



Citation for published version:

Catalano, M, Roviello, G, Conca, R, D'Angelo, A, Palmieri, VE, Panella, B, Petrioli, R, Ianza, A, Nobili, S, Mini, E & Ramello, M 2020, 'Clinical outcomes and safety of patients treated with NAb-Paclitaxel plus Gemcitabine in metastatic pancreatic cancer: the NAPA study', *Current Cancer Drug Targets*, vol. 20, no. 11, pp. 887-895. <https://doi.org/10.2174/1568009620999200918122426>

DOI:

[10.2174/1568009620999200918122426](https://doi.org/10.2174/1568009620999200918122426)

Publication date:

2020

Document Version

Peer reviewed version

[Link to publication](#)

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Clinical Outcomes and Safety of Patients Treated with NAb-Paclitaxel Plus Gemcitabine in Metastatic Pancreatic Cancer: the NAPA Study

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Abstract

Background: The phase III MPACT trial demonstrated the superiority of gemcitabine (Gem) combined with Nab-paclitaxel (Nab-P) versus gemcitabine alone in previously untreated patients with metastatic pancreatic ductal adenocarcinoma (PDAC). The purpose of this study was to evaluate the effect of Gem/Nab-P in routine clinical practice. **Methods:** From January 2015 to December 2018, patients with metastatic PDAC receiving first-line treatment with a combination of gemcitabine and Nab-paclitaxel were included in a multicentre retrospective observational study. Exploratory analyses of efficacy, and prognostic and predictive markers, were performed. **Results:** The cohort comprised 115 patients (median age 65 [range 50-84] years) with good performance status (ECOG PS 0-1). The median overall survival (OS) was 11 months (95% CI; 9-13) and the median progression-free survival (PFS) was 6 months (95% CI 5-7). Partial response and stable disease were achieved in 44 and 30 patients, respectively, yielding an overall disease control rate (DCR) of 64.3%. Grade 3-4 hematological toxicity frequency was 22.61% for neutropenia, 5.22% for anemia, and 3.48% for thrombocytopenia. Grade 3 asthenia was recorded in 2.61% of patients. No grade 4 non-hematological events were reported. Dose reduction was necessary in 51.3% of the patients.

Conclusion: Our results confirm the efficacy and safety of a first-line regimen comprising gemcitabine and Nab-paclitaxel in metastatic PDAC in a real-life population.

Keywords: Metastatic pancreatic adenocarcinoma, combined chemotherapy, nab-paclitaxel, gemcitabine, prognostic factor, cancer.

1. BACKGROUND

Pancreatic adenocarcinoma represents the fourth leading cause of cancer-related deaths in Europe and the United States [1, 2]. It is an aggressive disease characterized by a very poor prognosis leading to a median overall survival (OS) of less than 18 months and a five-year OS rate below 8% [3]. To date, surgery is the only curative treatment available, but this is limited to 20% of patients with resectable disease at the time of diagnosis and is often invalidated by recurrences. Bearing in mind the scarce initial symptomatology, most patients are diagnosed with locally advanced or metastatic disease, limiting the therapeutic approach to systemic chemotherapy [4] which has been associated with an improvement in disease-related symptoms and OS relative to the best supportive care [5]. Since 1997, based on pivotal trial results, single-agent gemcitabine has become the first-line standard of care in metastatic disease [5]. Subsequently, gemcitabine-based chemotherapy regimens have been compared with gemcitabine alone and, despite the higher response rates, have not improved OS significantly due to increased toxicity [5-9]. Recently, two effective regimens have been introduced based on the results of large-scale clinical trials. The first, the FOLFIRINOX regimen, (*i.e.*, 5-FU/leucovorin, irinotecan, and oxaliplatin), was introduced by the PRODIGE 4/ACCORD II trial which compared FOLFIRINOX with gemcitabine alone [10]. FOLFIRINOX treatment was shown to improve progression-free survival (PFS) and OS, respectively by 6.4 and 11 months, compared with 3.3 and 6.8 months obtained with gemcitabine. Due to the higher toxicity rate compared to gemcitabine, FOLFIRINOX is considered the preferred regimen for patients with metastatic pancreatic cancer and good performance status (PS) as well as normal organ functions [10]. Moreover, a second regimen with gemcitabine and Nab-paclitaxel (Gem/Nab-P) has been introduced through a larger randomized phase 3 trial (MPACT), demonstrating the superiority of the combination regimen over gemcitabine alone in previously untreated patients with metastatic pancreatic adenocarcinoma [11]. The median PFS was 5.5 months and OS was 8.5 months in the Gem/Nab-P group, compared to 3.7 and 6.7 months in the gemcitabine group, respectively. Thus, the combination of gemcitabine and Nab-paclitaxel has been established as another standard first-line treatment for metastatic pancreatic cancer [11]. The most common serious adverse events reported with the combination therapy were neutropenia, fatigue and neuropathy. Currently, FOLFIRINOX and Gem/Nab-P are recommended as the first-line regimens for metastatic pancreatic cancer; FOLFIRINOX is the option of choice in younger patients with good PS, but whether the combination is superior to Gem/Nab-P in advanced pancreatic cancer has not yet been clarified [12, 13]. The strict enrolment criteria and several intrinsic limitations related to randomized clinical trial protocols mean that the samples enrolled in trials to date have not been representative of the population in clinical practice. Phase IV studies on Gem/Nab-P treatment have not yet been performed. The aim of this retrospective study is to evaluate the effectiveness and safety of gemcitabine and Nab-paclitaxel treatment for metastatic pancreatic cancer in a real-world setting.

2. METHODS

2.1. Study Population

Patients with metastatic pancreatic ductal adenocarcinoma (PDAC), receiving first-line treatment with a combination of gemcitabine and Nab-paclitaxel from January 2015 to December 2018, were considered eligible for our retrospective analysis. Inclusion criteria were the following: age ≥ 18 years; histopathologically confirmed PDAC; Eastern Cooperative Oncology Group performance status (ECOG-PS) 0-1, adequate hematological function (neutrophil count $\geq 1500/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, and hemoglobin ≥ 9 g/dl); no hepatic or renal impairments. Patients with locally advanced cancer, patients who received previous chemotherapy treatment or histology other than PDAC were excluded. Written informed consent was obtained from each patient before starting treatment. This study was approved by the *Comitato Etico Regionale* for clinical experimentation of Toscana region (Italy) *area vasta centro* section, number:14565_oss treatment in accordance with the Declaration of Helsinki.

2.2. Treatment Schedule

The initial dose of Gem/Nab-P was chosen according to a previous phase III study (MPACT): 30-40 minutes of intravenous infusion of Nab-paclitaxel $125 \text{ mg}/\text{m}^2$, followed by 30 minutes of gemcitabine $1000 \text{ mg}/\text{m}^2$ diluted with 250 ml of saline solution administered intravenously on days 1, 8 and 15 every 4 weeks [11]. Dexamethasone 8mg and Ondansetron 8mg Slow bolus/15 min infusion and ranitidine 50mg Intravenous Slow bolus were used as premedication to start chemotherapy. Recombinant human granulocyte colony-stimulating factor and erythropoietin were administered as needed. Treatment was modified depending on physician/patient choice, and treatment was continued until disease progression or unacceptable toxicity.

2.3. Assessment

Tumor response evaluation was performed every 3 months by spiral computed tomography (CT). Disease progression was assessed as either radiological or clinical progression. The best response during Gem/Nab-P treatment was radiologically evaluated according to the Response Evaluation Criteria in Solid Tumour (RECIST) version 1.1 [14]. Blood tests were performed at baseline and every therapy cycle, while measurement of the carbohydrate antigen (CA)19-9 serum level was performed at baseline and every 12 weeks. Efficacy has been evaluated as OS and PFS. Adverse events during Gem/Nab-P treatment were monitored by investigators and reported in clinical charts. Treatment-related Adverse Events (AEs) were assessed using the Common Terminology Criteria of Adverse Events (CTCAE) version 4.0 [15]. Variables assessed for prognostic correlations included age ≥ 70 years, sex, ECOG-PS, primary tumor site, baseline CA19-9 level $\geq 659 \times \text{ULN}$, number of metastatic sites, basal levels of LDH, Gamma-GT, and ALP (calculated as the absolute neutrophil count divided by the absolute lymphocyte count measured in $\times 10^3/\text{ml}$), previous surgery, radiation therapy, and biliary stent implantation. In the event of unacceptable toxicity, doses could be reduced up to two times *per* therapeutic agent (to 100 or 75 mg/m^2 for Nab-

P and to 800 or 600 mg/m² for gemcitabine). A missing dose within four days of the scheduled administration was considered a dose delay.

2.4. Clinical Outcomes

The primary endpoints were OS and a PFS. The secondary endpoints were disease control rate (DCR) as well as the rate and severity of treatment-related AEs. Overall survival was defined as the time from the diagnosis of advanced pancreatic cancer to death from any cause or the date of the last follow-up visit. Progression-free survival was defined as the time from the initial assessment at the cancer center to the date of the disease progression, as reported by the clinician. Disease control rate was defined as the proportion of patients with the best overall response determined as complete response (CR), partial response (PR) or stable disease (SD). No CR was recorded in our sample.

Table 1. Patient characteristics.

	All Patients (N=115)
Age, years	65
Median	50-84
Range	38 (33%)
≥70	
ECOG PS	53 (46.1)
1	62 (53.9%)
Sex	
Male	61 (53%)
Female	54 (47%)
Site of metastatic disease	
Liver	64 (55.6%)
Lung	28 (24.3%)
Peritoneum	16 (13.9%)
Others	11 (9.6%)
Number of metastatic sites	
1-2	69 (60%)
≥3	46 (40%)
Carbohydrate antigen 19-9 — U/ml¶	
Median	659
Range	0.8-182922
LDH	163.5
Median	98-710
Range	72
GAMMA-GT	12-1119
Median	112
Range	19-1168
ALP	
Median	
Range	
Previous treatment	
Radiation Therapy	10 (8.7%)
Surgery	28 (24.3%)
Biliary stent	38 (33%)
Lines of treatment for metastatic disease	
2	47 (40.9%)
>2	15 (13%)
Pain	
Yes	48 (41.7%)

2.5. Statistical Analysis

All patients were included in the statistical analysis. Descriptive statistics were carried out on the clinical parameters of the PC. Time-dependent outcomes were estimated using the Kaplan-Meier method and compared, at univariate analysis, using the log-rank test. Parameters with a statistically significant log-rank test were considered independent variables and included in the multivariate Cox proportional hazard regression linear model to compare hazard ratio (HR) and 95% confidence interval (95% CI). A two-sided p-value < 0.05 was considered statistically significant. STATA v.2012 was used for statistical analysis.

3. RESULTS

3.1. Study Population

Overall, from January 2015 to December 2018, 143 patients with metastatic pancreatic cancer treated with Gem/Nab-P have been identified. Among them, 29 patients were excluded based on the exclusion criteria. Thus, a sample of 115 patients has been used for efficacy and safety analysis. Patients' characteristics are described in Table 1. The median age was 65 years (range 50-84) with a male: female ratio 61:54. ECOG-PS was 0 in 46.1% of patients and one in 53.9%. The most frequent metastatic sites were liver (56%), lung (24.3%), and peritoneum (13.9%); 69% of patients had 1-2 metastatic sites, and 40%

had three or more. Radiation therapy has been performed in 8.7% of the cohort, whereas 24.3% and 33% have been treated with surgery and biliary stent, respectively. None of the patients has received previous chemotherapy. Median baseline CA 19.9 was 659 U/ml (range 0.8-182,922 U/ml). Forty-eight (41.7%) patients reported cancer-related pain or other disease-related symptoms before treatment. Our population study presented with comorbidities: the most frequent was cardiovascular 48 (41.7%) (Table 1S), and 37 (32.2%) patients presented with >1 comorbidity.

3.2. Treatment

During the study, patients received a median of five cycles (range 1–17) of treatment with a starting dose of Nab-P 125 mg/m² plus Gem 1,000 mg/m². Dose reduction was necessary for 59 (51.3%) patients without significant difference between gemcitabine and Nab-paclitaxel; 63 (54.8%) required only one dose reduction, whereas 32 (27.8%) had two dose reductions. Dose delays and treatment interruption occurred in 43 (37.4%) and 44 (38.4%) patients, respectively. Neutropenia, peripheral neuropathy, and asthenia were the main cause of dose reductions, delays or stopping treatment.

3.3. Efficacy

Overall, the median follow-up period was 10 (range 1-54) months. The median OS was 11 months (95% CI; 9-13) and the median PFS was 6 months (95% CI 5–7). Partial response and stable disease were recorded in 44 and 30 patients, respectively, yielding an overall DCR of 64.3% (Table 2). For 9 (7.8%) patients, the response was not evaluable. Regarding survival, univariate analysis showed that age, ECOG-PS 1, Ca 19.9 U/ml \geq 659 U/ml and number of metastatic sites \geq 3 were negatively correlated with OS. In fact, OS was statistically lower according to age (9 vs. 13 months, $p = 0.002$, Fig. 1); ECOG-PS (10 vs. 13 months, $p = 0.04$, Fig. 1); Ca 19.9 (10 vs. 14 months, $p = 0.01$, Fig. 1) number of metastatic sites (8 vs. 13 months, $p < 0.001$, Fig.1). Conversely, previous surgery, cycles of Gem/Nab-P > 4 and more than one line of treatment for metastatic disease were correlated with a better OS that was statistically higher according to previous surgery (13 vs. 10 months, $p = 0.03$, Fig. 2); cycles of Gem/Nab-P (14 vs. 6 months, $p < 0.001$, Fig. 2); and lines of treatment (13 vs. 9 months, $p = 0.01$, Fig. 2). Other variables examined did not show statistically significant effects (Table 3). Multivariate analysis has confirmed metastatic sites \geq 3 (HR 1.68; 95% CI 1.15–3.15; $p = 0.04$) and CA 19.9 levels \geq 659 U/ml (HR 1.84; 95% CI 1.19–2.82; $p = 0.006$) were correlated with a worse OS (Table 4). On the other hand, previous surgery (HR 0.31; 95% CI 0.17–0.55; $p = 0.001$), cycles of Gem/Nab-P > 4 (HR 0.21; 95% CI 0.13–0.35; $p = 0.001$), and lines of treatment for metastatic disease > 1 (HR 0.47; 95% CI 0.30–0.73; $p = 0.001$), were correlated with a better overall survival (Table 4).

Table 2. The best response, PFS, and OS according to neutropenia grade.

	All Patients (N=115)
PR	44 (38.3%)
SD	30 (26.1%)
DCR (PR + SD)	74 (64.3%)
PD	32 (27.8%)
NE	9 (7.8%)
PFS M-months (95% IC)	6 (5-7)
OS M-months 95% IC	11 (9-13)
Cycles	
Median	5
Range	1-17
GCF-Prophylaxis	25 (21.9%)

Number (N), partial response (PR), stable disease (SD), disease control rate (DCR), progression disease (PD), not evaluable (NE); Median (median); progression free survival (PFS); overall survival (OS).

Regarding progression-free survival, univariate analysis showed that the number of metastatic sites \geq 3, the baseline level of CA 19.9 U/ml \geq 659 U/ml, and pain were negatively correlated with PSF (Table 3). Multivariate analysis has confirmed the number of metastatic sites \geq 3 (HR 2.73; 95% CI 1.41–5.27; $p = 0.003$) and CA 19.9 levels \geq 659 U/ml (HR 1.67; 95% CI 1.08–2.57; $p = 0.02$) as an independent, negative and prognostic indicators for PFS, respectively (Table 4).

3.4. Safety

Hematological and non-hematological adverse event frequencies are shown in Table 5. Overall, the treatment was well-tolerated, and most non-hematological toxicities were reported as grade 1 or 2. In our cohort, the frequency of grade 3 bone marrow toxicity was 15.56% for neutropenia, 2.61% for anemia, and 2.61% for thrombocytopenia. Grade 4 hematological toxicity comprised neutropenia in 8 patients (6.96%), anemia in 3 (2.61%), and thrombocytopenia in 1 (0.87%). The only grade 3 non-hematological toxicity was asthenia recorded in 3 patients (2.61%). No grade 4 non-hematological events were reported.

4. DISCUSSION

Our Italian retrospective study seems to confirm the treatment benefit of Gem/Nab-P treatment in patients with metastatic pancreatic cancer in a real-world setting, according to the result of the randomized phase III MPACT trial [11]. Several factors, including small sample size and differences in inclusion/exclusion criteria, meant that a direct comparison between the pivotal MPACT trial and this real-world experience was not fully possible. However, despite the limitations, we were able to confirm that the combination regimen with Gem/Nab-P was effective and safe in our population compared with the randomized controlled trial sample. Specifically, we observed 11 months median OS and 6 months median PFS with a DCR of 64.3%. When comparing our results with those of the pivotal trial, there are some differences in patients' characteristics that we need to consider. In the MPACT trial, patients were younger, with approximately 60% of the participants aged below 65, with a Karnofsky Performance Status (KPS) of 100-90% [16]. On the other hand, 33% of patients in our sample were older than 70 years and 46.1% have reported an ECOG-PS 0. Additionally, we treated 32% of patients with >1 concomitant comorbidities (Table 1s). All these data support the use of Gem/Nab-P in a "real-life" population of elderly patients with varying [SEP] comorbidities. Recent retrospective studies in patients with both metastatic and locally advanced disease have reported a difference in efficacy data between metastatic and locally advanced subgroups. For example, Wang *et al.* achieved an OS of 10.5 months in the total cohort and similar survival of 10 months in the metastatic subgroup [21]. Recently, Blomstrand *et al.* observed a trend towards better prognosis in the locally advanced group of 22 patients. PFS and OS were 6.8 and 17.1 months, respectively in the locally advanced group, compared to 4.5 and 9.4 months in the metastatic group of 53 patients, although the differences reported were not statistically significant [22]. In another multicentre retrospective study on elderly patients, PFS and OS were 12.1 and 21.8 months in 42 patients with locally advanced cancer and 5.9 and 13.3 months in 59 patients with metastasis, respectively [23]. In our study, according to the MPACT trial, we have enrolled only chemotherapy-naïve patients with upfront metastatic disease. Unfortunately, subgroup analysis on metastatic burden has shown a worse prognosis for patients with three or more metastases, a difference statistically significant in relation to OS (HR 1.68; 95% CI 1.15–3.15; $p=0.04$) and PFS (HR 2.73; 95% CI 1.41–5.27; $p=0.003$), suggesting the main role of tumor burden as a prognostic factor in metastatic pancreatic cancer. Several investigators have reported their experience with Gem/Nab-P in clinical practice in patients with locally advanced and metastatic pancreatic cancer, based on retrospective studies. De Vita and colleagues have reported a median PFS and OS of 6.7 and 10 months, respectively, enrolling a cohort of 41 patients [17]. Lo Re *et al.*, in a smaller previous study with 37 patients, have achieved a median PFS of

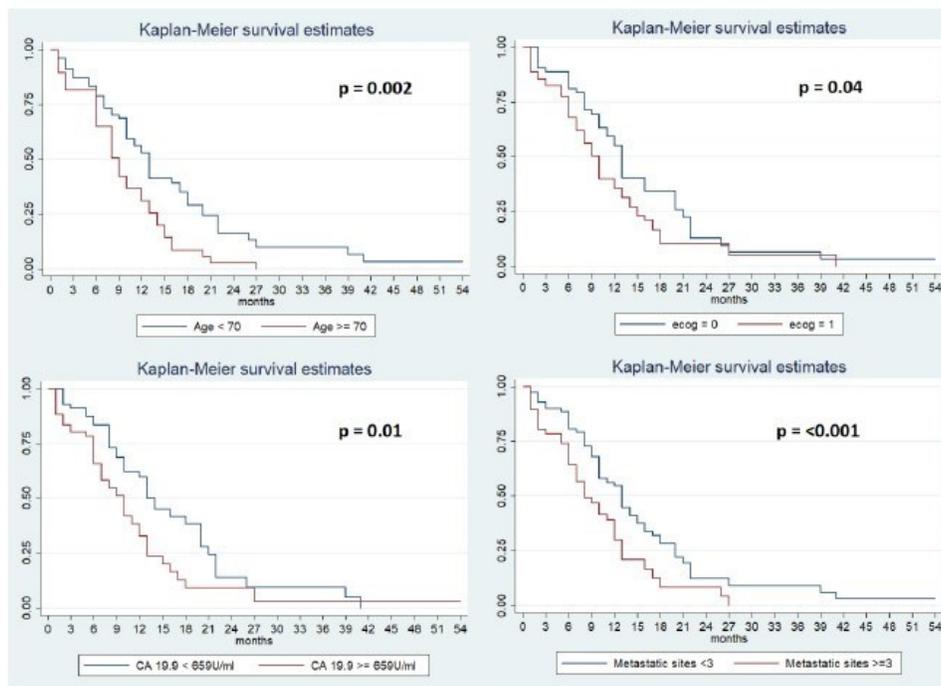


Fig. (1). Overall survival of Gem/Nab-P according to different prognostic factors: age, ECOG, CA 19.9, and metastatic sites. (A higher resolution / colour version of this figure is available in the electronic copy of the article.)

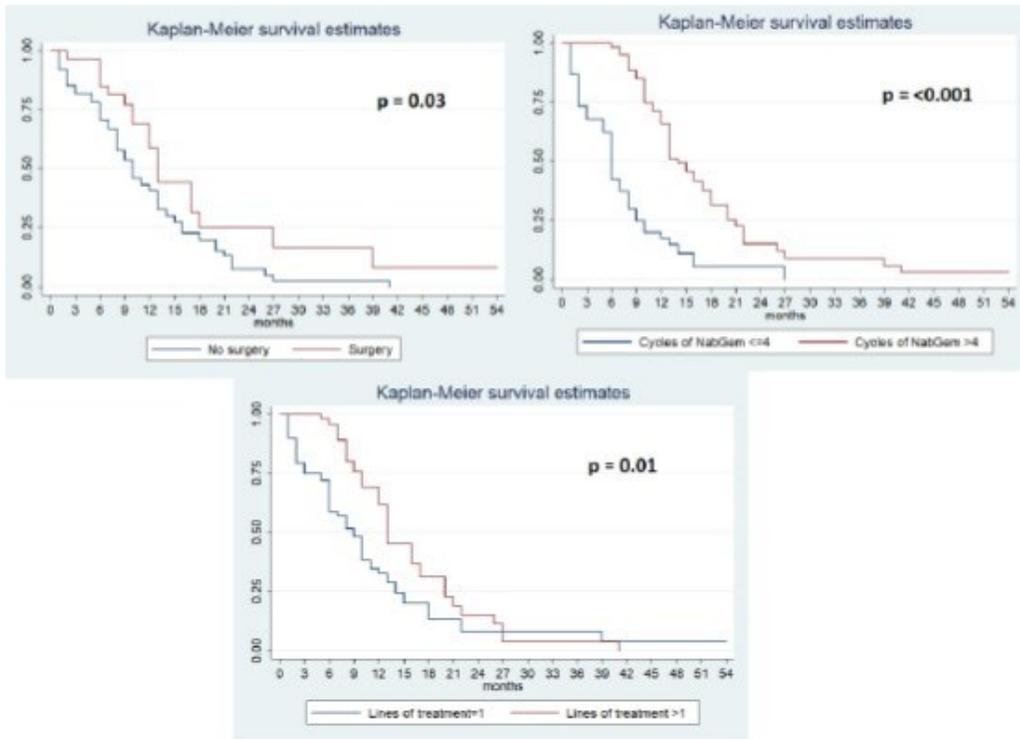


Fig. (2). Overall Survival of Gem/Nab-P according to different prognostic factors: surgery, cycles of therapy, and lines of treatment. (*A higher resolution / colour version of this figure is available in the electronic copy of the article.*)

Table 3. Univariate analysis for PFS and OS.

	HR	IC 95%	P
Progression free Survival			
Age ≥70	1.44	0.93-2.24	0.1
ECOG PS (1 vs 0)	1.17	0.78-1.77	0.4
Sex (male vs female)	1.08	0.71-1.64	0.7
N. of metastatic sites ≥3	3.85	2.06-7.20	0.001
Carbohydrate antigen 19-9 ≥ 659U/ml	1.86	1.23-2.83	0.003
Previous Radiation Therapy	0.63	0.29-1.37	0.2
Previous Surgery	0.76	0.47-1.26	0.2
Previous Biliary stent	0.75	0.48-1.17	0.2
Pain present	1.51	1-2.31	0.05
LDH ≥ 163.5 U/ml	0.80	0.51-1.25	0.3
Gamma-gt ≥ 72 U/ml	1.02	0.68-1.53	0.9
ALP ≥ 112 U/ml	0.98	0.66-1.50	0.9
Overall Survival			
Age ≥70	1.88	1.23-2.89	0.004
ECOG PS (1 vs 0)	1.52	1-2.31	0.05
Sex (male vs female)	1.20	0.79-1.83	0.4
N. of metastatic sites ≥3	3.91	2-7.63	<0.001
Carbohydrate antigen 19-9 ≥ 659U/ml	1.71	1.22-2.60	0.01
Previous Radiation Therapy	0.47	0.19-1.16	0.1
Previous Surgery	0.58	0.35-0.99	0.04
Previous Biliary stent	0.84	0.54-1.32	0.4
Pain present	1.50	0.98-2.29	0.06
LDH ≥ 163.5 U/ml	0.77	0.47-1.24	0.3
Gamma-gt ≥ 72 U/ml	1.08	0.71-1.65	0.7
ALP ≥ 112 U/ml	0.96	0.63-1.44	0.8
Cycles of NabGem >4	0.28	0.18-0.44	0.001
Lines of treatment for metastatic disease >1	0.60	0.39-0.91	0.01

5.5 and OS of 12.1 months [18]. Montes *et al.* recorded in a sample of 39 patients slightly longer PFS and OS (9 and 15 months, respectively), different from the study of Nea Papne- ja *et al.* that reported, in a cohort of 33 patients, a shorter PFS and OS of 4 and 9 months, respectively [19, 20]. Compared with all these studies, we evaluated a greater number of patients from different institutions, confirming the efficacy of Gem/Nab-P as a first-line treatment for metastatic pancreatic cancer. No standard second-line treatment following the failure of first-line chemotherapy has been available to date, and questions related to treatment choice and sequence are ongoing. However, second-line chemotherapy produced a survival benefit when compared with best supportive care and was found to be more effective in patients with early progression within 3 months after first-line treatment [24-26]. In our study, an increased OS was recorded in patients with two or more treatment lines for metastatic disease (HR 0.47; 95% CI 0.30–0.73; $p = 0.001$), supporting the role of a second or further line of treatment as prognostic of survival for metastatic pancreatic cancer. To note, the safety profile in our study was better compared to the pivotal trial and other previous studies [11, 18, 19, 28]. Adverse non-hematological events were generally of grade 2 or 1; no grade 3 or 4 peripheral neurotoxicity was observed in our cohort. Grade 3 asthenia was reported in 2.61% of patients, in contrast with data of the MPACT study (17%). Grade 3 or 4 hematological toxicity was observed in a lower percentage than the pivotal trial, consistent with the data reported in the previous studies in clinical practice [17, 18, 22, 23].

Table 4. Multivariate analysis for PFS and OS.

	HR	IC 95%	P
Progression-free Survival			
N. of metastatic sites ≥ 3	2.73	1.41-5.27	0.003
Carbohydrate antigen 19-9 ≥ 659 U/ml	1.67	1.08-2.57	0.02
Pain present	1.30	0.84-2.01	0.23
Overall Survival			
Age ≥ 70	1.18	0.74-1.87	0.5
ECOG PS (1 vs 0)	1.05	0.69-1.67	0.8
N. of metastatic sites ≥ 3	1.68	1.15-3.15	0.04
Carbohydrate antigen 19-9 ≥ 659 U/ml	1.84	1.19-2.82	0.006
Previous Surgery	0.31	0.17-0.55	0.001
Cycles of NabGem >4	0.21	0.13-0.35	0.001
Lines of treatment for metastatic disease >1	0.47	0.30-0.73	0.001

Table 5. Summary of most ≥ 3 adverse events for NabGem.

	Grade 3	Grade 4
Hematological		
Neutropenia	18 (15.65%)	8 (6.96%)
Anemia	3 (2.61%)	3 (2.61%)
Thrombocytopenia	3 (2.61%)	1 (0.87%)
Non-Hematological	15* (13.04%)	13** (11.30%)
Neuropathy	14* (12.17%)	7** (6.09%)
Diarrhea	3 (2.61%)	
Asthenia		

*Grade 1; ** Grade 2

Overall, the regimen was well tolerated, in line with previous studies, although some patients required dose reduction or treatment discontinuation. Based on a retrospective analysis of the MPACT trial, the dose reduction and/or delay of chemotherapeutic drugs to manage toxicities can be carried out with no reductions in the efficacy of the established starting dose [29]. Among other prognostic factors related to PFS and OS, we found that baseline CA 19.9 value ≥ 659 U/ml was linked to a worse OS. In line with these data, several studies retrospectively investigated the prognostic role of basal CA19.9 during first-line chemotherapy [30]. The role of CA 19.9 in pancreatic cancer is well established, National Comprehensive Cancer Network (NCCN) guidelines for pancreatic cancer recommends CA19.9 as the only biomarker of disease; in fact, CA 19.9 is strongly correlated with tumor burden [30]. Nonetheless, the optimal level of CA 19.9 as a prognostic factor remains uncertain, because while we found a value of 659 U/ml, other studies found both higher than lower values. Future prospective studies are awaited to define the best basal value of CA 19.9 as a predictor of survival during first-line Gem/Nab-P. In addition, we also found >4 cycles of therapy to be an independent positive prognostic factor associated with OS. In this context, Lo Re *et al.* [18] confirmed a longer OS for patients treated with ≥ 4 cycles of Gem/Nab-P. Although it might be intuitive that more cycles of therapy would correlate with a longer OS, it is worth noting that 6 cycles of Gem/Nab-P therapy are typical in order to try to avoid excessive toxicity. The optimal duration of Gem/Nab-P therapy therefore requires further investigation. Furthermore, >1 lines of treatment for metastatic disease correlated with a better OS (we will describe the role of second-line therapy after Gem/Nab-P therapy in a separate paper). Finally, no statistically significant correlation between OS and ECOG-PS was highlighted, contrasting with Lo Re *et al.* [18] who reported a correlation between PS <2 and a higher number of therapy cycles, allowing an increase in OS, supporting no efficacy of Gem/Nab-P for patients with PS=2. Our study has some limitations mainly owing to its retrospective nature. The largest sample compared to that of previous studies, and the enrolment of only metastatic patients, represent strengths aimed at increasing knowledge about the efficacy and safety of Gem/Nab-P in patients with stage IV disease.

CONCLUSION

Progress has recently been made in the first-line of chemotherapy in locally advanced and metastasized pancreatic cancer. Studies of further lines of therapy are ongoing. In the absence of randomized control trials, the choice of the first-line chemotherapy between Gem/Nab-P and FOLFIRI-

NOX in patients with metastatic pancreatic cancer is mainly based on careful patient selection, their performance status, comorbidity, and medical preference. Our study confirms the activity, efficacy, and safety of gemcitabine plus Nab-P as a first-line regimen, in a large group of patients with ex-clusive metastatic pancreatic cancer, in a real-world setting. Despite clinical efficacy and the overall good tolerance of therapy, the identification of serum or tissue markers could allow a personalized and even better-tolerated treatment.

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