Phase 1B trial of Nab-paclitaxel plus gemcitabine, capecitabine, and cisplatin (PAXG regimen) in patients with unresectable or borderline resectable pancreatic adenocarcinoma

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Background: Nab-paclitaxel–gemcitabine combination significantly improved overall survival over gemcitabine in metastatic pancreatic adenocarcinoma. A phase 1b trial was performed (ClinicalTrials.gov number, NCT01730222) to determine the recommended phase 2 dose (RP2D) of nab-paclitaxel in combination with cisplatin, capecitabine, and gemcitabine at fixed dose (800, 30, and 1250 mg m⁻² every 2 weeks, respectively; PAXG regimen).

Methods: Nab-paclitaxel doses were escalated from 100 (level one) to 125 (level two) and 150 mg m⁻² (level three) every 2 weeks in cohorts of 3–6 patients with pathologically confirmed unresectable or borderline resectable pancreatic adenocarcinoma.

Results: Between Dec 2012 and Apr 2014, 24 patients were enrolled (3 at level one, 5 at level two, 16 at level three) and received 117 cycles of PAXG. No dose-limiting toxicity occurred and level three was the RP2D. At this dose, nab-paclitaxel dose-intensity was 91%. Worse per patient grade 3/4 toxicity were neutropenia 25/31%; fatigue 19%; anaemia and hand-foot syndrome 12%, nausea 6%, and febrile neutropenia 6%. A partial response (PR) was observed in 16 (67%) and stable disease (SD) in 8 patients (33%). Among 21 patients with a baseline positive positron emission tomography (PET) scan, a complete metabolic response was observed in 9 (43%), PR in 10 (48%), SD in 2. CA19-9 decreased by ≥49% in all the 19 patients with elevated basal value. Six patients were resected after chemotherapy. Progression-free survival at 6 months (PFS-6) was 96%.

Conclusions: The RP2D of nab-paclitaxel in the PAXG regimen was 150 mg m⁻² every 2 weeks. The preliminary results are promising and warrant further exploration.

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Pancreatic adenocarcinoma is a rare disease, but is the seventh leading cause of cancer death (GLOBOCAN, 2015). Only 15–20% of patients present with resectable disease, whereas the majority of patients have metastatic disease at diagnosis, and nearly one-third have involvement of regional main vessels.

Randomised trials in locally advanced or borderline disease have been often prematurely interrupted for poor accrual (Chaueffert et al, 2008; Loehrer et al, 2011); thus the results have limited statistical strength. Therefore, standard of care for this stage of disease is still controversial.

Currently, chemoradiation and chemotherapy alone, or followed by chemoradiation, are regarded both as acceptable treatment options. Prospective trials, including patients with both locally advanced and metastatic disease treated with combination regimens failed to show any OS improvement over gemcitabine (Cunningham et al, 2009; Poplin et al, 2009; Colucci et al, 2010), with the notable exception of the PEFG regimen (cisplatin, epirubicin, 5-fluorouracil (5-FU), gemcitabine) that showed a significant progression-free survival (PFS) and OS improvement compared to gemcitabine monotherapy (Reni et al, 2005). PEFG was modified by substituting oral capecitabine for 5-FU, originating the PEXG regimen (Reni et al, 2012). The subsequent inclusion of docetaxel instead of epirubicin (PDXG regimen) reduced grade 3 and 4 neutropenia and improved radiological and biochemical responses, particularly in locally advanced disease (Reni et al, 2012). These results might be explained by the well-known synergy of taxanes with fluoropyrimidines increasing intratumour conversion of capecitabine into 5-FU through the promotion of intra-cellular activity of thymidine phosphorylase (Sawada et al, 1998). Furthermore, taxanes reduce multi-drug resistance proteins favoring cisplatin cytotoxicity (Maeda et al, 2004). These data have been further enriched by the findings of a significantly better outcome of stage 4 patients treated with nab-paclitaxel and gemcitabine compared with those receiving gemcitabine alone in a phase 3 trial (Von Hoff et al, 2013).

On the basis of this rational, a phase 1b trial was designed to determine the recommended phase 2 dose (RP2D) of nab-paclitaxel in combination with cisplatin, capecitabine, and gemcitabine (PAXG regimen).

### MATERIALS AND METHODS

Chemo-naive patients with 18–75 years, pathologic diagnosis of unresectable or borderline resectable pancreatic adenocarcinoma, without distant metastases and a Karnofsky Performance Status (KPS) ≥70 were eligible for the study. The study was conducted at a single institution with a high-volume pancreatic surgery unit (Balzano et al, 2008). Tumours were considered unresectable or borderline resectable on the basis of the National Comprehensive Cancer Network (NCCN) definition (Tempero et al, 2012). The assignment of tumours to the unresectable or borderline resectable category was jointly performed by a dedicated radiologist (RN) and an experienced pancreatic surgeon (GB). Patients were required to have adequate bone marrow (leucocytes ≥3500 mm$^{-3}$, absolute neutrophil count ≥1500 mm$^{-3}$; platelet count ≥100 000 mm$^{-3}$; haemoglobin ≥10 g dl$^{-1}$), liver (total bilirubin ≤2 mg dl$^{-1}$; aspartate aminotransferase and alanine aminotransferase ≤3 × upper limit of normal) and kidney function (serum creatinine ≤1.5 mg dl$^{-1}$) and the ability to swallow and absorb oral medications. Prior therapy for their cancer diagnosis, lactation or a positive pregnancy test, clinically significant cardiac disease, concurrent treatment with other experimental drugs, previous or concurrent malignancies at other sites with the exception of surgically cured carcinoma in situ of the cervix and basal or squamous cell carcinoma of the skin, and of other neoplasms without evidence of disease at least from 5 years, history of interstitial lung disease, of connective tissue disorders, or of psychiatric disabilities were all exclusion criteria. Written informed consent was obtained from all patients, and the study was approved by the Health Superior Institute and by the institutional Ethics Committee.

The trial was a single-arm phase 1 study to design a new treatment regimen. The primary endpoint was to determine the RP2D of nab-paclitaxel when used in combination with cisplatin, capecitabine, and gemcitabine (PAXG regimen). Secondary endpoints were OS, PFS, PFS at 6 months (PFS-6), response rate as defined by RECIST (Response Evaluation Criteria in Solid Tumours), carcinoantigen 19-9 (CA19-9) response, and resectability rate. A standard 3 × 3 dose-escalation schema was used with preplanned cohort expansion at the maximum tolerated dose (MTD). Each treatment cycle consisted of a 28-day period with intravenous cisplatin administered at 30 mg m$^{-2}$ on days 1 and 15, intravenous nab-paclitaxel on days 1 and 15, oral capecitabine at 1250 mg m$^{-2}$ on days 1 through 28, intravenous gemcitabine at 800 mg m$^{-2}$ on days 1 and 15 at a fixed-rate infusion (10 mg m$^{-2}$ min$^{-1}$). The dose of cisplatin, capecitabine, and gemcitabine was maintained fixed at any dose level cohort, whereas nab-paclitaxel dose was escalated from the starting dose level (DL1: 100 mg m$^{-2}$) to DL2 (125 mg m$^{-2}$), and DL3 (150 mg m$^{-2}$). Dose-limiting toxicity (DLT) was defined as any of the following events attributable to the administered study drugs during the initial 4 weeks of treatment: grade ≥4 neutropenia lasting 7 days or more; grade ≥3 febrile neutropenia or fever of unknown origin ≥38.5°C, grade 4 thrombocytopenia; grade 3 thrombocytopenia which required transfusions; grade ≥3 nausea or vomiting; grade ≥3 diarrhoea; any grade ≥2 neurological toxicity; any grade ≥3 toxicities or representing a shift by two grades from baseline (in case of abnormal baseline); failure to recover to grade ≤1 toxicity (except alopecia) or to baseline values after delaying the initiation of next cycle by >2 weeks. Treatment was continued until documented progressive disease, unacceptable toxicity, patient’s refusal, medical decision or a maximum of six cycles whichever happened before. Surgery and/or chemoradiation after the end of chemotherapy were allowed but were not part of the phase 1b protocol and AE/activity reporting applies to chemotherapy alone.

Pretreatment evaluation with review of inclusion/exclusion criteria, medical and medication history, physical examination, surgical assessment for resectability, KPS assessment, laboratory tests and CA19-9 was performed for all patients ≤14 days before enrolment. Radiological imaging by computed tomography (CT) was performed within 3 weeks before treatment initiation by a three-phase, high-resolution thorax and abdomen contrast-enhanced CT scan. An 18-fluorodeoxyglucose positron emission tomography (FDG-PET) scan was also performed at baseline whenever possible. Clinical evaluation and haematology panel were repeated at every drugs administration or whenever needed. Haematological and chemistry panel (CA19-9) were repeated on day 1 of every cycle. Radiographic disease assessment was performed every 8 weeks until disease progression using the revised RECIST (version 1.1) guidelines. A FDG-PET scan was repeated after two cycles and at the end of treatment. Metabolic response was assessed according to Weber’s criteria (Weber, 2005). Re-evaluation for surgical resectability was performed after four and six cycles. PFS was defined as the time from the day of treatment start to the disease progression or death (for any cause), whichever occurs first. OS was defined as the time interval between treatment start and the date of death, and censored at the date of the last study assessment. Best overall response was defined as the best response recorded from the start of treatment until disease progression.

Biochemical response was defined in relation to percentage of CA19-9 variation on nadir (minor value assessed while on
treatment) with respect to basal value only in patients with CA19-9 level elevated (namely over superior normal laboratory level), after normalisation of serum bilirubin levels. Patients were classified as non-responders if CA19-9 variation was <50%; minor responders if CA19-9 variation was between 50 and 89%; major responders if CA 19-9 variation was >89% (Reni et al., 2009).

Safety was evaluated at the beginning of each treatment cycle based on patient-reported symptoms, physical examination findings, and clinical laboratory abnormalities. Toxicities were noted by grade and organ system using the National Cancer Institute Common Toxicity Criteria (CTC) (version 4.0), with the frequency and severity of all adverse events (grades 1–4) summarised descriptively. OS and PFS endpoints were measured according to the method of Kaplan and Meier.

## RESULTS

Between December 2012 and April 2014, 24 patients with unresectable or borderline resectable pancreatic ductal adenocarcinoma, were enrolled. Patients’ characteristics are reported in Table 1. None of the patients enrolled in the trial (three at DL1, five at DL2 and sixteen at DL3) experienced a DLT. Accordingly, DL3, which was expanded to obtain additional safety and efficacy information, was considered as RP2D. Both for the entire study cohort and for the RP2D, the median number of cycles was five (range: 3–6). One patient discontinued therapy due to disease progression at cycle five. One patient discontinued therapy due to poor subjective tolerance after 3.5 cycles; ten patients completed 6 months of therapy, whereas twelve patients discontinued treatment after 3–5 months due to medical decision, including four patients who were taken to surgery for resection and eight patients who were addressed to chemoradiation (Figure 1).

After eighty cycles at RP2D the dose-intensity was 90.5% for nab-paclitaxel (which was always administered at the planned dose but in two cycles in a single patient); 91% for cisplatin; 80.5% for gemcitabine with a dose reduction in 46% of cycles; and 75% for capecitabine. Chemoradiation, consisting of 44.25 Gy in fifteen fractions delivered with tomotherapy concomitant to capecitabine at 1250 mg m⁻² daily was administered to all patients: at the end of chemotherapy to sixteen patients, after surgery to seven patients, and at time of recurrence in one patient. Sixteen patients (67%) experienced at least one grade 3–4 haematological and fifteen patients (60%) one grade 3–4 non-haematological adverse event at any point during therapy. Grade 3–4 neutropenia and grade 3 fatigue, neuropathy, anaemia, nausea, diarrhoea, hand-foot syndrome occurred in at least 5% of patients. Adverse events are summarised in Table 2. Granulocyte colony-stimulating factor was used in a single patient. No toxic death was observed.

### Table 1. Characteristics of the patients at baseline

| Characteristic                                      | Value                |
|----------------------------------------------------|----------------------|
| Age (year) Median                                 | 63                   |
| Range                                             | 50–75                |
| Sex no. (%)                                        |                      |
| Female                                            | 7 (29)               |
| Male                                              | 17 (71)              |
| Karnofsky Performance Status Score–no. (%)        |                      |
| 90–100                                            | 21 (88)              |
| 70–80                                             | 3 (12)               |
| Pancreatic tumour location–no. (%)                |                      |
| Head                                              | 17 (71)              |
| Body/tail                                         | 7 (29)               |
| Surgical assessment–no. (%)                       |                      |
| Borderline resectable                             | 6 (25)               |
| Unresectable                                      | 18 (75)              |
| Biliary stent–no. (%)                             |                      |
| Yes                                               | 8 (33)               |
| No                                                | 16 (67)              |
| Level of carbohydrate 19-9 antigen–U ml⁻¹         |                      |
| Median                                            | 295                  |
| Range                                             | 16–4591              |
| > ULN no. (%)                                     | 19 (79)              |

Abbreviations: PS = performance status; ULN = upper limit of normal range.

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![Figure 1. CONSORT flow diagram. PD = progressive disease; Pts = patients.](image-url)
All patients were assessable for efficacy analyses and had a radiographically measurable disease. Sixteen patients (67%) had partial response according to RECIST criteria, whereas eight (33%) had stable disease. Among nineteen patients with elevated basal CA19-9 value, one was a CA19-9 non-responder (CA19-9 had stable disease). Among twenty-two patients. All but one was FDG avid. A complete metabolic response was observed in nine (43%), partial metabolic response in ten (45%), and a stable disease in two patients (9%). After chemotherapy, 17 patients remained unresectable by radiological criteria, whereas 7 patients were taken to surgery. In six cases (three borderline, three unresectable) resection was successfully performed, whereas one patient was found unresectable at surgical exploration: three had macroscopically free surgical margins (R0) and three microscopically infiltrated margins (R1); four had negative nodes (N0) and two had positive nodes (N1).

At time of report, all patients had disease progression; all patients but one were progression free at 6 months (PFS-6, 96%) and twelve (50%) were progression free at 1-year; median PFS was 12 months. Site of progression was local only in 3 patients; systemic only in 14 patients; both local and systemic in 6 patients and unknown in 1 patient. Noteworthy, the main site of recurrence was peritoneum (N = 10), whereas liver metastases were observed only in 7 patients. Nineteen patients died of disease progression and five were alive at a median follow-up of 25 months (range: 22.2–28.9); mOS was 18.1 months; 1yOS and 2yOS were 83.3 and 29.2%, respectively. Efficacy results are summarised in Table 3.

DISCUSSION

This phase 1 trial was designed to define the RP2D of nab-paclitaxel in combination with cisplatin, gemcitabine, and capcitabine as first-line treatment for patients with chemo-naive, borderline or unresectable pancreatic cancer. Overall, the four-drug combination was safely administered. None of the dose levels of nab-paclitaxel, which included the recommended dose of 150 mg m$^{-2}$ in many other indications, was associated with toxicity consistent with MTD, and albeit the rate of grade 3–4 neutropenia (56%) and febrile neutropenia (6%) at the RP2D seems higher as compared to nab-paclitaxel–gemcitabine trial (38% and 3%) (Von Hoff et al, 2013), this may be related to small sample size of our series and appears acceptable in the neoadjuvant setting. Furthermore, despite the number of patients with a biliary stent

### Table 2. Selected non-haematologic and haematologic events treatment-related adverse events

| Adverse event         | Dose level 1 (n = 3) | Dose level 2 (n = 5) | Dose level 3 (n = 16) |
|-----------------------|----------------------|----------------------|-----------------------|
| **Nausea**            |                      |                      |                       |
| Grade 1               | 1 33 3 60 6 50       |                      |                       |
| Grade 2               | 0 0 0 0 0            |                      |                       |
| Grade 3               | 0 0 0 0 0            |                      |                       |
| Grade 4               | 0 0 0 0 0            |                      |                       |
| **Vomiting**          |                      |                      |                       |
| Grade 1               | 1 33 1 20 2 38       |                      |                       |
| Grade 2               | 0 0 0 2 12           |                      |                       |
| Grade 3               | 0 0 0 0 0            |                      |                       |
| Grade 4               | 0 0 0 0 0            |                      |                       |
| **Fatigue**           |                      |                      |                       |
| Grade 1               | 0 3 60 6 38          |                      |                       |
| Grade 2               | 2 67 1 20 3 31       |                      |                       |
| Grade 3               | 1 33 1 20 3 19       |                      |                       |
| Grade 4               | 0 0 0 0 0            |                      |                       |
| **Diarrhoea**         |                      |                      |                       |
| Grade 1               | 1 33 1 20 8 50       |                      |                       |
| Grade 2               | 1 33 1 20 3 19       |                      |                       |
| Grade 3               | 0 0 0 0 0            |                      |                       |
| Grade 4               | 0 0 0 0 0            |                      |                       |
| **Sensory neuropathy**|                      |                      |                       |
| Grade 1               | 1 33 1 20 2 12       |                      |                       |
| Grade 2               | 1 33 1 20 3 19       |                      |                       |
| Grade 3               | 0 0 0 0 0            |                      |                       |
| Grade 4               | 0 0 0 0 0            |                      |                       |
| **Hand-foot syndrome**|                      |                      |                       |
| Grade 1               | 0 0 2 12             |                      |                       |
| Grade 2               | 1 33 1 20 3 19       |                      |                       |
| Grade 3               | 0 0 0 0 0            |                      |                       |
| Grade 4               | 0 0 0 0 0            |                      |                       |
| **Neutropenia**       |                      |                      |                       |
| Grade 1               | 0 2 40 4 23           |                      |                       |
| Grade 2               | 0 0 0 1 6             |                      |                       |
| Grade 3               | 2 67 1 20 4 25       |                      |                       |
| Grade 4               | 1 33 0 5 31          |                      |                       |
| **Anaemia**           |                      |                      |                       |
| Grade 1               | 1 33 2 40 2 44       |                      |                       |
| Grade 2               | 2 67 2 40 6 38       |                      |                       |
| Grade 3               | 0 0 20 2 12          |                      |                       |
| Grade 4               | 0 0 0 0 0            |                      |                       |
| **Thrombocytopenia**  |                      |                      |                       |
| Grade 1               | 2 67 2 40 6 38       |                      |                       |
| Grade 2               | 1 33 1 20 4 25       |                      |                       |
| Grade 3               | 0 0 0 0 0            |                      |                       |
| Grade 4               | 0 0 0 0 0            |                      |                       |
| **Fatigue**           |                      |                      |                       |
| Grade 1               | 0 0 0 0 0            |                      |                       |
| Grade 2               | 0 0 0 0 0            |                      |                       |
| Grade 3               | 0 0 1 6 0            |                      |                       |
| Grade 4               | 0 0 0 0 0            |                      |                       |

### Table 3. Response rates, progression-free and overall survival for all patients, in the RP2D cohort, borderline resectable and unresectable patients

| Response (RECIST) | All patients | RP2D | Borderline resectable | Unresectable |
|-------------------|--------------|------|-----------------------|--------------|
| **All patients**  |              |      |                       |              |
| Stable            | 8 33 6 37    | 1 17| 7 39                  |              |
| Partial           | 16 67 10 63 | 5 83| 11 61                 |              |
| **Borderline**    |              |      |                       |              |
| Stable            | 10 53 7 54  | 2 40| 6 43                  |              |
| Partial           | 10 48 7 44  | 2 40| 8 50                  |              |
| **Unresectable**  |              |      |                       |              |
| Stable            | 2 9 2 13     | 0 0 | 2 12                  |              |

| Progression-free survival | All patients | RP2D | Borderline resectable | Unresectable |
|---------------------------|--------------|------|-----------------------|--------------|
| Median (mo.)              | 12.0         | 11.1 | 12.5                  | 9.8          |
| 6-month (%)               | 96           | 100  | 83                    | 100          |
| 12-month (%)              | 50           | 50   | 83                    | 44           |

| Overall survival          | All patients | RP2D | Borderline resectable | Unresectable |
|---------------------------|--------------|------|-----------------------|--------------|
| Median (month)            | 18.1         | 18.1 | 14.5                  | 19.9         |
| 1-year (%)                | 83.3         | 81.3 | 67                    | 89           |

Abbreviations: CA19-9 = carcinoma antigen 19-9; FDG-PET = 18fluorodeoxyglucose positron emission tomography; RECIST = Response Evaluation Criteria in Solid Tumours.
(47% of those with tumour located in the pancreatic head) appears higher in our series as compared to the nab-paclitaxel–gemcitabine (40%) phase III trial (Von Hoff et al, 2013), only one patient experienced a febrile neutropenia. In addition, secondary end-points analysis showed encouraging preliminary anti-tumour activity. In particular, results are numerically superior to those of our previous experience in a comparable patients population that was selected by the same team of surgeons, radiologists, and medical oncologists, and treated with other four-drug regimens, namely cisplatin, epirubicin, 5-fluorouracil, gemcitabine (PEFG), cisplatin, capecitabine, gemcitabine plus either epirubicin (PEXG) or docetaxel (PDXG) (René et al, 2005, 2009, 2012). Data should be considered with caution in view of the small cohort of patients enrolled in this phase 1 trial at the RP2D. However, the PAXG regimen reported here obtained numerically superior results in terms of measurable response, disease control rate, mPFS and PFS at 6 months (vs 62.5–82.1%). The relevance of the observations should also be weighted in light of the high resectability rate of 25% obtained in spite of the fact that borderline resectability was present in only six patients at diagnosis. Albeit all patients recurred, OS at 1-year and 2-year (83.3 and 29.2%, respectively) are obtained in spite of the fact that borderline resectability was sometimes preliminary, with short follow-up, and retrospective or observational, they support the concept that further prospective randomised studies of combination chemotherapy should be conducted in this setting.

Currently, the combination of nab-paclitaxel and gemcitabine is considered a standard therapy of metastatic pancreatic adenocarcinoma based on the significant survival improvement over single agent gemcitabine that was demonstrated in a large randomised phase III trial (Von Hoff et al, 2013). The 2-drug regimen has a manageable safety profile, and represents a suitable backbone for building more effective chemotherapy. Another phase 1 trial has tested the addition of capecitabine to nab-paclitaxel and gemcitabine in the AGX regimen in patients with metastatic pancreatic adenocarcinoma, but results were disappointing (Ko et al, 2012). The AGX regimen has several differences in respect to PAXG regimen reported here. The first is the presence of platinum in the PAXG. Platinum compounds are among the most active drugs for pancreatic cancer, and are used in first and second-line setting in the clinical practice. In addition, platinum compounds are synergistic with other drugs in PAXG (Sawada et al, 1998; Maeda et al, 2004). Another relevant difference is the planned dose-intensity of nab-paclitaxel (75 vs 50 mg m$^{-2}$ week$^{-1}$ in AGX) and gemcitabine (8750 vs 5250 mg m$^{-2}$ week$^{-1}$) that is substantially greater in PAXG, whereas that of gemcitabine is 20% lower (400 vs 500 mg m$^{-2}$ week$^{-1}$). Finally, the order of drug administration was different. In the PAXG regimen nab-paclitaxel is given before gemcitabine, as in the original phase 3 trial (Von Hoff et al, 2013), whereas in AGX the inverse sequence is used (Ko et al, 2012). Of note, pre-clinical studies showed that nab-paclitaxel decreases cytidine-deaminase levels (Freese et al, 2012), and increases the integration and interaction of gemcitabine-triphosphate with mRNA and favoring gemcitabine activity (Ricotti et al, 2003; Von Hoff et al, 2011).

In conclusion, the study proved the possibility of including nab-paclitaxel in the regimen and allowed to define the RP2D. An ongoing phase 2 trial is randomizing patients with unresectable, borderline resectable or metastatic pancreatic adenocarcinoma to receive the PAXG regimen or the standard nab-paclitaxel–gemcitabine combination.

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CONFLICT OF INTEREST

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