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Phase II trial of capecitabine plus *nab*-paclitaxel in patients with metastatic pancreatic adenocarcinoma

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INTRODUCTION

- Metastatic pancreatic adenocarcinoma (mPC) is a lethal disease with a median survival of approximately 6 months in the gemcitabine ± erlotinib era[1]
- Introduction of the combination of 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX), as well as the better tolerated *nab*-paclitaxel plus gemcitabine, represented significant advances in the treatment of mPC[2,3]
- Preclinical data demonstrate a biochemical rationale for the combination of taxanes with the oral 5-FU prodrug capecitabine: taxanes upregulate thymidine phosphorylase in liver tissue, potentially increasing the tumour concentration and efficacy of capecitabine[4]
- In view of the recently described excellent therapeutic index of capecitabine plus *nab*-paclitaxel in metastatic breast cancer,[5] we initiated the present phase II trial to evaluate this combination as first-line therapy in mPC
- The primary objective of the trial was to determine the objective response rate (ORR) in patients receiving capecitabine plus *nab*-paclitaxel as first-line treatment for mPC. Secondary objectives included determination of the disease control rate (DCR; abrogation of progressive disease [PD]), progression-free survival (PFS), and overall survival (OS), as well as evaluation of the safety and tolerability of this combination when administered according to an intra-individual dose escalation schedule
- The trial is registered with the European Medicines Agency as EudraCT 2013-001714-15

METHODS

Inclusion criteria

- Histologically confirmed mPC
- Measurable disease, as assessed by computerised tomography and defined by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria
- Age ≥18 years
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
- Adequate haematological, hepatic, and renal function
- No previous chemotherapy for metastatic disease
- Adjuvant gemcitabine was permitted if the last cycle was completed ≥6 months prior to trial entry

Trial medication

- Patients received capecitabine (825 mg/m² orally twice daily on Days 1–15) and *nab*-paclitaxel (125 mg/m² intravenously on Days 1 and 8) every 3 weeks. In patients with adequate bone marrow function (neutrophils ≥1,500/µL, thrombocytes ≥100,000/µL) and with no clinically relevant adverse reactions (defined as adverse events [AEs], other than alopecia or fatigue, that were of grade ≤2 severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 4.0) after the first cycle of treatment, the *nab*-paclitaxel dose was escalated to 100 mg/m² on Days 1, 8, and 15 of each subsequent cycle, and was maintained at this level if tolerated
- Granulocyte-colony stimulating factor was recommended in case of neutropenia of grade >2. In patients with an objective treatment response or with stable disease (SD), treatment was continued until the development of PD
- In patients who derived a clinical benefit, and in whom either capecitabine or *nab*-paclitaxel had to be discontinued for toxicity reasons (for example, hand-foot syndrome associated with capecitabine, or neuropathy associated with *nab*-paclitaxel), continuation with the non-dose-limiting component of the combination as monotherapy was recommended

Trial design and statistical considerations

Design

- This was a single-centre, open-label, phase II, clinical trial

Endpoints

- The primary endpoint of the trial was the ORR according to RECIST version 1.1 criteria. This was evaluated at baseline and every 2 months thereafter, with assessments carried out by an independent radiological review committee
- Secondary endpoints included DCR, PFS, and OS, in addition to evaluations of the safety and tolerability of capecitabine plus *nab*-paclitaxel in mPC. Safety and tolerability were assessed by the incidence of treatment-related AEs according to NCI-CTCAE version 4.0

Statistical power and sample size

- In order to demonstrate, with 80% power, that capecitabine plus *nab*-paclitaxel, administered according to an intra-individual dose-escalation schedule, would yield an ORR of ≥30%, it was estimated that we needed to enrol 32 patients to obtain a sample size of 29 evaluable patients

RESULTS

Patients

- Between December 2013 and January 2015, 30 patients were enrolled
- Patients' median age was 63 years
- All patients had an ECOG PS of 0–1, most patients (93.3%) had multiple metastatic sites, 80.0% had liver metastases, and 23.3% had biliary stents in place at the time of trial entry
- Median CA19-9 was 1,004 U/mL (0.9–100,000 U/mL)
- Patients' baseline characteristics are shown in Table 1

Table 1. Baseline characteristics (N=30)

Age	Median, years (range)	63 (37–79)
	≥65 years, n (%)	14 (46.7)
Sex, n (%)	Male	16 (53.3)
ECOG PS, n (%)	0	27 (90.0)
	1	3 (10.0)
International Staging System stage IV disease at primary diagnosis, (%)	Yes	30 (100)
Pancreatic primary tumour location, n (%)	Head ± body	24 (80.0)
	Tail	6 (20.0)
Current site(s) of metastasis, n (%)	Lung	3 (10.0)
	Liver	24 (80.0)
	Peritoneum	3 (10.0)
No. of metastatic sites, n (%)	1	2 (6.7)
	2	11 (36.7)
	≥3	17 (56.7)
Previous surgery, n (%)	Yes	2 (6.7)
Biliary stent, n (%)	Yes	7 (23.3)
CA19-9	Normal, n (%)	4 (13.3)
	Median, U/mL (range)	1,004 (0.9–100,000)

Treatment efficacy

- Among the 29 RECIST response-assessable patients, the ORR was 41.4% (95% confidence interval [CI] 23.5–59.3), and SD was noted in 34.5% (Table 2). This gave a DCR of 75.9%

Table 2. Treatment response rates

Best response (N=29)	No. of patients, n (%)
Objective response	12 (41.4)
SD	10 (34.5)
PD	7 (23.1)

- After a median follow-up of 10.3 months (95% CI 1.9–19.0 months), the median PFS is 5.6 months (95% CI 1.9–16.0), and median OS is 10.3 months (95% CI 2.0–19.0+), with 13/30 (43.3%) patients remaining alive at present

Safety

- All 30 enrolled patients were included in the safety analysis. In all except two of these patients, it was possible to escalate the *nab*-paclitaxel dose after the first treatment cycle
- A total of 180 cycles of *nab*-paclitaxel and 193 cycles of capecitabine were administered per protocol
- A summary of treatment-related AEs by severity is presented in Table 3. The only AEs of grade 3 severity were peripheral neuropathy (23.3%), afebrile neutropenia (16.7%), hand-foot syndrome (13.3%), and phototoxic skin reaction (10%). No grade 4 AEs occurred

Table 3. Treatment-related AEs

	Incidence, n (%)			
AE	Grade 1	Grade 2	Grade 3	Grade 4
Afebrile neutropenia	9 (30.0)	4 (13.3)	5 (16.7)	0
Febrile neutropenia	0	0	0	0
Anaemia	3 (10.0)	2 (6.7)	0	0
Thrombocytopenia	4 (13.3)	2 (6.7)	0	0
Alopecia	8 (26.7)	16 (53.3)	N/A	N/A
Fatigue	6 (20.0)	5 (16.7)	0	0
Hand-foot syndrome	3 (10.0)	2 (6.7)	4 (13.3)	0
Peripheral neuropathy	6 (20.0)	10 (33.3)	7 (23.3)	0
Phototoxic skin reaction	0	2 (6.7)	3 (10.0)	0
Anorexia	4 (13.3)	1 (3.3)	0	0
Nausea/vomiting	4 (13.3)	1 (3.3)	0	0
Stomatitis	2 (6.7)	2 (6.7)	0	0
Constipation	0	2 (6.7)	0	0
Diarrhoea	7 (23.3)	3 (10.0)	0	0

N/A, not applicable – no CTCAE assessment criteria

- Table 4 shows the number of patients who required capecitabine or *nab*-paclitaxel dose modifications during the course of the trial
- Two patients required capecitabine dose reductions. In each of the six patients who required *nab*-paclitaxel dose reductions, the dose was reduced to the starting level of 125 mg/m² on Days 1 and 8 every 3 weeks for 13 cycles
- *nab*-paclitaxel and capecitabine dosing delays were required by 19 and eight patients, respectively
- Three patients had to discontinue *nab*-paclitaxel; these patients continued treatment with capecitabine alone. All 29 evaluable patients were able to remain on capecitabine for the duration of the trial

Table 4. Dose modifications

Modification required	Drug	No. of patients	No. of cycles with dose modification
Dose reduction	*nab*-paclitaxel	6	13
	Capecitabine	2	2
Dose withdrawal	*nab*-paclitaxel	3	2
	Capecitabine	0	0
Dose delay	*nab*-paclitaxel	19	36
	Capecitabine	8	10

CONCLUSIONS

- The combination of capecitabine plus *nab*-paclitaxel shows substantial antitumour activity when administered as first-line chemotherapy in mPC
- The described dose regimen of capecitabine plus *nab*-paclitaxel can be administered safely in this indication

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DISCLOSURES

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