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Tumor treating fields in combination with gemcitabine or gemcitabine plus nab-paclitaxel in pancreatic cancer: Results of the PANOVA phase 2 study

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ABSTRACT

Background: Tumor Treating Fields (TTFields), low intensity alternating electric fields with antimitotic activity, have demonstrated survival benefit in patients with glioblastoma. This phase 2 PANOVA study was conducted to examine the combination of TTFields plus chemotherapy in patients with pancreatic ductal adenocarcinoma (PDAC).

Methods: Forty patients with newly-diagnosed, locally advanced or metastatic PDAC received continuous TTFields (150 KHz for ≥18 h/day) plus gemcitabine (1000 mg/m^2), or gemcitabine plus nab-paclitaxel (125 mg/m^2). The primary endpoint was safety and secondary endpoints included compliance to TTFields, progression-free survival (PFS), and overall survival (OS).

Results: Seventeen patients (85%) in each cohort reported Grade ≥3 adverse events (AEs). No increase in serious AEs (SAEs) was observed compared to that anticipated with systemic chemotherapy alone. Twenty-one patients reported TTFields-related skin toxicity, of which 7 were Grade 3; all resolved following temporary reduction of daily TTFields usage. No TTFields-related SAEs were reported. Compliance to TTFields was 68–78% of the recommended average daily use in both cohorts. Median PFS was 8.3 months (95% CI 4.3, 10.3) and median OS was 14.9 months (95% CI 6.2, NA) in the TTFields + gemcitabine cohort. In the TTFields + gemcitabine + nab-paclitaxel cohort, the median PFS was 12.7 months (95% CI 5.4, NA); median OS has not been reached.

Conclusion: The PANOVA trial demonstrated that the combination of TTFields and systemic chemotherapy is safe and tolerable in patients with advanced PDAC. Based on the safety and preliminary efficacy results of this phase 2 study, a randomized phase 3 study (PANOVA-3) is underway.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the eighth leading cause of cancer mortality in men and ninth in women worldwide [1]. At diagnosis, only 15% of patients are candidates for curative surgical resection [2]. FOLFIRINOX (leucovorin, 5-FU, irinotecan, oxaliplatin) [3] or gemcitabine, alone or combined with nab-paclitaxel [4], are commonly prescribed for unresectable pancreatic cancer patients with modest survival benefit. FOLFIRINOX is reserved for patients with good performance status and a favorable comorbidity profile, while gemcitabine in combination with nab-paclitaxel is currently the most common initial regimen for advanced, unresectable patients [5].

Tumor Treating Fields (TTFields) are a non-invasive, regional antimitotic treatment with minimal systemic toxicity. Based on the

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results of Phase 3 trials, TTFields are approved for recurrent and newly diagnosed glioblastoma [6,7]. TTFields are low intensity (1–3 V/cm), intermediate frequency (100–300 kHz) alternating electric fields delivered using transducer arrays placed on the skin surrounding the tumor region. TTFields act during two phases of mitosis: at metaphase by disrupting the formation of the mitotic spindle, and at cytokinesis by dielectrophoretic dislocation of intracellular organelles resulting in apoptosis (Fig. 1) [8–11]. Ongoing research suggests that TTFields inhibit DNA damage repair, tumor cell migration and invasion and also induces autophagy that leads to immunogenic cell death.

The anti-mitotic effect of TTFields has been shown in multiple tumor models including pancreatic cancer [9,11–14]. TTFields at 150 kHz led to significantly reduced proliferation *in vitro* [8],

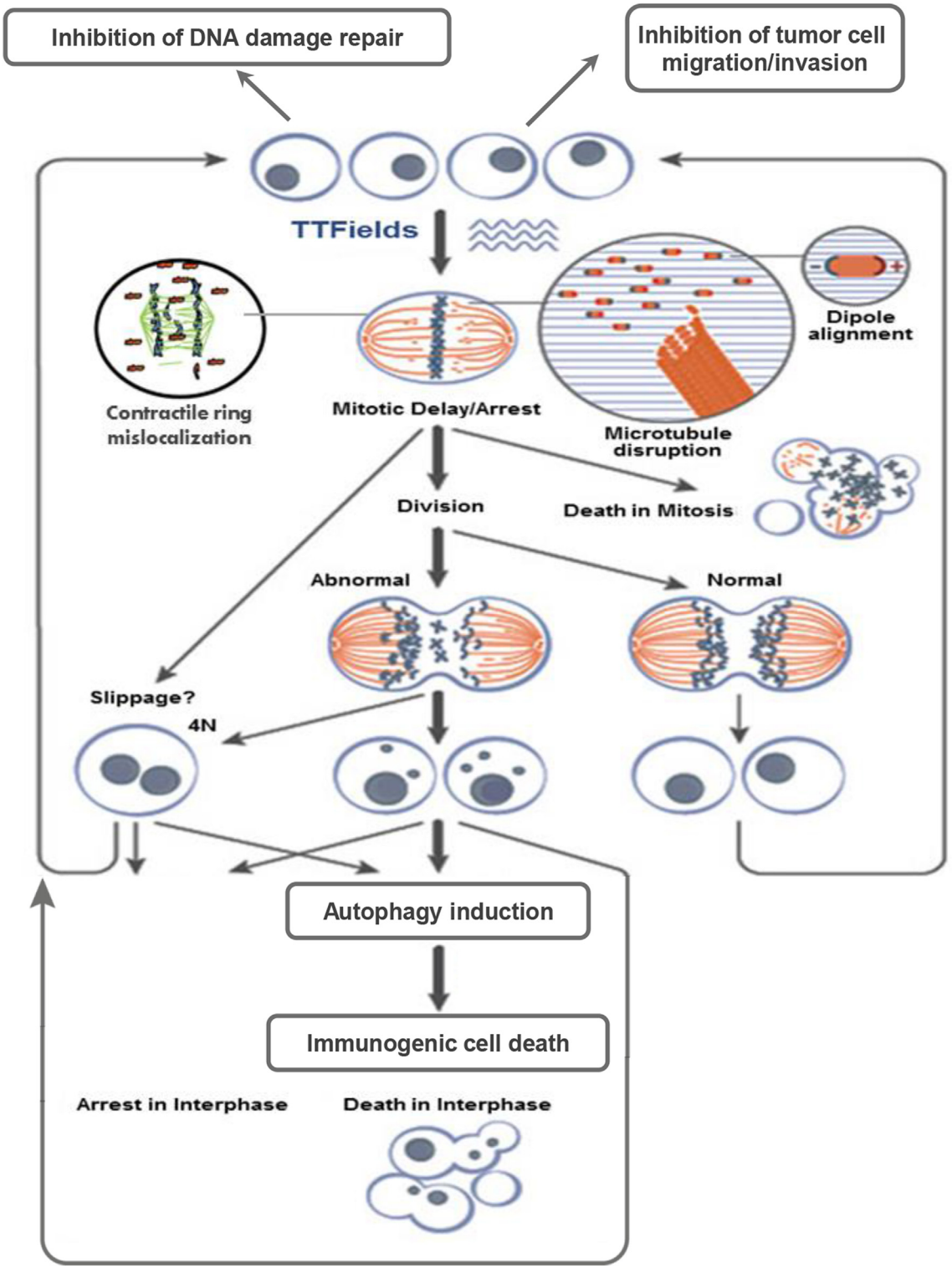

Fig. 1. Mechanism of action of TTFields.

followed by decreased clonogenic potential, possibly due to TTFields-induced chromosomal abberations [12]. *In vivo*, tumor volumes of animals treated with TTFields were significantly reduced. The combination of TTFields with gemcitabine or with paclitaxel was superior to either treatment alone [13].

Preclinical models have shown that the effect of TTFields is intensity-dependent with a therapeutic threshold of 1 V/cm. Computational simulations are a standard tool for estimating TTFields distribution within the body. A realistic anatomic computer model of human pancreatic cancer demonstrated that mean therapeutic TTFields intensities of above 1 V/cm could be delivered to the site of the tumor [13]. Layouts with one pair of arrays placed on the back and front of the patient and one pair placed on the lateral aspects of the patient delivered two almost perpendicular fields with average intensities in the pancreas of above the therapeutic threshold of 1 V/cm.

Based on the results from our pre-clinical testing and the favorable toxicity profile of TTFields observed to date, we conducted the phase 2 PANOVA study to examine the combination of TTFields plus chemotherapy in patients with advanced PDAC.

Methods

Phase 2 clinical study

The PANOVA (NCT01971281) study was conducted at six sites in Spain and Switzerland in accordance with the Declaration of Helsinki and Good Clinical Practice. The study was approved by the local ethical committees of all participating centers and the relevant authorities. Patients were enrolled between January 2014 and May 2016 and all gave written informed consent. Eligibility criteria included age ≥18 years and a histologically or cytologically confirmed unresectable, locally advanced or

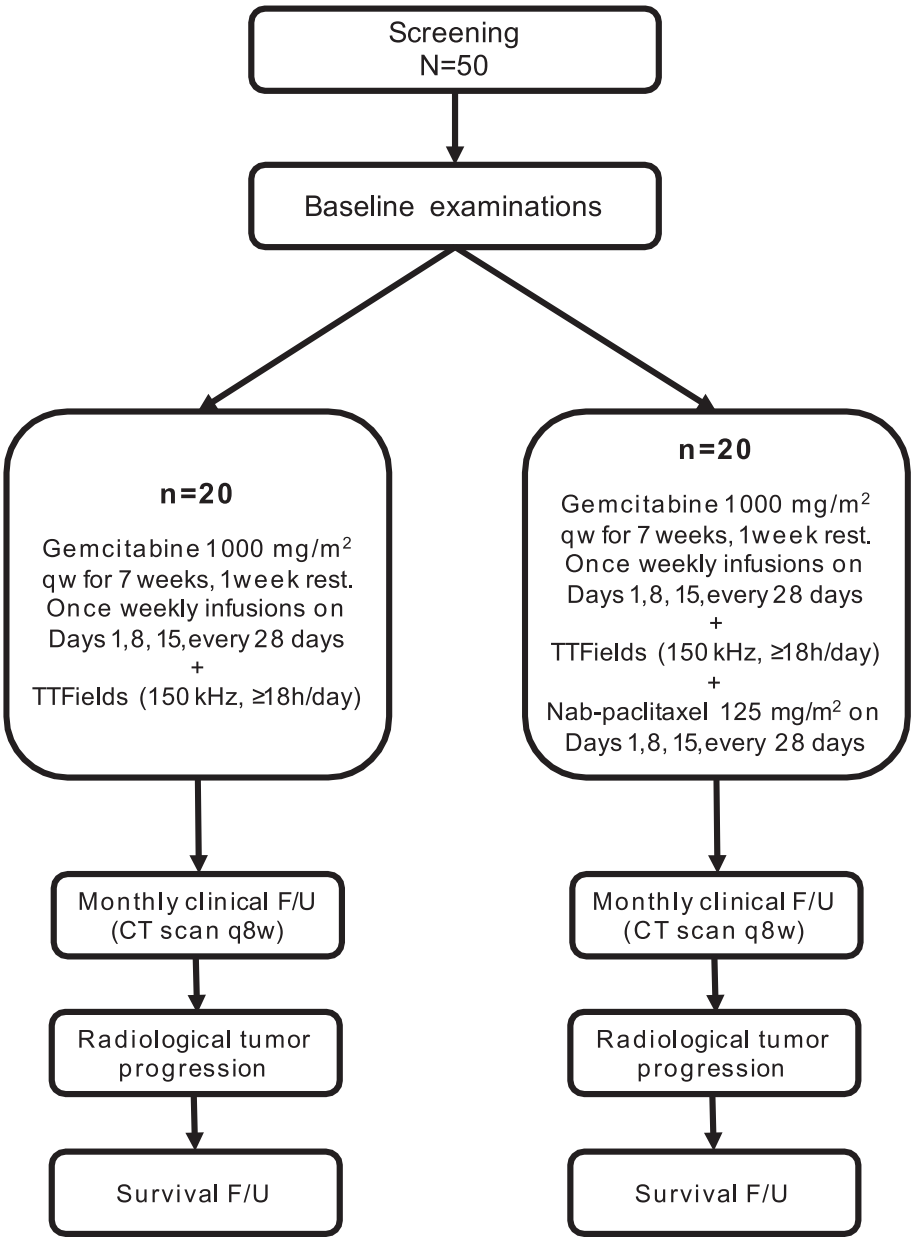

Fig. 2. PANOVA Study schema.

Fig. 3. The NovoTTF-100L(P) System is a portable device delivering alternating electric fields to the abdomen using 4 transducer arrays. The System is portable when operated using a battery, allowing normal daily life. *The models presented are actors and not patients.*

metastatic adenocarcinoma of the pancreas with measurable disease as defined by the Response Evaluation Criteria in Solid Tumor (RECIST), version 1.1. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1 and adequate bone marrow, liver and kidney functions. No concurrent anti-tumor therapy was allowed beyond the protocol treatments. No chemotherapy or radiation therapy was allowed prior to study enrollment. Prior surgery was allowed for local disease if a measurable lesion was seen on the baseline CT scan. Patients with brain metastases or other clinically-relevant malignancies or significant comorbidities that could affect patients' prognoses were excluded. Patients with implantable electronic medical devices such as pacemakers were excluded due to potential interference of their operation by the TTFields device.

Study design

This was a multicenter, non-randomized, open-label phase 2 study (Fig. 2). The primary endpoint was safety of TTFields in combination with gemcitabine, or gemcitabine plus nab-paclitaxel. Secondary endpoints were compliance with TTFields therapy, progression free survival (PFS) and overall survival (OS). Patients

Table 1
Baseline demographics and disease characteristics.

Characteristic	TTFields + Gem (n = 20)	TTFields + Gem + nab-P (n = 20)
Age, median (range)	73 (49–81)	69 (58–81)
Gender, n (%)		
Male	8 (40)	13 (65)
Female	12 (60)	7 (35)
ECOG performance Status, n (%)		
0	3 (15)	6 (30)
1	17 (85)	14 (70)
Ethnicity, n (%)		
Caucasian	20 (100)	20 (100)
Histology, n (%)		
Adenocarcinoma	20 (100)	20 (100)
Disease Stage		
Locally advanced (unresectable)	8 (40)	8 (40)
Metastatic	12 (60)	12 (60)
Past Smoker	10 (50)	8 (40)

Abbreviations: ECOG, Eastern European Cooperative Oncology Group; Gem, gemcitabine; nab-P, albumin bound paclitaxel.

Table 2
Adverse events occurring in >10% of patients (Grade 1 and 2) or ≥5% of patients (Grade 3 and 4) irrespective of whether the event was considered by the investigator to be treatment-related.

	TTFields + Gem (n = 20); n (%)		TTFields + Gem + nab-P (n = 20); n (%)	
Adverse event	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Hematologic events				
Anemia	4 (20)	1 (5)	8 (40)	1 (5)
Leukopenia	2 (10)	0	4 (20)	1 (5)
Neutropenia	2 (10)	4 (20)	2 (10)	7 (35)
Thrombocytopenia	3 (15)	0	5 (25)	3 (15)
Non-hematologic events				
Abdominal pain	10 (50)	1 (5)	7 (35)	3 (15)
Constipation	6 (30)	2 (10)	6 (30)	0
Diarrhea	3 (15)	2 (10)	7 (35)	1 (5)
Nausea	15 (75)	0	8 (40)	0
Vomiting	9 (45)	1 (5)	3 (15)	0
Peripheral edema	5 (25)	0	6 (30)	1 (5)
Pyrexia	5 (25)	0	7 (35)	0
Loss of appetite	9 (45)	0	9 (45)	1 (5)
Dizziness	3 (15)	0		
Peripheral neuropathy	1 (5)	0	5 (25)	2 (10)
Polyneuropathy	0	0	2 (10)	1 (5)
Fatigue	5 (25)	2 (10)	1 (5)	3 (15)
Insomnia	0	0	3 (15)	0
Cough	1 (5)	0	3 (15)	0
Dyspnea	2 (10)	1 (5)	1 (5)	2 (10)
Pulmonary embolism	0	0	0	2 (10)
Epistaxis	0	0	3 (15)	0
Dermatitis	3 (15)	2 (10)	0	1 (5)
Erythema	3 (15)	0	1 (5)	0
Non-specified skin lesion	6 (30)	0	3 (15)	4 (20)
Alopecia	0	0	5 (25)	0
Hypertension	1 (5)	0	1 (5)	1 (5)

Abbreviations: Gem, gemcitabine; nab-P, albumin bound paclitaxel.

continued treatment until disease progression or unacceptable toxicity.

Treatment plan

TTFields: The NovoTTF-100L(P) System (Novocure, Israel; Fig. 3), a portable, home-use, battery-operated medical device was pre-programmed to deliver 150 kHz TTFields in two sequential, perpendicular field directions at a maximal intensity of 1414 mA RMS through two pairs of transducer arrays connected to the electric field generator. No adjustments to the device could be performed by investigators or patients. Patients were advised to use the device for at least 18 h per day, with breaks in treatment allowed for personal needs (e.g. showering). Treatment continued until radiological disease progression, death or unacceptable device-related adverse events. Placement of the non-invasive transducer arrays was approved by the study investigator for each individual patient prior to start of treatment, optimized for the anatomical location of the tumor. Patients were advised to maintain good skin hygiene, and to be aware of the signs of potential skin toxicity and the treatment with topical steroids.

Concomitant Chemotherapy: All patients received standard doses either of gemcitabine alone or gemcitabine plus nab-paclitaxel in combination with TTFields. Chemotherapy continued until disease progression, death or unacceptable toxicity. Gemcitabine was administered at a dose of 1000 mg/m^2 once weekly for up to 7 weeks, followed by a week of rest and subsequent weekly infusions on days 1, 8 and 15 of a 28-day cycle. Nab-paclitaxel was administered at a dose of 125 mg/m^2 immediately followed by gemcitabine (1000 mg/m^2) on Days 1, 8 and 15 of each 28-day cycle. Dose modifications or interruptions for each chemotherapy in the event of toxicity was managed according to the respective package insert. Patients received the best supportive care available at each site for their symptoms.

Treatment outcomes

Safety, the primary endpoint, was based on the incidence and severity of treatment-emergent adverse events, evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 guidelines. The protocol predefined endpoints were 1) an absolute increase of 15% in incidence of Grade ≥3 adverse events (AEs) as the upper limit allowed for the combination of TTFields + gemcitabine compared to gemcitabine alone, and 2) an absolute increase of 15% in the incidence of neutropenia, or incidence higher than 25% in device- or other chemotherapy-related serious adverse events in patients treated with the combined TTFields + gemcitabine + nab-paclitaxel.

An increase of 15% and 25%, respectively, in the incidence of Grade 3 AEs based on historical data [4] was used as threshold for the two cohorts treated with gemcitabine + TTFields or gemcitabine + nab-paclitaxel + TTFields. Since toxicity was almost similar in the two arms of the historical study, an increase of 15% in neutropenia, the AE that had the highest incidence in gemcitabine + nab-paclitaxel treated patients was used for the assessment of the primary endpoint.

Patient compliance was assessed using the device log file, which was regularly downloaded from the NovoTTF-100L(P) system. Progression-free survival (PFS) was based on investigator assessment and local evaluation of CT scans. PFS was defined as time from enrollment on trial to progression, date-of-death, or censored as the last follow up. Overall survival (OS) was measured as time from enrollment on trial to date-of-death, or censored as the last follow up. Radiological response was determined according to the RECIST 1.1 criteria by each investigator, based on CT scans.

Statistical analysis

The sample size in the TTFields plus gemcitabine cohort was determined based on the assumption that gemcitabine alone leads to Grade ≥3 toxicity in approximately 30% of patients, and the incidence of the only common Grade ≥3 AE (neutropenia) occurred in 38% of pancreatic cancer patients treated with gemcitabine plus nab-paclitaxel in a recent phase 3 trial [4]. The analysis of PFS was based on the intent-to-treat principle. PFS rates were estimated using the Kaplan-Meier (KM) method. Radiological response rate was calculated, and the exact binomial distribution 95% confidence interval was estimated. One year survival and PFS at 6 months (PFS6) were performed based on the Kaplan-Meier estimated proportions with 95% confidence interval of patients alive at 12 months and patients alive and who did not progress at 6 months respectively.

Results

Patient characteristics and compliance with study treatments

Baseline demographics and disease characteristics were similar in the two treatment cohorts (Table 1). The majority of patients in both cohorts had an ECOG score of 1, and 60% of patients in both groups had distant metastases. All patients started TTFields treatment in combination with chemotherapy.

The median numbers of gemcitabine and TTFields cycles administered to the 20 patients receiving TTFields in combination with gemcitabine alone were 4 and 5, respectively. The median compliance rate with TTFields with gemcitabine alone was 78% of the recommended 18 h/day (14 h/day). The median numbers of gemcitabine/nab-paclitaxel and TTFields cycles administered to the other 20 patients were both 5. The median compliance rate in the TTFields plus gemcitabine and nab-paclitaxel group was 68% of the recommended 18 h/day (12.2 h/day).

Safety

The safety results are summarized in Table 2. All patients reported at least 1 AE (any grade) during the study period.

TTFields + gemcitabine cohort: The most commonly reported non-hematological AEs of any grade were nausea (75%), abdominal pain (55%), vomiting (50%) and loss of appetite (45%). The most commonly reported hematological AEs of any grade were neutropenia (30%) and anemia (25%). Seventeen patients (85%) reported at least one Grade ≥3 AE during the study period, the most common of which were neutropenia (20%), constipation (10%), diarrhea (10%), fatigue (10%) and dermatitis (10%). Fourteen patients (70%) reported an SAE; there were no TTFields-related SAEs. Ten patients (50%) had TTFields-related skin toxicity, mostly dermatitis. Only 2 patients had Grade 3 dermatitis related to the study treatment.

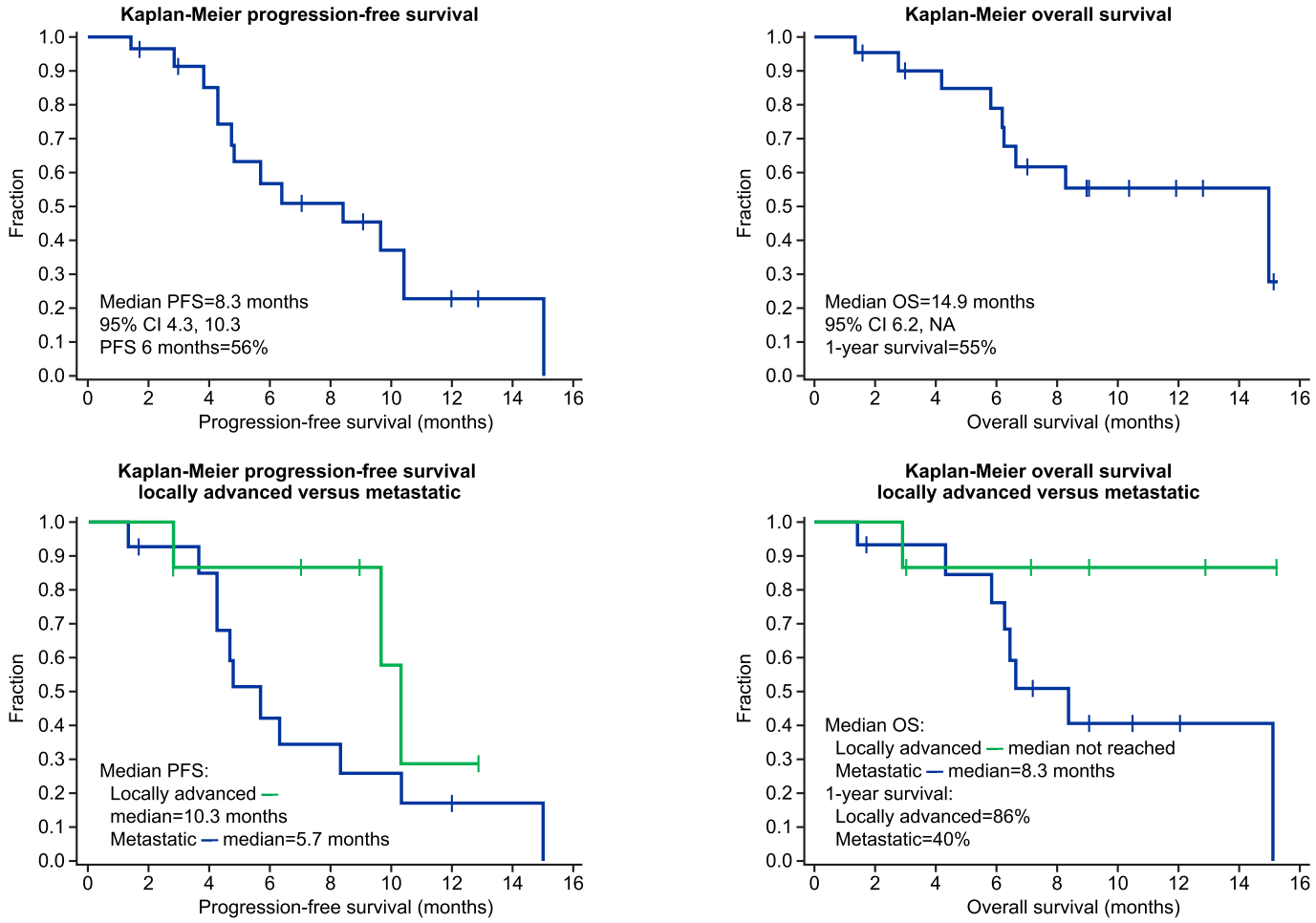

Fig. 4. Efficacy results of the TTFields-gemcitabine group of the PANOVA Study. Upper panel: PFS (left) and OS (right) Kaplan-Mayer curves for the Intent-to-treat population in the gemcitabine-TTFields group of the PANOVA Study. The median PFS was 8.3 months (95% CI 4.3, 10.3) and the median OS was 14.9 months (95% CI 6.2, NA). Lower panel: Breakdown of PFS (left) and OS (right) K-M curves of the intent-to-treat population per disease stage.

TTFields + gemcitabine + nab-paclitaxel cohort: The most commonly reported non-hematological AEs of any grade were abdominal pain (50%), loss of appetite (50%), nausea (40%) and diarrhea (40%). The most commonly reported hematological AEs of any grade were neutropenia (45%) and anemia (45%). Seventeen patients (85%) reported at least one Grade ≥3 AE during the study period, the most common of which were neutropenia (35%), non-specified skin lesion (20%), thrombocytopenia (15%), abdominal pain (15%) and fatigue (15%). Ten patients (50%) experienced an SAE, none of which were related to TTFields therapy. Eleven patients had TTFields-related skin toxicity and 5 patients had a Grade 3 skin reaction. Peripheral neuropathy led to temporary interruption of nab-paclitaxel administration in 4 (20%) patients but none had Grade 4 neuropathy.

Skin toxicities related to TTFields were mostly the result of dermatitis beneath the transducer arrays delivering the electrical fields, which are attached to the skin using medical-grade adhesives. These toxicities were symptomatically-treated using a high potency topical steroid that was applied to the inflamed skin at the time of array replacements (typically every 3–4 days). In order to minimize skin irritation, patients were instructed to slightly shift the location of arrays on each array replacement and to maintain good skin hygiene. In patients with Grade 3 skin toxicities, a median decrease in the compliance of TTFields daily usage to 12.5% (3 h) was observed during the toxicity period.

There was no absolute increase of 15% in incidence of Grade 3 or higher toxicity for the combined TTFields + gemcitabine and no absolute increase of 15% in the incidence of neutropenia, or incidence higher than 25% in device- or other chemotherapy-related serious adverse events in the combined TTFields + gemcitabine + nab-paclitaxel cohort. Therefore, the primary endpoint of the PANOVA study was successfully met.

Efficacy

TTFields + gemcitabine: The median PFS in the intent-to-treat population of this treatment cohort was 8.3 months (95% CI 4.3, 10.3). PFS rate at 6 months (PSF6) was 56% (95% CI 31, 75) (Fig. 4). Of 11 patients with available CT scans, 5 (45%) had a partial response, 5 (45%) had stable disease and 1 (10%) had progressive disease. The median OS was 14.9 months (95% CI 6.2, NA) and 1-year survival rate was 55% (95% CI 29, 75). Locally advanced patients had a median PFS of 10.3 months versus 5.7 months in metastatic patients. The median OS in locally advanced patients had not been reached at the end of the follow up period and was 8.3 months in metastatic patients. The one-year survival rates for locally-advanced and metastatic patients were 86% and 40%, respectively (see Fig. 4).

TTFields + gemcitabine + nab-paclitaxel: The median PFS of the intent-to-treat population in this treatment cohort was 12.7 months (95% CI 5.4, NA). PFS6 was 65% (95% CI 40, 81) (Fig. 5). Of the 15 patients with available CT scans, 6 (40%) had a partial response, 7 (47%) had stable disease and 2 (13%) had progressive disease. The

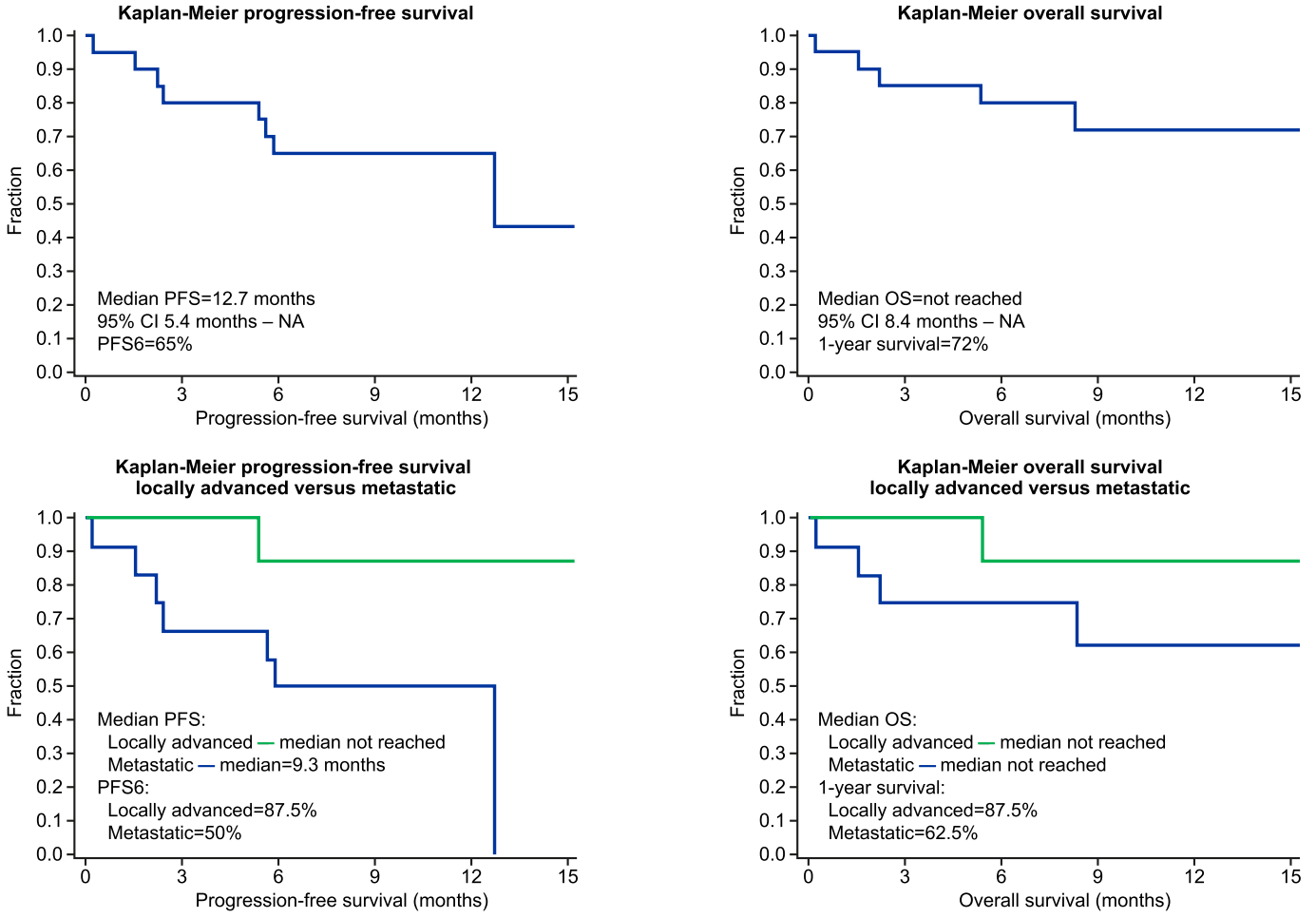

Fig. 5. Efficacy results of the TTFields + gemcitabine + nab-paclitaxel group of the PANOVA Study. Upper panel: PFS (left) and OS (right) Kaplan-Mayer curves for the Intent-to-treat population in the gemcitabine-nab-paclitaxel-TTFields group of the PANOVA Study. The median PFS was 12.7 months (95% CI 5.4, NA) and the median OS was not reached. Lower panel: Breakdown of PFS (left) and OS (right) K-M curves of the intent-to-treat population per disease stage.

median OS was not reached, and the 1-year survival rate was 72% (95% CI 44, 88). The median PFS has not been reached in locally advanced patients (PFS6 was 87.5%) and was 9.3 months in patients with metastatic disease; PFS6 was 50%. The median OS in both stages of disease had not been reached at the end of the follow up period. The 1-year survival rates were 87.5% and 62.5% in locally-advanced and metastatic patients, respectively.

Discussion

TTFields have demonstrated survival benefit in glioblastoma, an aggressive primary brain tumor [14,15]. The treatment benefit of TTFields in a number of malignancies, including non-small-cell lung cancer [16], ovarian carcinoma [17], mesothelioma [18] and brain metastases [19] is under investigation. Based on preclinical data of TTFields in pancreatic cancer models [12] we initiated this first proof-of-concept clinical study of TTFields in pancreatic cancer.

Patient characteristics in this study reflected the standard profile of patients enrolled in trials for advanced pancreatic adenocarcinoma. TTFields treatment was well tolerated by the majority of patients, and compliance was 68–78% of the recommended average daily use per study protocol ($\geq$18 h/day). TTFields-related dermatitis [15,16,18,20] resulting from skin irritation beneath the transducer arrays was reported in 50% of the patients; however, it only reached Grade 3 severity in 17.5% of the patients. In these patients a slight reduction in daily TTFields compliance to 12.5% allowed the skin to recover and for the patients to resume therapy. For patients with mild dermatitis, courses of topical anti-inflammatory agents alleviated skin symptoms.

No systemic toxicity was attributed to TTFields in the PANOVA study. The majority of systemic AEs were related to the underlying malignancy or systemic therapies administered, and are typical of the safety profile reported in other trials [3,4]. A higher number of hematological toxicities and peripheral neuropathy was reported in patients treated with nab-paclitaxel-gemcitabine compared to gemcitabine alone, as previously reported [4]. A limitation of this study is the small number of patients enrolled and the inclusion of both locally advanced and metastatic patients. The efficacy results observed are nevertheless encouraging. Compared to the results of a phase 3 trial comparing nab-paclitaxel plus gemcitabine with gemcitabine alone in metastatic patients [4], the preliminary survival results in this study are encouraging (median OS not reached vs. 8.5 months in the gemcitabine plus nab-paclitaxel arm of historical controls; 14.9 months vs. 6.7 months in the gemcitabine arm of historical controls). The same was true for 1-year survival rates (72% vs. 35% in the gemcitabine plus nab-paclitaxel arms, and 55% vs. 22% in the gemcitabine arms). No prospective data are available for locally-advanced patients treated with nab-paclitaxel. About 40% of the patients included in PANOVA who were locally advanced, showed encouraging results that justify further testing of TTFields in this disease setting. In the recently-published LAP07 study [21] of chemoradiotherapy vs. chemotherapy in locally advanced pancreatic cancer, the median OS with gemcitabine alone was 13.6 months (not yet reached in PANOVA) and the median PFS in LAP07 was 7.8 months (10.3 months in PANOVA). The comparison of the PANOVA efficacy results to historical data is also encouraging as a predictor for phase III testing [22].

In summary, the PANOVA trial has showed that the combination of TTFields with either gemcitabine or gemcitabine plus nab-paclitaxel are tolerable and safe for patients with adenocarcinoma of the pancreas. The preliminary efficacy results are encouraging and warrant further investigation in a prospective, randomized trial. The magnitude of benefit seen in locally advanced patients and the loco-regional application of TTFields suggest that further clinical testing should be focused on locally-advanced patients, in whom TTFields combination with chemotherapy may contribute to better disease control and potentially higher resectability rates. A phase III trial (PANOVA-3, NCT03377491) exploring the efficacy of TTFields concomitant with gemcitabine plus nab-paclitaxel in locally advanced pancreatic cancer is currently underway.

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Provision of study materials or patients: Sponsor and all investigators.
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