59)
Patients with baseline and week-8 measurements (landmark), *n*	252	202
Change[b] from baseline at week 8, median (min, max), %	−70 (−100, 1230)	−57 (−100, 1 43 268)
Category of change from baseline at week 8, *n* (%)		
No change or any increase	46 (18)	43 (21)
Any decrease	206 (82)	159 (79)
≥20% decrease	197 (78)	141 (70)
≥60% decrease	146 (58)	95 (47)
≥90% decrease	59 (23)	34 (17)

[a]Patients in the intention-to-treat population.
[b]Negative % change means decrease in CA19-9.
Gem, gemcitabine; *nab*-P, *nab*-paclitaxel.

Table 2. Correlation between CA19-9 decrease from baseline to week 8 and OS: pooled analysis

Change in CA19-9 from baseline	Patients with the specified decrease		Patients without the specified decrease		*P* value[a]
	n	Median OS (months)	*n*	Median OS (months)	
Any decrease	365	11.1	89	8.0	0.005
≥20% decrease	338	11.1	116	8.2	0.004
≥60% decrease	241	11.9	213	8.5	<0.001
≥90% decrease	93	11.1	361	9.7	0.189

[a]*P* value based on a log-rank test stratified by geographic region (Australia versus Eastern Europe versus North America versus Western Europe), Karnofsky performance status (70–80 versus 90–100), and the presence of liver metastases (yes versus no).
OS, overall survival.

An evaluation of discrete, nonoverlapping subsets at week 8 revealed that a ≥60% to <90% decrease in CA19-9 from baseline was a predictor for the longest OS in both treatment groups (*nab*-P + Gem $n = 87$, median OS 14.3 months, and Gem-alone $n = 61$, median OS 10.4 months, Table 4).

predictive and prognostic value of CA19-9 kinetics over time

A steep decline in CA19-9 levels was observed in each of the two treatment arms during the first 8 weeks of treatment, with a plateau after week 16 (Figure 2). A steeper velocity of decline in CA19-9 levels during the first 8 weeks generally correlated with improved OS, PFS, and confirmed ORR (supplementary Table S3, available at *Annals of Oncology* online) for the two treatment arms. In the *nab*-P + Gem arm, patients in the top (≥17.7% decrease/week) and middle (7% to <17.7% decrease/week) versus the lowest tertile of velocity (<7% decrease/week) had better outcomes (median OS, 13.4 and 13.2 versus 8.3 months; median PFS, 8.5 and 7.6 versus 5.9 months; ORR, 51% and 29% versus 19%, supplementary Table S3, available at *Annals of Oncology* online). The trend was not as evident in the Gem-alone arm (supplementary Table S3, available at *Annals of Oncology* online).

radiologic response by week 8 and outcomes

The correlations between achieving a RECIST-defined radiologic response [unconfirmed complete response (CR) or partial response (PR)] by week 8 and OS were examined for the CA19-9–assessable patients. A CR or PR was achieved in 16% (40/252) of patients in the *nab*-P + Gem arm and 6% (13/202) of patients in the Gem-alone arm by week 8. Thirty-eight of the 40 patients in the *nab*-P + Gem arm and all 13 patients in the Gem-alone arm with CR/PR had a decrease in CA19-9 at week 8. The median OS for patients with a radiologic response was 13.7 and 14.7 months, respectively.

Most CA19-9 assessable patients had unconfirmed stable disease (SD) by week 8: 79% (199/252) and 84% (170/202) in the *nab*-P + Gem and Gem-alone arms, respectively, with corresponding median OS of 11.1 and 9.0 months. Among patients with SD, 79% (158/199) in the *nab*-P + Gem arm and 78% (133/170) in the Gem-alone arm had a CA19-9 decrease at week 8, with corresponding median OS of 13.2 and 9.4 months, respectively. Median OS for SD patients without CA19-9 decrease at week 8 was 8.3 and 7.1 months, respectively.

discussion

This analysis demonstrated that any decrease in CA19-9 level at week 8—which occurred in 82% and 79% of 454 overall assessable patients treated with *nab*-P + Gem and Gem-alone, respectively—was associated with improved outcomes, representing a valuable tool for early prediction of treatment benefit. CA19-9 decrease versus no decrease correlated with larger survival

Table 3. Efficacy summary by category of CA19-9 changes from baseline to week 8

Decreases in CA19-9 level	*n*	*nab*-P + Gem	*n*	Gem	RRR or HR	*P* value[a]
Any decrease (>0%)						
ORR (%)	206	40	159	15	2.64	<0.001
PFS, median (months)[b]	193	7.7	139	5.6	0.66	0.005
OS, median (months)	206	13.2	159	9.4	0.60	<0.001
1-year survival rate (%)	206	53	159	35	–	–
No change or any increase						
ORR (%)[c]	46	13	43	5	2.80	0.167
PFS, median (months)[b]	42	5.5	34	5.2	0.91	0.777
OS, median (months)	46	8.3	43	7.1	0.96	0.885
1-year survival rate (%)	46	27	43	22	–	–
OS HR[d]	0.53		0.84		–	
95% CI	0.36–0.78		0.56–1.27			
P value	0.001		0.404			
Decrease ≥20%						
ORR (%)[c]	197	40	141	17	2.36	<0.001
PFS, median (months)[b]	187	7.7	125	5.7	0.66	0.007
OS, median (months)	197	13.2	141	9.4	0.59	<0.001
1-year survival rate (%)	197	53	141	34	–	–
Decrease <20%						
ORR (%)[c]	55	16	61	3	4.99	0.016
PFS, median (months)[b]	48	5.9	48	4.4	0.78	0.426
OS, median (months)	55	8.3	61	8.0	0.95	0.819
1-year survival rate (%)	55	30	61	27	–	–
OS HR[d]	0.55		0.85		–	
95% CI	0.38–0.78		0.59–1.23			
P value	0.001		0.396			
Decrease ≥60%						
ORR (%)[c]	146	45	95	23	1.95	0.001
PFS, median (months)[b]	142	9.0	87	6.2	0.63	0.017
OS, median (months)	146	14.2	95	9.8	0.55	<0.001
1-year survival rate (%)	146	58	95	37	–	–
Decrease <60%						
ORR (%)[c]	106	21	107	4	5.55	<0.001
PFS, median (months)[b]	93	5.8	86	5.2	0.84	0.368
OS, median (months)	106	8.7	107	8.0	0.81	0.183
1-year survival rate (%)	106	35	107	28	–	–
OS HR[d]	0.54		0.69		–	
95% CI	0.39–0.73		0.50–0.97			
P value	<0.001		0.033			
Decrease ≥90%						
ORR, %[c]	59	63	34	35	1.78	0.011
PFS, median (months)[b]	58	8.5	33	5.6	0.44	0.006
OS, median (months)	59	13.4	34	9.8	0.47	0.005
1-year survival rate (%)	59	57	34	23	–	–
Decrease <90%						
ORR, %[c]	193	26	168	8	3.17	<0.001
PFS, median (months)[b]	177	6.7	140	5.5	0.81	0.155
OS, median (months)	193	10.8	168	8.9	0.73	0.013
1-year survival rate (%)	193	45	168	35	–	–
OS HR[d]	0.75		0.95		–	
95% CI	0.52–1.09		0.62–1.45			
P value	0.132		0.812			

[a]Between-treatment arm *P* values were based on a χ^2 test for ORR, or a stratified log-rank test for OS and PFS. The associated HR and 95% CI were estimated using a stratified Cox model for OS and PFS. Stratification was not applied for OS and PFS if the number of patients was <50 in either arm.
[b]PFS measure excludes patients with a date of disease progression before week 8.
[c]Confirmed ORR by RECIST.
[d]Within-treatment arm *P* values for the indicated comparison were based on a stratified log-rank test for OS. The associated HR and 95% CI were estimated using a stratified Cox model for OS. Stratification was not applied for OS if the number of patients was <50 in either arm.
Gem, gemcitabine; HR, hazard ratio; *nab*-P, *nab*-paclitaxel; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; RRR, relative response rate.

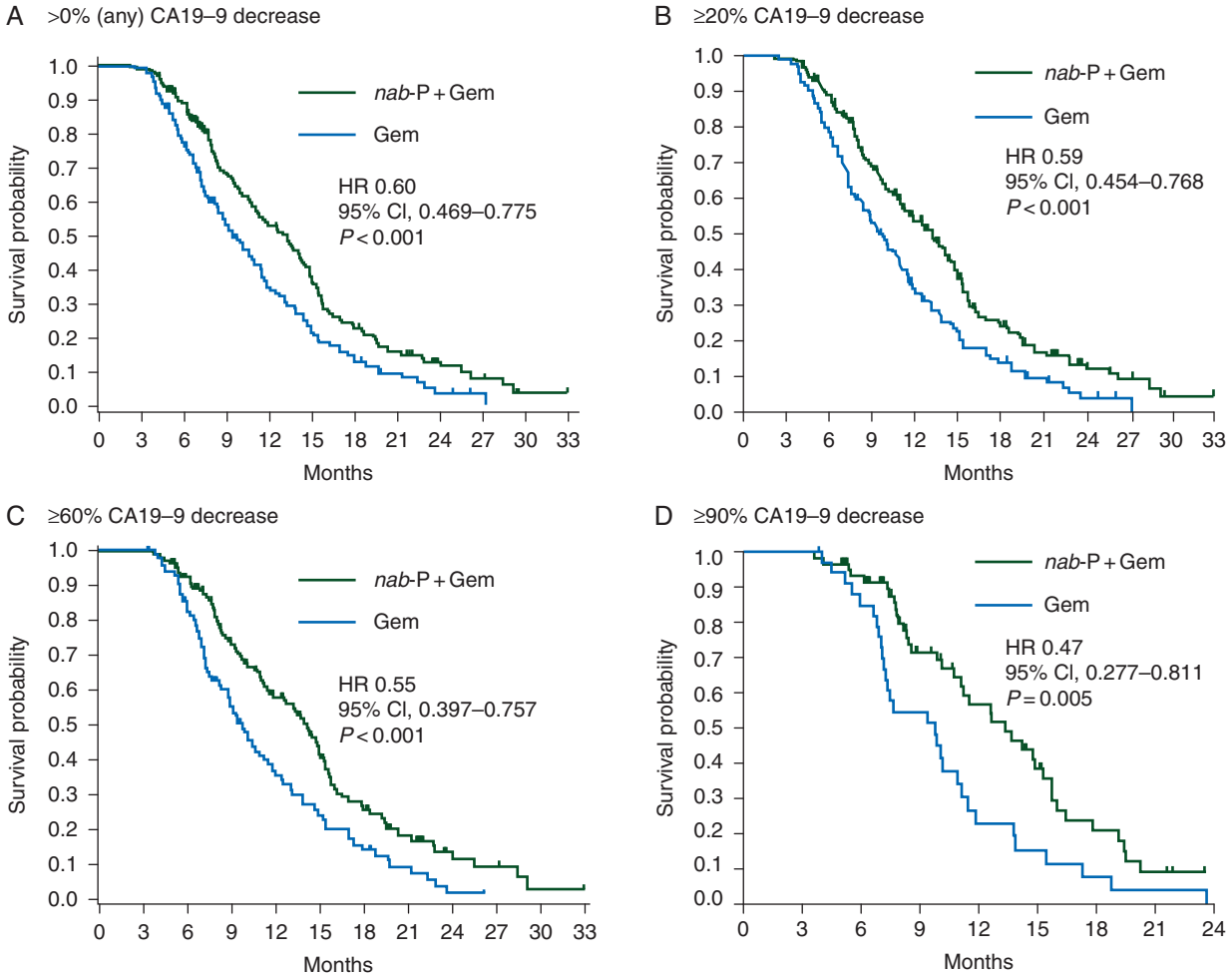

Figure 1. OS in patients with any, ≥20%, ≥60%, and ≥90% CA19-9 level decreases from baseline at week 8. Kaplan–Meier survival curves for patients with any (A), ≥20% (B), ≥60% (C), and ≥90% (D) reductions in CA19-9 level from baseline at week 8. Gem, gemcitabine; HR, hazard ratio; *nab*-P, *nab*-paclitaxel.

benefit with *nab*-P + Gem {4.9 months improvement in median OS [13.2 versus 8.3 months; HR 0.53 (95% CI 0.36–0.78); $P = 0.001$]} compared with Gem alone [2.3 months of improvement in median OS (9.4 versus 7.1 months); HR 0.84 (95% CI 0.56–1.27); $P = 0.404$]. The robust predictive value of a week-8 CA19-9 decrease with *nab*-P + Gem is particularly relevant as this regimen is widely used and has become one of the standard first-line treatments for metastatic pancreatic cancer.

A recent retrospective analysis of the phase III ACCORD11/PRODIGE4 study also reported a correlation between CA19-9 decreases and improved efficacy outcomes in 160 overall assessable patients treated with FOLFIRINOX or Gem alone [19]. In the pooled population, a CA19-9 decrease of ≥20% versus <20% at week 8 significantly correlated with longer OS (median 10.3 versus 7.8 months; HR 0.57 [95% CI 0.40–0.81]; $P = 0.002$), whereas in the FOLFIRINOX and Gem-alone arms, a CA19-9 decrease of ≥20% was observed in 59% and 52% of patients, respectively, and associated with a median OS of 13.5 and 8.6 months, respectively ($P = 0.021$). Our data similarly show that a week-8 CA19-9 decrease is predictive of superior efficacy outcomes and that *nab*-P + Gem is more likely than Gem alone to achieve these results. In the intention-to-treat (ITT) population of MPACT, the final median OS was 8.7 months in the *nab*-P + Gem arm ($n = 431$) [15]. Patients in this treatment arm who achieved any CA19-9 decrease at week 8 ($n = 206$) had a median OS of 13.2 months. Likewise, the median OS in the ITT population in the Gem-alone arm ($n = 430$) was 6.6 months, and in patients with any CA19-9 decrease ($n = 159$), the median OS was 9.4 months. Thus, achieving any reduction in CA19-9 was an indicator of OS benefit in both treatment arms.

The treatment benefit of *nab*-P + Gem was predicted early, at week 8, by CA19-9 decline, whereas the Kaplan–Meier survival curves did not begin to show a benefit for *nab*-P + Gem versus Gem alone until later, at ≈5 months, when the OS curves begin to separate for every cutoff of CA19-9 decrease (Figure 1). This observation was also noted for the ITT population of MPACT [14]. Although larger decreases in CA19-9 appeared to associate with higher ORRs (Table 3), the association with OS seemed less pronounced. However, the majority of patients with 'any' CA19-9 decrease (66%, 241/365) had in fact a ≥60% decrease in CA19-9, and this patient cohort had the longest OS (14.2 months), which likely influenced the overall OS in the *nab*-P + Gem arm (Tables 3 and 4). Nevertheless, the overall findings of this study suggest that any CA19-9 decrease at week 8 may

Table 4. Subgroup analysis of OS based on CA19-9 change at week 8

Change in CA19-9 level at week 8	*nab*-P + Gem (n = 252)	Gem (n = 202)
Decrease		
≥90%, *n*	59	34
OS, median (months)	13.4	9.8
≥60% to <90%, *n*	87	61
OS, median (months)	14.3	10.4
≥40% to <60%, *n*	36	27
OS, median (months)	10.5	7.9
≥20% to <40%, *n*	15	19
OS, median (months)	8.1	8.4
>0% to <20%, *n*	9	18
OS, median (months)	10.5	9.0
Increase		
0% to ≤20%, *n*	11	12
OS, median (months)	8.7	7.1
>20% to ≤40%, *n*	9	12
OS, median (months)	9.2	6.9
>40%, *n*	26	19
OS, median (months)	8.1	6.1

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

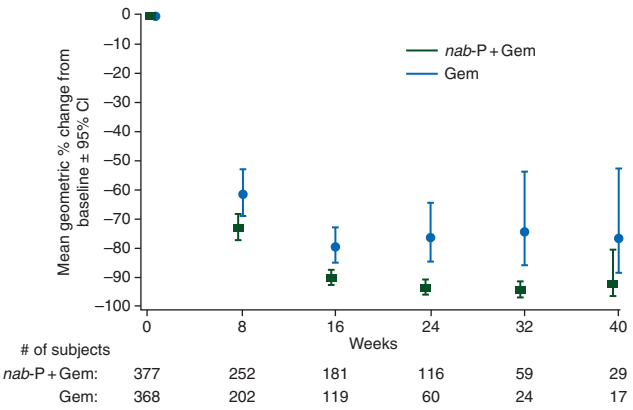

Figure 2. Decrease from baseline over time (velocity) in CA19-9 level for evaluable patients on study treatment. CA19-9 levels were measured at baseline and every 8 weeks. Gem, gemcitabine; *nab*-P, *nab*-paclitaxel.

have relevance as an early surrogate for outcome in future clinical trials.

A higher proportion of patients treated with *nab*-P + Gem versus Gem alone had a steeper decrease in CA19-9 during the first 8 weeks. The top two velocity tertiles were associated with a nearly 5-month longer OS versus the lower tertile for *nab*-P + Gem, while less benefit was observed within the Gem-alone group (≈1-month longer OS for the top two velocity tertiles versus the lower tertile). Achieving a reduction in CA19-9 at a greater velocity may be an additional marker of early treatment efficacy, especially for treatment with *nab*-P + Gem.

Although 82% of assessable patients in the *nab*-P + Gem arm had any CA19-9 decrease at week 8 with an associated median OS of 13.2 months, only 16% of patients in this arm met RECIST criteria for unconfirmed radiologic response at week 8 with an associated median OS of 14 months. In addition, 62% of patients had SD by RECIST criteria and a decrease in CA19-9 with a median OS of 13.2 months. In the Gem-alone arm, patients with an unconfirmed RECIST response (6%) had the longest OS (median 15 months), while 79% of patients had a CA19-9 decrease (median OS 9.4 months). Patients with SD and any CA19-9 decrease at week 8 (66%) also had a median OS of 9.4 months. Particularly in the *nab*-P + Gem arm, the median OS of patients with RECIST response or any CA19-9 decrease at week 8 seemed comparable, and furthermore, patients with SD and any CA19-9 decrease had similarly improved survival. These results suggest that a week-8 CA19-9 decline may be a more sensitive early predictor of survival than RECIST response.

CA19-9 evaluations coincided with radiologic assessments, which occurred every 8 weeks. Thus, a limitation of this study was that the first CA19-9 evaluation was not made until week 8. Future prospective studies should evaluate if CA19-9 is also prognostic at earlier time points.

In conclusion, this analysis supports the utility of CA19-9 as an early marker for antitumor activity in patients with metastatic pancreatic cancer and demonstrates that any degree of reduction in CA19-9, as well as the kinetics of decline in CA19-9 levels, are important indicators of treatment benefit, particularly with the *nab*-P + Gem regimen.

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A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction

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Background: Neoadjuvant therapy improves long-term survival after oesophagectomy, treating oesophageal cancer, but the evidence to date is insufficient to determine which of the two main neoadjuvant therapy types, chemotherapy (nCT) or chemoradiotherapy (nCRT), is more beneficial. We aimed to compare the effects of nCT with those of nCRT.

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