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Original Research

# Nab-paclitaxel/gemcitabine combination is more effective than gemcitabine alone in locally advanced, unresectable pancreatic cancer – A GISCAD phase II randomized trial

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**KEYWORDS**
Advanced pancreatic cancer;
Paclitaxel and gemcitabine;
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**Abstract** ***Background:*** The role of combination chemotherapy has not yet been established in unresectable locally advanced pancreatic cancer (LAPC) lacking dedicated randomized trials.

***Methods:*** This phase II trial tested the efficacy of Nab-paclitaxel (NAB-P)/Gemcitabine (G) versus G alone. Patients were randomized, 1:1 to G 1000 mg/m$^2$ on days 1, 8 and 15 every 28 days versus NAB-P 125 mg/m$^2$ on days 1, 8 and 15 every 28 days plus G 1000 mg/m$^2$ on days 1, 8 and 15 every 28 days. Disease progression rate after three cycles of chemotherapy was the primary end-point. Progression-free survival (PFS), overall survival (OS) and response rate were secondary end-points.

***Findings:*** A total of124 patients were enrolled. The study showed a reduction of a progressive disease from 45.6% with G to 25.4% with NAB-P/G (P = 0.01) at 3 months. Noteworthy, at 6 months in the G arm, 35.6% of patients present a metastatic spread versus 20.8% in the NAB/G arm. The response rate was 5.3% in the G arm and 27% in the NAB/G arm. Median PFS was 4 months for the G arm and 7 months for the NAB-P/G arm. Median OS was 10.6 in the G arm and 12.7 months in the NAB-P/G arm. One patient died during treatment with G due to a stroke.

***Interpretation.:*** NAB-P/G reduced the rate of LAPC patients progressing after three cycles of chemotherapy compared with G, especially in terms of distant relapses. It positively affects PFS. To the best of our knowledge, this is the first randomized trial providing evidence that combination chemotherapy is superior to gemcitabine alone in this setting.

***ClinicalTrials.gov Identifier:*** NCT02043730.



## 1. Introduction

Pancreatic adenocarcinoma is one of the most challenging cancer diseases. In fact, in the next few years, it will be the second cause of mortality for cancer in Western countries. It is mainly due to the advanced stage at presentation: a metastatic disease in half of the patients and a locally advanced unresectable disease (LAPC) in one-third [1–3].

In LAPC, one of the major problems was the lack of a clear definition of this stage entity, leading to the inclusion of a heterogeneous patient population in several studies. Recently, however, 'unresectability' was better defined focussing, apart from the presence of a metastatic disease, on anatomic criteria such as the involvement of a major arterial axis [4]. However, despite their localized disease, most patients develop a metastatic disease in a few months. So far, based on its biology, it is reasonable to consider even this disease stage a systemic disease [5]. Moreover, this may contribute to explain the failure of local treatments such as radiotherapy as upfront treatment [6–8]. Therefore, chemotherapy represents a common upfront therapeutic approach for this subgroup of patients. Two regimens, FOLFIRINOX and Nab-paclitaxel/gemcitabine (NAB-P/G), have applied also in the setting of LAPC because of their higher response rates and improved survival compared with gemcitabine alone in metastatic patients [9,10]. Unfortunately, no randomized trials have been performed in LAPC patients. Many case series with FOLFIRINOX for LAPC patients have been published in the past 5 years, but the trial design and the sample size of most studies did not allow to draw definitive conclusions. Even a specific meta-analysis based on these trials was not conclusive [11]. Because of this, a phase III trial comparing gemcitabine with FOLFIRINOX (PRODIGE 29-NEOPAN) is currently recruiting patients.

Recently, the results of a large phase II study of Nab-paclitaxel/gemcitabine were reported. This combination was demonstrated to be safe and interesting response rate, resection rate and survival were found. Nevertheless, the bias of patient selection, typical of a phase II trial, may potentially question the real value of these findings [12].

Finally, we should consider that the applicability of results from stage IV trials to stage III trials may be tricky. A good example for this is the GERCOR/GISCAD trial, comparing a combination of gemcitabine/oxaliplatin to gemcitabine alone. Although it showed a benefit for the combination in the metastatic setting, it failed to show any benefit in LAPC [13]. This is why, ESMO guidelines as well as a recent expert opinion consensus, suggest that monotherapy with gemcitabine continues to be the standard of care in LAPC [14,15]. Based on the uncertainty about the role of combination chemotherapy in this setting, we designed a randomized phase II comparative trial testing a combination of NAB-P/G with G alone in LAPC.

## 2. Patients and methods

This national multicentre randomized comparative not blinded phase II trial (GAP trial) took place at 21 sites. It was approved by the institutional review board and ethics committee of each centre. Eligible patients with a pathological diagnosis of PDAC were classified as locally advanced unresectable according to NCCN criteria [16]. Patients had to have adequate bone marrow, liver and kidney functions. Criteria of exclusion were reported in the attached protocol. Patient registration and data collection were centralized at the Clinical Trials Unit of the National Cancer Institute of Naples. Patient registration and randomization were web-based and data collection was electronic. Patients were randomized to receive either an intravenous infusion of G at 1000 mg/m$^2$ on days 1, 8 and 15 (arm A) or an intravenous infusion of NAB-P at 125 mg/m$^2$ followed by G at 1000 mg/m$^2$ on days 1, 8 and 15 (arm B). NAB-P was provided by Celgene s.r.l., Italy. In both arms, treatment was administered every 28 days (1 cycle). The response was measured, according to version 1.1 Response Evaluation Criteria in Solid Tumours, after three cycles for the primary end-point and every three further cycles in patients continuing the treatment. At any radiological assessment, patients were evaluated for surgery. Surgery was indicated when a gross radical resection could be predicted, in absence of radiological or biological (CA19.9) tumour progression. At the end of three cycles of chemotherapy, patients who were unsuitable for resection and were still progression-free could receive concomitant chemoradiotherapy consisting of oral capecitabine at 1250 mg/m$^2$/daily and of 40–44.25 Gy by tomotherapy in 15 fractions. The same chemoradiotherapy was also recommended after resection. A basal computed tomography (CT) or magnetic resonance scan of the chest, abdomen and pelvis was performed within 3 weeks before randomisation. Tumour markers were assessed every 4 weeks. The worst toxicity observed for each patient was recorded.

The primary end-points of the study were the progression rate after three cycles of chemotherapy and progression-free survival (PFS). The secondary end-points were responses according to RECIST criteria; overall survival (OS), time to metastatic disease and safety profile.

Toxicity was defined according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.

### 2.1. Statistical analysis

The analysis was performed on an intention-to-treat basis, therefore all randomised patients were included in the analysis according to the assigned arm.

The safety population was defined as all patients who received at least one dose of study treatment(s).

Response rates in the two arms were described with their 95% confidence limits and were compared with the chi-square test in a 2 × 2 contingency table (responders/non-responders × treatment arms). The response analysis was performed with data collected approximately at week 12.

For each patient and each type of toxicity, the worst degree suffered during treatment was registered for the safety analysis.

PFS curves were described by the Kaplan–Meier product-limit method. The log-rank test was applied to test the statistical significance of the differences. Data were also presented as median, 95% confidence interval of the median and point estimates at 6 and 12 months.

OS curves were described according to the Kaplan–Meier product-limit method. The log-rank test was applied to test the statistical significance of the differences. Data were also presented as median, 95% confidence interval of the median and point estimates at 12 and 24 months.

Assuming an expected 3-month progression rate in the control arm of 40% and an auspicated progression rate in the experimental arm of 20%, with one-tailed alpha = 0.05, 80% power, 124 patients were required for the final analysis.

With 124 enrolled patients and after 109 observed events (progression or death without progression), the study had 80% power, with one-tailed alpha = 0.05, to detect a 0.62 HR and 61% power to detect a 0.69 HR in PFS.

### 2.2. Role of the funding source

The protocol was designed by GISCAD and Naples Cancer Institute. Celgene provided nab-paclitaxel for free to all study sites. Data were collected by the study investigators and analysed by biostatisticians, at Naples Cancer Center. Data were interpreted by all authors. All authors had access to raw data.

## 3. Results

Between June 2016 and January 2019, 124 patients were randomised to receive G (61 patients), (arm A) or NAB-P/G (63 patients), arm B. Four patients enrolled in the G arm withdrew consent at the time of randomization and they were excluded from the study analysis (Fig. 1).

Selected baseline characteristics of the patient population, including the four patients withdrawing consent in the G arm are reported in Table 1.

The three cycles treatment was completed by 46 patients (80.7%) in the G arm and by 55 patients (87.3%) in the NAB/G arm. There were no differences in treatment discontinuation due to toxicity (Table 2).

Concerning the primary end-point, after three cycles of treatment, 26 of 57 patients (45.6%) experienced a

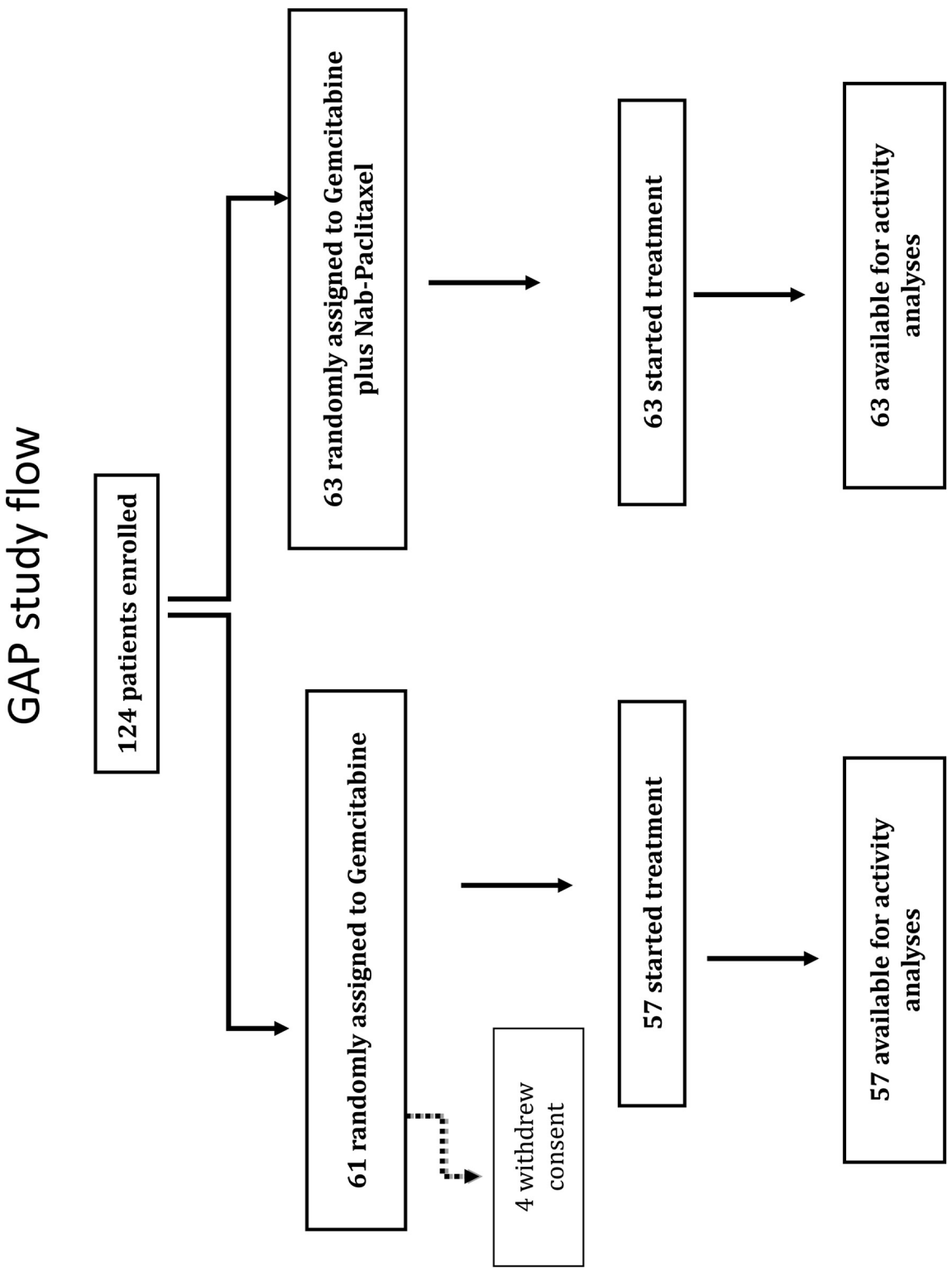


Fig. 1. Trial profile.

Table 1
Baseline characteristics of the study population.

| | G N = 61* | | NAB-P/G N = 63 | |
|---|---|---|---|---|
| **Age, (years)** | | | | |
| Median (range) | 72 | (42–79) | 68 | (36–74) |
| **Sex, n (%)** | | | | |
| Male | 26 | (42.6) | 28 | (44.4) |
| Female | 35 | (57.4) | 35 | (55.6) |
| **Performance status, n (%)** | | | | |
| 0 | 41 | (67.2) | 41 | (65.1) |
| 1 | 20 | (32.8) | 22 | (34.9) |
| **T, n (%)** | | | | |
| 1 | 2 | (3.3) | 2 | (3.2) |
| 2 | 9 | (14.7) | 6 | (9.5) |
| 3 | 12 | (19.7) | 16 | (25.4) |
| 4 | 35 | (57.4) | 39 | (61.9) |
| Missing | 3 | (4.9) | – | |
| **N, n (%)** | | | | |
| 1 | 28 | (45.9) | 29 | (46.0) |
| 2 | 30 | (49.2) | 34 | (54.0) |
| Missing | 3 | (4.9) | – | |
| **Stent biliare, n (%)** | | | | |
| No | 44 | (72.1) | 44 | (69.8) |
| Yes | 14 | (23.0) | 19 | (30.2) |
| Missing | 3 | (4.9) | – | (30.2) |

NAB-P, Nab-paclitaxel; G, Gemcitabine.

Table 2
Patients' compliance with planned treatment.

| | G (N = 57) | NAB-P/G (N = 63) |
|---|---|---|
| **No. of chemo cycles,** median (IQR) | 3 (3–3) | 3 (3–3) |
| **Cause of chemotherapy discontinuation, n (%)** | | |
| Completion | 46 (80.7%) | 55 (87.3%) |
| Progression or death | 7 (12.3%) | 6 (9.5%) |
| Toxicity | 2 (3.5%) | 2 (3.2%) |
| Refusal | 2 (3.5%) | – |

NAB-P, Nab-paclitaxel; G, Gemcitabine; IQR, interquartile range.

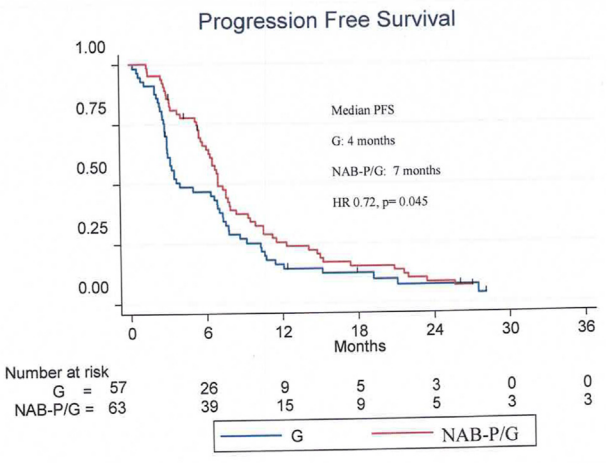


Fig. 2. Progression-free survival.

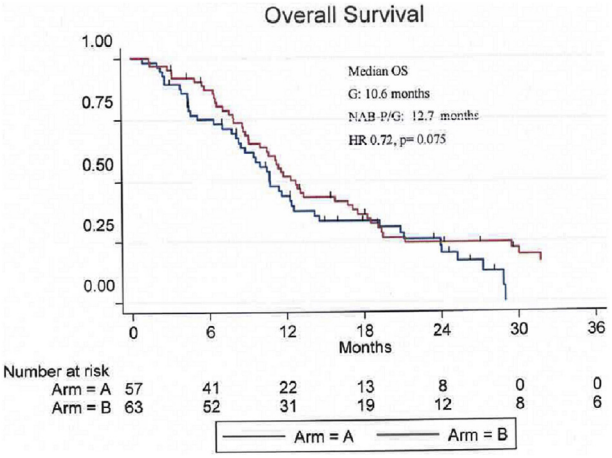


Fig. 3. Overall survival.

progressive disease in arm A versus 16 of 63 patients (25.4%) in arm B (p = 0.01). The site of progressive disease at 3 months was distant in 27.8% and 9.9%, and locally in 5.3% and 7.9%, in arms A and B, respectively. The response rate was 5.3% in A arm and 27% in B arm (p = <0.001).

Median PFS was 4 months in arm A and 7 months in arm B (p = 0.045; Fig. 2). Median OS was 10.6 months in arm A and 12.7 months in arm B (p = 0.075; Fig. 3).

Sixteen patients (28.1%) received radiotherapy in arm A and 24 patients (38.1%) in arm B. Four patients in arm B underwent a radical surgery versus 1 patient in G arm.

In Table 3, the rates of patients free from distant metastases at 3, 6, 9, 12, 15 and 18 months are reported in both arms. They were different at 3, 6, 9 and 12 months whilst at 15 and 18 months they were not. The median time to the onset of a metastatic disease was 7.5 months in arm A and 11.5 months in arm B (p = <0.05).

There were no unexpected toxicities. One patient died due to a stroke in arm A. In Table 4, toxicities were summarized in both arms. A waterfall plot is represented in Fig. 4.

Table 3
Patients free from distant metastases.

| Months | Gem (n = 57) | NAB-P/G (N = 63) |
|---|---|---|
| 3 | 72.2% (90%CI 60.7–80.9) | 90.1% (90%CI 81.4–94.8) |
| 6 | 64.4% (90%CI 52.5–74.1) | 79.2% (90%CI 68.6–86.5) |
| 9 | 47.2% (90%CI 35.2–58.3) | 57.3% (90%CI 45.1–67.6) |
| 12 | 38.9% (90%CI 27.0–50.6) | 48.1% (90%CI 36.0–59.2) |
| 15 | 38.9% (90%CI 27.0–50.6) | 40.1% (90%CI 28.1–51.7) |
| 18 | 34.0% (90%CI 21.6–46.9) | 37.2% (90%CI 25.4–49.0) |

NAB-P, Nab-paclitaxel; G, Gemcitabine; CI, confidence interval.

Table 4
Worst patient toxicity (≥5% of patients) according to CTCAE v4.0 criteria.

| | G (n = 56) | | | | | | | | | | NAB-P/G (n = 62) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Grade | 0 | | 1 | | 2 | | 3 | | 4 | | 0 | | 1 | | 2 | | 3 | | 4 | |
| | N | | n | | n | | n | | N | % | n | | n | | n | | n | | n | |
| **Anaemia** | 31 | 55% | 8 | 14% | 17 | 30% | 0 | 0% | 0 | 0% | 30 | 48% | 19 | 31% | 9 | 15% | 4 | 6% | 0 | 0% |
| **Febrile neutropenia** | 55 | 98% | 0 | 0% | 0 | 0% | 1 | 2% | 0 | 0% | 58 | 94% | 0 | 0% | 0 | 0% | 2 | 3% | 2 | 3% |
| **Oedema** | 53 | 95% | 1 | 2% | 1 | 2% | 1 | 2% | 0 | 0% | 55 | 87% | 4 | 6% | 1 | 2% | 3 | 5% | 0 | 0% |
| **Fatigue** | 35 | 63% | 13 | 23% | 8 | 14% | 0 | 0% | 0 | 0% | 32 | 52% | 18 | 29% | 5 | 8% | **7** | **11%** | **0** | **0%** |
| **Fever** | 42 | 75% | 10 | 18% | 4 | 7% | 0 | 0% | 0 | 0% | 51 | 82% | 9 | 15% | 2 | 3% | 0 | 0% | 0 | 0% |
| **Pain** | 41 | 73% | 6 | 11% | 7 | 13% | 2 | 4% | 0 | 0% | 52 | 84% | 4 | 6% | 5 | 8% | 1 | 2% | 0 | 0% |
| **Constipation** | 43 | 77% | 6 | 11% | 6 | 11% | 1 | 2% | 0 | 0% | 49 | 79% | 8 | 13% | 4 | 6% | 1 | 2% | 0 | 0% |
| **Diarrhoea** | 51 | 91% | 2 | 4% | 3 | 5% | 0 | 0% | 0 | 0% | 48 | 77% | 7 | 11% | 5 | 8% | 1 | 2% | 1 | 2% |
| **Mucositis** | 54 | 96% | 2 | 4% | 0 | 0% | 0 | 0% | 0 | 0% | 56 | 90% | 3 | 5% | 3 | 5% | 0 | 0% | 0 | 0% |
| **Nausea** | 45 | 80% | 7 | 13% | 3 | 5% | 1 | 2% | 0 | 0% | 53 | 85% | 5 | 8% | 2 | 3% | 2 | 3% | 0 | 0% |
| **Vomiting** | 49 | 84% | 5 | 9% | 4 | 7% | 0 | 0% | 0 | 0% | 57 | 92% | 4 | 6% | 1 | 2% | 0 | 0% | 0 | 0% |
| **ALT** | 47 | 84% | 4 | 7% | 3 | 5% | 2 | 4% | 0 | 0% | 53 | 85% | 6 | 10% | 3 | 5% | 0 | 0% | 0 | 0% |
| **AST** | 47 | 84% | 7 | 13% | 2 | 4% | 0 | 0% | 0 | 0% | 57 | 92% | 5 | 8% | 0 | 0% | 0 | 0% | 0 | 0% |
| **Bilirubin** | 45 | 80% | 2 | 4% | 4 | 7% | **2** | **4%** | **3** | **5%** | 59 | 95% | 2 | 3% | 1 | 2% | 0 | 0% | 0 | 0% |
| **GGT** | 54 | 96% | 1 | 2% | 0 | 0% | 1 | 2% | 0 | 0% | 59 | 95% | 3 | 5% | 0 | 0% | 0 | 0% | 0 | 0% |
| **Neutropenia** | 41 | 73% | 4 | 7% | 6 | 11% | 4 | 7% | 1 | 2% | **27** | **44%** | **7** | **11%** | **9** | **15%** | **13** | **21%** | **6** | **10%** |
| **Leucopenia** | 45 | 80% | 6 | 11% | 4 | 7% | 1 | 2% | 0 | 0% | 47 | 76% | 4 | 6% | 8 | 13% | 2 | 3% | 1 | 2% |
| **Piastrinopenia** | 29 | 52% | 15 | 27% | 9 | 16% | 2 | 4% | 1 | 2% | 40 | 65% | 10 | 16% | 9 | 15% | 3 | 5% | 0 | 0% |
| **Anorexia** | 47 | 84% | 7 | 13% | 2 | 4% | 0 | 0% | 0 | 0% | 57 | 92% | 1 | 2% | 0 | 0% | 4 | 6% | 0 | 0% |
| **Hyperglycaemia** | 50 | 89% | 1 | 2% | 1 | 2% | **4** | **7%** | **0** | **0%** | 61 | 98% | 1 | 2% | 0 | 0% | 0 | 0% | 0 | 0% |
| **Musculoskeletal pain** | 55 | 98% | 0 | 0% | 1 | 2% | 0 | 0% | 0 | 0% | 57 | 92% | 3 | 5% | 2 | 3% | 0 | 0% | 0 | 0% |
| **Periph sens neuropathy** | 56 | 100% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 50 | 81% | 7 | 11% | 2 | 3% | **3** | **5%** | **0** | **0%** |
| **Dyspnoea** | 53 | 95% | 1 | 2% | 0 | 0% | 1 | 2% | 1 | 2% | 60 | 97% | 0 | 0% | 1 | 2% | 1 | 2% | 0 | 0% |
| **Alopecia** | 56 | 100% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 53 | 85% | 4 | 6% | 5 | 8% | 0 | 0% | 0 | 0% |
| **Skin rash** | 53 | 95% | 2 | 4% | 1 | 2% | 0 | 0% | 0 | 0% | 54 | 87% | 2 | 3% | 6 | 10% | 0 | 0% | 0 | 0% |
| **Hypertension** | 55 | 98% | 0 | 0% | 0 | 0% | 1 | 2% | 0 | 0% | 62 | 100% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% |
| **Hypotension** | 56 | 100% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 60 | 97% | 1 | 2% | 1 | 2% | 0 | 0% | 0 | 0% |
| **Thromboembolic event** | 54 | 96% | 0 | 0% | 0 | 0% | 1 | 2% | 1 | 2% | 61 | 98% | 0 | 0% | 1 | 2% | 0 | 0% | 0 | 0% |
| **Total** | | | 110 | | 86 | | **25** | | **7** | | | | 137 | | 85 | | **47** | | **10** | |

NAB-P, Nab-paclitaxel; G, Gemcitabine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

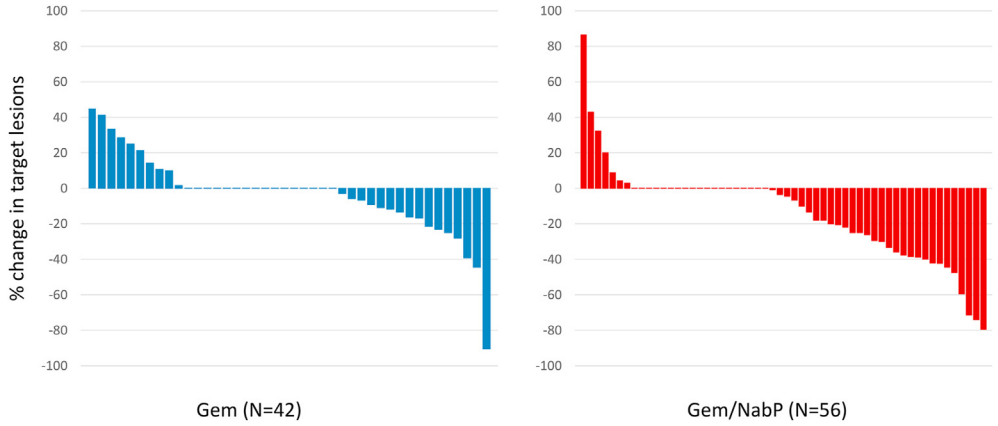


Fig. 4. Best response for the target lesion by patient in gemcitabine arm and gemcitabine/nab-paclitaxel arm.

## 4. Discussion

In the last few years, LAPC patients have commonly received FOLFIRINOX or NAB-P/G as the consequence of the applicability of the results obtained in the metastatic setting. The use of FOLFIRINOX was supported by a meta-analysis of single-arm phase II studies and retrospective series [11]. Eleven studies, including 315 patients, were assessed. The main limitation of this patient-level meta-analysis is that all the studies were non-randomized and most of them had a retrospective design. Moreover, the results may be biased because

different definitions for LAPC were used: NCCN criteria in three studies [16], the AHPBA/SSO/SSAT criteria in three studies [17] and even retrospective evaluations of pretreatment imaging in five studies. Overall, the quality of evidence supporting this regimen use in the clinical practice is quite low and the risk-benefit ratio provided by this strategy is unknown. To fulfil this gap of evidence, a phase III trial comparing gemcitabine with FOLFIRINOX in patients with LAPC (PRODIGE 29-NEOPAN) is currently recruiting patients.

There are fewer experiences with the NAB-P/G regimen. Recently, a large phase II study assessed the role of NAB/G combination in LAPC [12]. One hundred and seven patients, satisfying the NCCN criteria [16], were enrolled in this trial. Thirty-five patients (32.7%) achieved a partial response with a disease control rate of 77.6%. The median PFS was 10.9 months and the median OS was 18.8 months. In 16 patients (15%), an R0/R1 resection was feasible after the induction treatment. This favourable outcome was quite surprising in LAPC. Nevertheless, criteria for defining disease as locally advanced unresectable were not collected during the trial and no central review of the imaging was done, so that most of the resected patients could have a borderline resectable disease rather than a locally advanced unresectable disease.

The conflicting results obtained in the GERCOR/GISCAD trial [13], where the combination of oxaliplatin/gemcitabine was more effective than gemcitabine alone in the metastatic patients but not in patients with LAPC, contributed to increase the uncertainty about the optimal regimen to be used in this setting as highlighted by ESMO guidelines and a recent expert opinion consensus [14,15].

This is why we designed the GAP trial, a multicentre, randomized, comparative phase II trial testing the efficacy of NAB-P/G versus G alone. The primary end-point of the trial was the disease progression rate after three cycles of therapy and the PFS. In around 40% of patients, a metastatic spread happens, generally, in the first 3 months of treatment and it is associated with a poorer outcome [18]. PFS was demonstrated in a meta-analysis on 24 clinical trials with gemcitabine as control arm as a potential surrogate end-point for OS for patients with LAPC [19].

To reduce the potential bias of radiological staging and surgical assessment in the interpretation of our results, all the CT scans were reviewed by an independent radiologist.

In our study, NAB-P/G reduced the rate of LAPC patients progressing after three cycles of chemotherapy compared with G alone, mainly in terms of metastatic spread (Table 4). The disease progression rate at 3 months was 45.6% in the arm G and 25.4% in the arm NAB-P/G. It is of interest also the timing of the metastatic spread. In fact, at 12 months, about 50% of patients did not progress systemically and only 10% more will present a systemic disease failure at 18 months. The reduction of the metastatic spread by combination chemotherapy and the identification of the time when the risk of a systemic spread is smaller could reopen the discussion around the role of radiation therapy, going beyond the negative results of the LAP 07 trial [20]. In fact, radiotherapy should be offered to patients receiving a combination chemotherapy and not progressing at 12 months to contribute to the overall control of the disease.

Another relevant aspect for the outcome of these patients is the number of patients undergoing a radical surgery. In the FOLFIRINOX meta-analysis, around 26% of patients underwent a resection, of whom 78% had an R0 resection. However, there was a considerable heterogeneity across the studies included in this analysis in the percentage of resection. This is probably explained by the different definitions for LAPC and, probably, to the inclusion of borderline resectable tumours [11].

In the LAPACT trial, 16 of 107 patients (15%) underwent a resection [12]. In our trial, one patient had a radical surgery in the G arm and four (6%) in the NAB-P/G arm. The number of patients undergoing a resection is lower in comparison with those observed in FOLFIRINOX meta-analysis and LAPACT trial. Most likely it is the consequence of a more rigid selection of patients leading to the inclusion in our study of really unresectable tumours. It seems to be confirmed also by the findings of a randomized phase II trial comparing nab-paclitaxel/gemcitabine with or without capecitabine and cisplatin (PAXG) in locally advanced unresectable or borderline tumours. None of the 29 patients with locally advanced disease (16 in the PAXG arm and 13 in the NAB-P/G arm) underwent surgery, while 17 of 25 patients with borderline resectable disease received a radical surgery (equally distributed in the two arms, 8 and 9, respectively) [21].

The NEOLAP trial compared FOLFIRINOX and NAB-P/G regimens in LAPC. It was designed to demonstrate superiority in the resection rate of FOLFIRINOX versus Nab-paclitaxel/gemcitabine. It failed to show this superiority, as well as any difference in terms of response rate, disease control rate, PFS and pathological response rate suggesting that FOLFIRINOX is not more effective than NAB-P/G [22].

A future clinical trial could be the comparison of NAB-P/G regimen with the PAXG regimen. In fact, in a randomized phase II trial, PAXG determined a better disease control rate and response rate in comparison with NAB-P/G in a cohort of patients with LAPC [21].

To the best of our knowledge, this is the first randomized trial providing evidence that combination

chemotherapy is superior to gemcitabine in LAPC patients. Thus, a combination of NAB-P/G should be offered to LAPC patients in the clinical practice.

## Contributors

Conception/design: SC, MCP, FP, RL and CG. Provision of study material or patients: RB, RB, DB, AZ, DF, SM, AS, LC, SL, FN, GDB, AS, MB, AM, AB, RM, DF, SN, CM and ACG. Collection and/or assembly of data: MCP and FP. Data analysis and interpretation: MVCP, FP and SC. Manuscript writing: SC, FP and MCP. Final approval of manuscript: SC, MCP, FP, RL, CG, RB, RB, DB, AZ, DF, SM, AS, LC, SL, FN, GDB, AS, MB, AM, AB, RM, DF, SN, CM and ACG.

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## Conflict of interest statement

Dr Cascinu reports grants from Celegne during the conduct of the study; other from Celegne; other from Servier, outside the submitted work; and the remaining authors have nothing to disclose.

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