Tumor Treating Fields With Gemcitabine and Nab-Paclitaxel for Locally Advanced Pancreatic Adenocarcinoma: Randomized, Open-Label, Pivotal Phase III PANOVA-3 Study

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DOI https://doi.org/10.1200/JCO-25-00746

ABSTRACT

PURPOSE Tumor treating fields (TTFields) use alternating electric fields to disrupt cancer cell proliferation. Feasibility of TTFields therapy with gemcitabine/nab-paclitaxel was previously demonstrated in patients with advanced pancreatic adenocarcinoma. PANOVA-3 was designed to confirm safety and efficacy of TTFields in patients with unresectable locally advanced pancreatic adenocarcinoma (LA-PAC).

METHODS In this global phase III trial, 571 patients with newly diagnosed LA-PAC were randomly assigned to receive gemcitabine 1,000 mg/m² and nab-paclitaxel 125 mg/m² by intravenous infusion once a day on days 1, 8, and 15 of a 28-day cycle with or without TTFields. The primary end point was overall survival (OS). Secondary end points included progression-free survival (PFS), local PFS, pain-free survival, and overall response rate (ORR). Distant PFS was analyzed post hoc.

RESULTS OS was significantly prolonged using TTFields with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel (median, 16.2 months [95% CI, 15.0 to 18.0] *v* 14.2 months [95% CI, 12.8 to 15.4]; hazard ratio [HR], 0.82 [95% CI, 0.68 to 0.99]; $P = .039$). PFS, local PFS, and ORR were not improved. Pain-free survival was significantly prolonged with TTFields with gemcitabine/nab-paclitaxel (median, 15.2 months [95% CI, 10.3 to 22.8] *v* 9.1 months [95% CI, 7.4 to 12.7]; HR, 0.74 [95% CI, 0.56 to 0.97]; $P = .027$), as was distant PFS (median, 13.9 months [95% CI, 12.2 to 16.8] *v* 11.5 months [95% CI, 10.4 to 12.9]; HR, 0.74 [95% CI, 0.57 to 0.96]; $P = .022$). Device-related skin adverse events (AEs) were experienced by 76.3% of patients. Most device-related skin AEs were mild to moderate, with 7.7% of patients reporting a grade 3 AE.

CONCLUSION This study demonstrated significant OS, pain-free survival, and distant PFS benefits for TTFields with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel in patients with unresectable LA-PAC, with no additive systemic toxicity.

ACCOMPANYING CONTENT

Editorial, p. 2339

Listen to the podcast by Dr Li and Dr O'Reilly at https://ascopubs.org/do/jco-asco-annual-meeting-ttfields-locally-advanced-pancreatic-adenocarcinoma

Appendix

Data Sharing Statement

Data Supplement

Protocol

Accepted May 1, 2025
Published May 31, 2025

J Clin Oncol 43:2350-2360

View Online Article

INTRODUCTION

Most patients with pancreatic adenocarcinoma present with advanced disease at diagnosis,[1] which remains difficult to treat. With 5-year survival rates between 8% and 13%,[1,2] prognosis for patients with pancreatic adenocarcinoma is poor. The current standard of care for unresectable locally advanced pancreatic adenocarcinoma (LA-PAC) consists of chemotherapy with or without radiation[1,3] and is extrapolated from trials in metastatic or unspecified advanced disease.[4-8] Gemcitabine emerged as a standard of care in 1997[4]; the addition of nab-paclitaxel to gemcitabine improved median overall survival (OS) to 8.5 months.[7] First-line fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) increased OS to 11.1 months in metastatic disease but is recommended for patients with good performance status because of significant toxicities.[1,3,6] Novel therapies for advanced pancreatic adenocarcinoma have mostly been investigated in metastatic populations and less so in LA-PAC.[9-11] Targeted agents and immunotherapies such as erlotinib, olaparib, and

CONTEXT

Key Objective

Is the application of tumor treating fields (TTFields; electric fields that disrupt cancer cell processes, delivered by a portable device) concomitant with gemcitabine/nab-paclitaxel safe and effective in patients with unresectable locally advanced pancreatic adenocarcinoma (LA-PAC) compared with gemcitabine/nab-paclitaxel alone?

Knowledge Generated

In the phase III PANOVA 3 trial, TTFields therapy with gemcitabine/nab-paclitaxel significantly improved overall survival, pain-free survival, and distant progression-free survival compared with gemcitabine/nab-paclitaxel in patients with LA-PAC. The adverse events most commonly associated with TTFields therapy were skin events; TTFields therapy did not exacerbate the toxicity associated with chemotherapy or the disease itself.

Relevance *(E.M. O'Reilly)*

The combination of TTFields combined with chemotherapy in a population relatively understudied in clinical trials, locally advanced pancreas cancer, provides benefit and serves as a new standard paradigm in this patient population. The data are aligned with benefit observed from the use of this novel modality in other challenging to treat solid organ malignancies.*

*Relevance section written by *JCO* Associate Editor Eileen M. O'Reilly, MD, FASCO.

pembrolizumab have limited benefit and/or only benefit patients harboring specific alterations.[5,12,13]

Tumor treating fields (TTFields) is a noninvasive therapy using low-intensity electric fields that disrupt cellular processes critical for cancer cell viability and tumor progression.[14] TTFields have shown significant activity in vitro and in vivo in pancreatic cancer models, with enhanced efficacy with chemotherapy.[15] TTFields therapy with gemcitabine ± nab-paclitaxel was feasible, safe, and active in patients with advanced pancreatic adenocarcinoma in the phase II PANOVA trial (ClinicalTrials.gov identifier: NCT01971281).[16]

We present the results of the pivotal phase III PANOVA-3 trial (ClinicalTrials.gov identifier: NCT03377491), which evaluated the efficacy and safety of TTFields with gemcitabine/nab-paclitaxel as first-line therapy for unresectable LA-PAC.

METHODS

Trial Design and Oversight

PANOVA-3 was a global, randomized, open-label, multicenter, phase III clinical trial in patients with LA-PAC (196 sites in 20 countries; Data Supplement, online only). The study was approved by relevant ethics committees and competent authorities at participating sites and conducted in adherence with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. The study was designed by the sponsor (Novocure GmbH) and investigators. Data were collected by the investigators and analyzed by sponsor-employed or sponsor-funded statisticians. All authors contributed to data interpretation and vouch for completeness, accuracy, and fidelity of the study to the protocol.

Patients

Adults aged 18 years and older with unresectable, locally advanced, biopsy-confirmed, and previously untreated pancreatic adenocarcinoma were eligible if they had a life expectancy ≥3 months and Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2.[3,17] Patients could not have implantable electronic medical devices, such as pacemakers, in the torso or known severe hypersensitivity to medical adhesives or hydrogel or to one of the chemotherapies used. Full inclusion and exclusion criteria are provided in the Data Supplement.

Random Assignment and Treatment

Patients were centrally randomly assigned using an Interactive Web Response System in a 1:1 ratio to receive TTFields with gemcitabine/nab-paclitaxel or gemcitabine/nab-paclitaxel alone. Patients were stratified by ECOG PS (0/1 *v* 2) and region (North America, Eastern Europe, Western Europe, Israel, and rest of the world). TTFields therapy (150 kHz) was delivered by the NovoTTF-200T System (Novocure, Baar, Switzerland) with a recommended average usage of ≥75% (≥18 hours/d). Device support specialists provided guidance on device usage and prevention and management of skin adverse events (AEs). TTFields array placement was adapted to individual patients (Data Supplement, Fig S1); arrays were replaced two to three times/wk and shifted approximately 2 cm to prevent skin reactions. Usage was tracked by the device and sent to investigators monthly.

Nab-paclitaxel 125 mg/m² was infused intravenously once per day, immediately followed by gemcitabine 1,000 mg/m² intravenously once per day on days 1, 8, and 15 of each 28-day cycle. Treatment continued until local disease progression according to RECIST v1.1,[18] lack of compliance, intolerable toxicity, pregnancy, or withdrawal of consent.

Follow-up visits were every 4 weeks. Chest and abdomen computed tomography (CT), brain CT, or magnetic resonance imaging (if indicated) were performed every 8 weeks to assess disease progression.

Objectives

The primary objective was to determine whether first-line TTFields with gemcitabine/nab-paclitaxel improves OS, defined as the time from random assignment to the date of death or censoring, compared with gemcitabine/nab-paclitaxel alone. Secondary end points included progression-free survival (PFS), local PFS (time from random assignment until the date of local disease progression or death), 1-year survival rate, pain-free survival (time from random assignment until ≥20-point increase from baseline in a patient-reported visual analog scale [VAS] for pain or death),[19-21] puncture-free survival (time from random assignment until the first need for paracentesis or death), overall response rate (ORR; percentage of evaluable patients with partial or complete response between the time of random assignment and death), resectability rate (percentage of patients whose tumors were deemed resectable by a multidisciplinary team consisting of at least 1 surgeon, 1 medical oncologist, and 1 radiologist, and who underwent surgery), and safety (frequency and severity of investigator-recorded AEs using Common Terminology Criteria for Adverse Events v4.03).[22] A modified grading system was used for device-related skin AEs (Data Supplement, Table S1). Distant PFS (time from the date of random assignment until distant disease progression or death) was analyzed post hoc.

Statistical Analysis

Efficacy end points were analyzed in the intention-to-treat (ITT) population (all randomly assigned patients). OS, PFS, and ORR were also analyzed in a modified ITT (mITT) population (patients who completed ≥1 treatment cycle). Safety data were analyzed in patients who received any amount of study treatment. A sample size of 556 patients in the ITT population, assuming 10% loss to follow-up, was required to provide 80% power to detect a hazard ratio (HR) of death of <0.75 with TTFields with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel.

Kaplan-Meier survival curves were compared using a two-sided log-rank test stratified by region with $\alpha = .04794$ for OS and $\alpha = .05$ for other survival end points. After the primary end point was met, establishing the directionality of the treatment effect, 1-year survival rates were estimated using the Kaplan-Meier method and compared using a one-sided t-test.

To avoid statistical multiplicity, OS and PFS were analyzed hierarchically. Patients lost to follow-up or still in follow-up at the time of OS analyses were censored at the last date they were known to be alive. For PFS, local PFS, distant PFS, and pain-free survival analyses, patients who discontinued the study for any reason were censored at the last follow-up visit they were reported alive and event free or at study closure. For pain-free survival analysis, patients who had not experienced an event at study closure were censored at the date of their last VAS assessment. Deaths were considered events if they occurred within 8 weeks of the last VAS assessment. Patients with no VAS assessments were censored at the date of random assignment. ORR and resectability rate were assessed using one-sided Fisher exact test with $\alpha = .05$.

RESULTS

Patients and Treatment

Between May 2018 and March 2023, 571 patients were randomly assigned to either TTFields with gemcitabine/nab-paclitaxel (N = 285) or gemcitabine/nab-paclitaxel (N = 286; Fig 1). Patient baseline demographics and characteristics were balanced between study arms (Table 1). Overall, 52.4% of patients were female, with a higher proportion of them in the gemcitabine/nab-paclitaxel arm (Table 1). The number of patients who completed 1 treatment cycle and were included in the mITT analysis was 198 for the TTFields with gemcitabine/nab-paclitaxel arm and 207 for the gemcitabine/nab-paclitaxel arm; the reasons for patient discontinuation during the first cycle of treatment are presented in Figure 1.

At data cutoff on October 16, 2024, the median (range) duration of exposure to gemcitabine and nab-paclitaxel was 24.1 (0.1-232.4) and 23.0 (0.1-232.4) weeks, respectively, in the TTFields arm and 22.1 (0.1-134.1) and 21.4 (0.1-134.1) weeks, respectively, in the gemcitabine/nab-paclitaxel arm (Data Supplement, Table S2). The median duration of TTFields exposure was 27.6 weeks (range, 0.1-234.4); the median device usage was 62.1% (range, 0%-99.0%) of each day, and mean device usage was 59.3% (standard deviation, 21.2%) of each day.

A total of 146 patients (51.2%) in the TTFields with gemcitabine/nab-paclitaxel arm and 134 patients (46.9%) in the gemcitabine/nab-paclitaxel arm received salvage therapy (Data Supplement, Table S3). Distribution of salvage therapies administered was similar between treatment arms. By study end, 201 and 230 deaths had occurred in the TTFields with gemcitabine/nab-paclitaxel and gemcitabine/nab-paclitaxel arms, respectively.

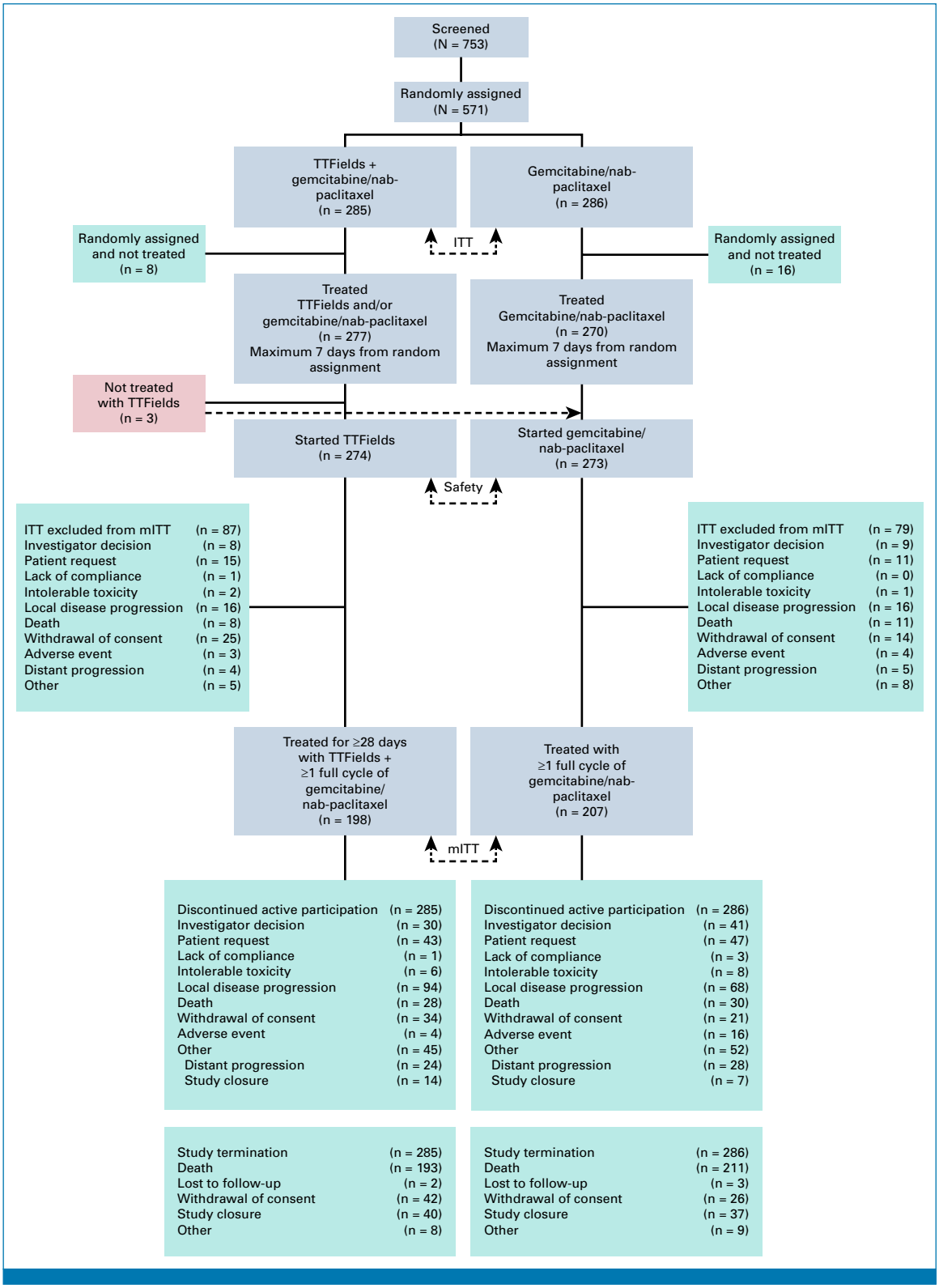

FIG 1. CONSORT diagram of enrolled patients. ITT, intention-to-treat; mITT, modified ITT; TTFields, tumor treating fields.

Primary Efficacy End Point

OS was statistically improved with TTFields with gemcitabine/nab-paclitaxel, with a median of 16.2 months (95% CI, 15.0 to 18.0) versus 14.2 months (95% CI, 12.8 to 15.4) with gemcitabine/nab-paclitaxel (HR, 0.82 [95% CI, 0.68 to 0.99]; log rank $P = .039$; Fig 2). The 1-year survival rate was significantly improved with concomitant TTFields

TABLE 1. Baseline Patient and Tumor Characteristics

Characteristic	TTFields With Gemcitabine/Nab-Paclitaxel (n = 285)	Gemcitabine/Nab-Paclitaxel (n = 286)	Overall (n = 571)
Age, years, median (range)	67 (31-90)	67.5 (40-88)	67 (31-90)
Sex, No. (%)			
Male	147 (51.6)	125 (43.7)	272 (47.6)
Female	138 (48.4)	161 (56.3)	299 (52.4)
Race, No. (%)			
American Indian or Alaska Native	9 (3.2)	4 (1.4)	13 (2.3)
Asian	44 (15.4)	44 (15.4)	88 (15.4)
Black	16 (5.6)	14 (4.9)	30 (5.3)
White	202 (70.9)	204 (71.3)	406 (71.1)
Other	3 (1.1)	5 (1.7)	8 (1.4)
Not reported	11 (3.9)	15 (5.2)	26 (4.6)
Region, No. (%)			
North America	123 (43.2)	125 (43.7)	248 (43.4)
Eastern Europe	43 (15.1)	42 (14.7)	85 (14.9)
Western Europe and Israel	62 (21.8)	61 (21.3)	123 (21.5)
Rest of the world	57 (20.0)	58 (20.3)	115 (20.1)
ECOG PS, No. (%)			
0	109 (38.2)	111 (38.8)	220 (38.5)
1	166 (58.2)	163 (57.0)	329 (57.6)
2	10 (3.5)	12 (4.2)	22 (3.9)
BMI, kg/m^2, No. (%)			
<25	166 (58.2)	174 (60.8)	340 (59.5)
≥25	117 (41.1)	108 (37.8)	225 (39.4)
Target lesion site, No. (%)			
Head of the pancreas	143 (50.2)	148 (51.7)	291 (51.0)
Body of the pancreas	79 (27.7)	80 (28.0)	159 (27.8)
Tail of the pancreas	9 (3.2)	18 (6.3)	27 (4.7)
Other	79 (27.7)	63 (22.0)	142 (24.9)
CA 19-9, No. (%)			
Low (≤37 U/mL)	48 (16.8)	44 (15.4)	92 (16.1)
Moderate (38-1,000 U/mL)	140 (49.1)	152 (53.1)	292 (51.1)
High (>1,000 U/mL)	88 (30.9)	79 (27.6)	167 (29.2)
Untested	9 (3.2)	11 (3.8)	20 (3.5)

Abbreviations: CA 19-9, carbohydrate antigen 19-9; ECOG PS, Eastern Cooperative Oncology Group performance status; TTFields, tumor treating fields.

versus gemcitabine/nab-paclitaxel (68.1% [95% CI, 62.0 to 73.5] *v* 60.2% [95% CI, 54.2 to 65.7]; *P* = .029). Median OS was also significantly prolonged in the mITT population (18.3 *v* 15.1 months; HR, 0.73; Data Supplement, Fig S2A).

Secondary Efficacy End Points

No significant difference in PFS was noted (median, 10.6 months [95% CI, 9.2 to 12.2] *v* 9.3 months [95% CI, 7.6 to 11.1]; HR, 0.85 [95% CI, 0.68 to 1.05]; log rank *P* = .137; Fig 3A). However, the 1-year PFS rate was higher with TTFields than with gemcitabine/nab-paclitaxel alone (43.9% [95% CI, 36.9 to 50.6] *v* 34.1% [95% CI, 27.1 to 41.2]; *P* = .026). Similar results were observed in the mITT population (Data Supplement, Fig S2B).

Local PFS was not significantly different between study arms in either population (Fig 3B; Data Supplement, Fig S2C). Pain-free survival was significantly prolonged with TTFields with gemcitabine/nab-paclitaxel compared with gemcitabine/nab-paclitaxel (median, 15.2 months [95% CI, 10.3 to 22.8] *v* 9.1 months [95% CI, 7.4 to 12.7]; HR, 0.74 [95% CI, 0.56 to 0.97], log rank *P* = .027; Fig 3C). In the TTFields with gemcitabine/nab-paclitaxel and gemcitabine/nab-paclitaxel arms, 244 and 243 patients were evaluable for response, respectively. ORR with TTFields with gemcitabine/

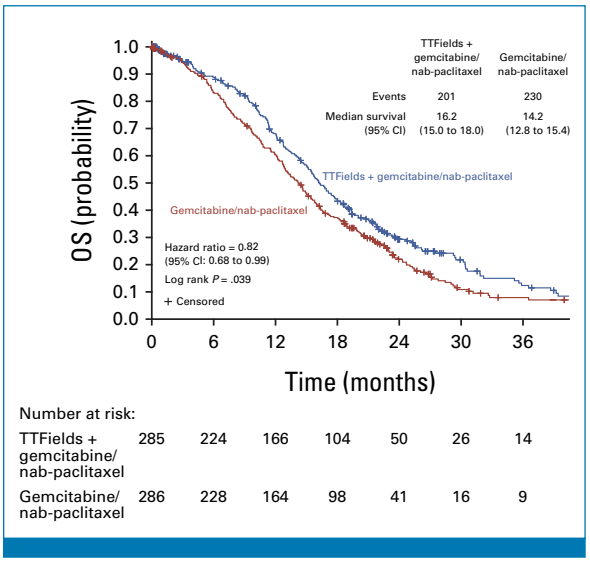

FIG 2. OS analysis for the ITT population. ITT, intention-to-treat; OS, overall survival; TTFields, tumor treating fields.

nab-paclitaxel was 36.1% (95% CI, 30.0 to 42.4) versus 30.0% (95% CI, 24.3 to 36.2) with gemcitabine/nab-paclitaxel (P = .094; Table 2).

No significant difference in resectability rate between patients receiving TTFields with gemcitabine/nab-paclitaxel and gemcitabine/nab-paclitaxel was observed (7.0% [95% CI, 4.3 to 10.6] *v* 10.1% [95% CI, 6.9 to 14.2]). Puncture-free survival was also not significantly different between study arms (75 and 78 events, respectively; P = .128).

Post Hoc Efficacy End Point

Distant PFS was significantly improved with TTFields with gemcitabine/nab-paclitaxel compared with gemcitabine/nab-paclitaxel (median, 13.9 months [95% CI, 12.2 to 16.8] *v* 11.5 months [95% CI, 10.4 to 12.9]; HR, 0.74 [95% CI, 0.57 to 0.96]; log rank P = .022; Fig 3D). Results were similar for the mITT population (Data Supplement, Fig S2D).

Safety

AEs of any cause were experienced by 97.8% and 98.9% of patients in the TTFields with gemcitabine/nab-paclitaxel and gemcitabine/nab-paclitaxel arms, respectively (Table 3). Grade ≥3 AEs were experienced by 88.7% and 84.3% of patients, respectively; the most frequent AEs were neutropenia (47.8% and 47.7%) and anemia (21.9% and 22.3%; Table 3).

Serious AEs (SAEs) occurred in 147 patients (53.6%) receiving TTFields with gemcitabine/nab-paclitaxel and 131 patients (48.0%) receiving gemcitabine/nab-paclitaxel (Table 3). The most common SAEs were sepsis (6.9% *v* 9.5%), cholangitis (5.8% *v* 3.7%), bile duct obstruction (5.5% *v* 3.3%), and pneumonia (5.1% *v* 3.3%; Data Supplement, Table S4). Most SAEs were related to chemotherapy or the underlying disease.

Device-related AEs were mainly mild-to-moderate skin reactions (Data Supplement, Table S5), which were experienced by 209 patients (76.3%); the most frequent events were dermatitis (n = 76, 27.7%), rash (n = 48, 17.5%), pruritus (n = 41, 15.0%), maculopapular rash (n = 33, 12.0%), and erythema (n = 29, 10.6%). Twenty-six patients (7.7%) experienced grade ≥3 device-related AEs, most frequently dermatitis (n = 8, 2.9%), rash (n = 4, 1.5%), and maculopapular rash (n = 3, 1.1%).

Device-related AEs leading to TTFields discontinuation occurred in 23 patients (8.4%); 47 (17.2%) and 43 (15.8%) patients discontinued chemotherapy because of chemotherapy-related AEs in the TTFields with gemcitabine/nab-paclitaxel arm and gemcitabine/nab-paclitaxel arm, respectively. No patient died due to AEs related to TTFields. Overall, four patients (0.7%) died due to chemotherapy-related AEs (Table 3). One patient receiving TTFields with gemcitabine/nab-paclitaxel experienced a SAE of diarrhea judged by the investigator to be related to gemcitabine/nab-paclitaxel and probably related to TTFields.

DISCUSSION

Improving OS in LA-PAC using a multidisciplinary approach has seen little progress in the past decade, with 5-year survival rates remaining low.[1,2] To date, the standard of care for this patient population has been extrapolated from phase III trials in metastatic cancer or mixed populations. Gemcitabine/nab-paclitaxel was established as the standard of care in 2013[7] in patients with metastatic disease. Since then, the single-arm phase II LAPACT trial[23] of gemcitabine/nab-paclitaxel showed OS of 18.8 months in the locally advanced population, while all phase III trials conducted in patients with unresectable locally advanced disease failed, notably the LAP-07 study[24] and the recent LAPIS trial of FOLFIRINOX or gemcitabine/nab-paclitaxel with or without pamrevlumab.[11] This may be explained in part by the numerous challenges in the design and conduct of controlled clinical trials in this population, including the lack of uniform criteria and observer variability in assessing vascular involvement, potential peritoneal carcinomatosis, and risk of complications due to biliary obstruction, which all affect patient suitability for surgical resection. In this context, it is particularly noteworthy that PANOVA-3 demonstrates for the first time, to our knowledge, significantly improved OS in unresectable LA-PAC.

Results for the key secondary end point pain-free survival and post hoc analysis of distant PFS support the benefit of TTFields with gemcitabine/nab-paclitaxel. PANOVA-3 is, to our knowledge, the first phase III trial to demonstrate a clinically and statistically meaningful improvement in pain-free survival (median, 15.2 *v* 9.1 months). Pain is a common and debilitating morbidity in patients with advanced

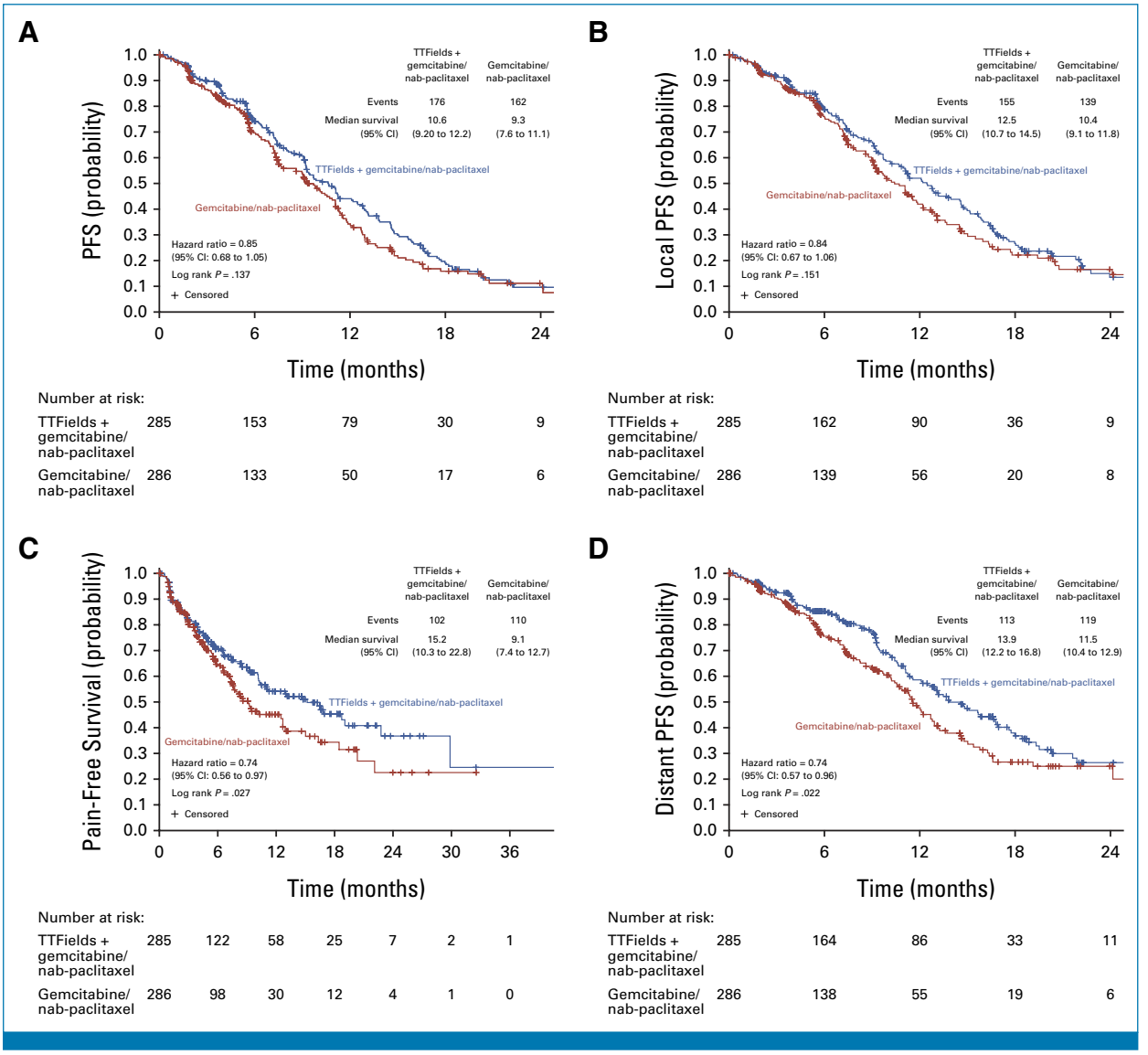

FIG 3. Survival analysis for the ITT population: (A) PFS, (B) local PFS, (C) pain-free survival, (D) distant PFS. ITT, intention-to-treat; PFS, progression-free survival; TTFields, tumor treating fields.

TABLE 2. ORR in the ITT Population

Variable	TTFields With Gemcitabine/Nab-Paclitaxel (n = 244)	Gemcitabine/Nab-Paclitaxel (n = 243)
Best overall response, No. (%)		
Complete response	3 (1.2)	0
Partial response	85 (34.8)	73 (30.0)
Stable disease	142 (58.2)	150 (61.7)
Progressive disease	14 (5.7)	20 (8.2)
ORR, % (95% CI)	36.1 (30.0 to 42.4)	30.0 (24.3 to 36.2)
Mean difference in ORR, % (95% CI)	6.0 (−2.4 to 14.4)	
One-sided *P*	.094	

Abbreviations: ITT, intention-to-treat; ORR, overall response rate; TTFields, tumor treating fields.

TABLE 3. Summary of AEs in the Safety Analysis Population

Event	TTFields With Gemcitabine/Nab-Paclitaxel (n = 274), No. (%)		Gemcitabine/Nab-Paclitaxel (n = 273), No. (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any AE	268 (97.8)	243 (88.7)	270 (89.9)	230 (84.2)
Serious AE	147 (53.6)	143 (52.2)	131 (48.0)	130 (47.6)
AE leading to device discontinuation	23 (8.4)		NA	
AE leading to chemotherapy discontinuation	47 (17.2)		43 (15.8)	
Serious AE leading to death	17 (6.2)		16 (5.9)	
AEs occurring in ≥20% of patients by system organ class and preferred term				
Blood and lymphatic system disorders				
Neutropenia	172 (62.8)	131 (47.8)	180 (65.9)	130 (47.6)
Anemia	161 (58.8)	60 (21.9)	158 (57.9)	61 (22.3)
Thrombocytopenia	122 (44.5)	39 (14.2)	133 (48.7)	32 (11.7)
Leukopenia	85 (31.0)	47 (17.2)	98 (35.9)	42 (15.4)
GI disorders				
Diarrhea	119 (43.4)	11 (4.0)	125 (45.8)	15 (5.5)
Nausea	107 (39.1)	11 (4.0)	121 (44.3)	7 (2.6)
Vomiting	82 (29.9)	7 (2.6)	79 (28.9)	15 (5.5)
Abdominal pain	73 (26.6)	11 (4.0)	83 (30.4)	12 (4.4)
Constipation	65 (23.7)	1 (0.4)	57 (20.9)	0
General disorders and administration site				
Fatigue	165 (60.2)	29 (10.6)	148 (54.2)	21 (7.7)
Edema peripheral	107 (39.1)	5 (1.8)	99 (36.3)	2 (0.7)
Pyrexia	74 (27.0)	6 (2.2)	64 (23.4)	2 (0.7)
Investigations				
Hepatic enzyme increased	75 (27.4)	35 (12.8)	72 (26.4)	24 (8.8)
Metabolism and nutrition disorders				
Anorexia	94 (34.3)	8 (2.9)	101 (37.0)	10 (3.7)
Hypokalemia	63 (23.0)	12 (4.4)	70 (25.6)	20 (7.3)
Musculoskeletal and connective tissue				
Musculoskeletal pain	70 (25.5)	3 (1.1)	79 (28.9)	5 (1.8)
Nervous system disorders				
Neuropathy peripheral	112 (40.9)	20 (7.3)	81 (29.7)	18 (6.6)
Skin and subcutaneous tissue disorders				
Alopecia	71 (25.9)	0	86 (31.5)	2 (0.7)
Rash	71 (25.9)	5 (1.8)	23 (8.4)	1 (0.4)
Dermatitis	82 (29.9)	8 (2.9)	8 (2.9)	0
Pruritus	61 (22.3)	0	23 (8.4)	0

Abbreviations: AE, adverse event; NA, not applicable; TTFields, tumor treating fields.

pancreatic adenocarcinoma and a predictor of survival.[25,26] Thus, by mitigating cancer pain, TTFields may preserve the quality of life of patients with LA-PAC, further supporting TTFields' utility as first-line treatment of this disease.

With a 27.6-week median treatment duration and 62% median daily usage, TTFields were well tolerated and not associated with systemic AEs in addition to those of chemotherapy. Most device-related AEs were mild-to-moderate skin reactions, consistent with previous trials of TTFields and real-world evidence[16,27-31] and can be managed with topical steroids and calcineurin cream, in addition to appropriate skin-care routines.[32] Additionally, the 8% discontinuation rate because of AEs and minimal systemic AEs indicate good tolerability.

Although the benefit observed here is clinically meaningful in this challenging patient population, the OS in both study arms was lower than recently reported in LAPIS[11] and LAPACT.[23] This is potentially attributable to differences in patient selection criteria and trial conduct. PANOVA-3 was conducted in globally distributed community and academic

centers during the COVID-19 pandemic. Although the OS benefit of 2 months (TTFields with gemcitabine/nab-paclitaxel: 16.2 months; gemcitabine/nab-paclitaxel: 14.2 months; HR, 0.82) might be considered modest in the ITT population, it was more pronounced in the mITT population, with a benefit of 3.2 months (18.3 *v* 15.1 months; HR, 0.77). The relatively high number of discontinuations in both arms during the first 28 days after inclusion was reportedly related mostly to disease progression or patients' decision which may be indicative of a higher number of patients with more advanced disease and/or micrometastases in PANOVA-3 than in LAPIS or LAPACT (eg, patients with ECOG PS of 2 and patients with high baseline carbohydrate antigen 19-9). In addition, it should be noted that the recent NAPOLI 3 trial showed clinically relevant OS benefit with liposomal irinotecan, fluorouracil, leucovorin, and oxaliplatin in patients with metastatic disease compared with gemcitabine/nab-paclitaxel (11.1 *v* 9.2 months), with a comparable HR of death of 0.83 to that reported for PANOVA-3.[33] Finally, the imbalance between male and female patients between the two treatment arms may have biased OS favorably in the control arm, as women with pancreatic cancer have been reported to have better survival than men in several studies or meta-analyses.[34-38]

Although OS and distant PFS were extended with TTFields and gemcitabine/nab-paclitaxel, ORR and PFS were not improved. Radiologic response to treatment in LA-PAC is difficult to assess as the distinction between local inflammation, fibrotic tissue, and true tumor progression may be challenging on CT scans.[39] In pancreatic cancer, OS is connected to the ability to systemically control the disease, highlighting the importance of the improvement in distant PFS observed in this study. Further analyses are needed to explore the lack of difference in ORR and local PFS, characterize progression patterns in patients treated with TTFields, and identify prognostic and predictive factors of TTFields benefit.

In addition to the antimitotic effects of TTFields,[40] preclinical evidence has shown induction of adaptive immunity through activation of inflammasomes in glioblastoma,[41] while in lung cancer, models have shown that TTFields induce immunogenic cell death.[42] Furthermore, TTFields application reduced the spread, seeding, and growth of lung metastases from solid tumors in rabbits, an effect accompanied by extensive immune cell infiltration of the primary tumor.[43] Thus, TTFields may exert a systemic immune effect, potentially limiting metastatic spread and/or controlling already existing micrometastases, which is consistent with the observed improvement in distant PFS.

There is preclinical evidence that TTFields impair DNA damage repair[44] and induce DNA replication stress[40] as well as ER stress, triggering immunogenic cell death.[42] Future development of TTFields in pancreatic adenocarcinoma includes concomitant use of TTFields with FOLFIRINOX and other novel therapies. Whether the proimmunogenic effects of TTFields can sensitize pancreatic adenocarcinoma to immunotherapy is currently being investigated in an ongoing trial of TTFields concomitant with first-line gemcitabine/nab-paclitaxel and the PD-L1 inhibitor atezolizumab in metastatic pancreatic adenocarcinoma (PANOVA-4; ClinicalTrials.gov identifier: NCT06390059).

The survival benefit observed in this study was achieved with a median daily device usage of 62%, which is below the 75% recommended in the study protocol on the basis of data from a phase III study of TTFields in patients with glioblastoma.[45] However, usage requirements may vary according to the region of the body where the therapy is applied. Consistent with these findings, in the LUNAR study in patients with metastatic non–small cell lung cancer that has progressed on or after platinum-based therapy, adding TTFields therapy to either a PD-(L)1 inhibitor or docetaxel significantly extended OS with a median device usage of 56% over the first 3 months.[28] Additional analyses are needed to determine optimal usage recommendations for pancreatic cancer.

Limitations of the PANOVA-3 trial include investigator assessment of CT scans, which may have influenced patient selection as well as interpretation of PFS and ORR. The open-label study design and lack of a sham device in the control arm could have affected objective assessments despite rigorous data collection methodologies aimed at minimizing bias. While postprogression chemotherapy was permitted in both arms, neither cross-over to TTFields at progression in the control arm nor continuation of TTFields beyond local progression was permitted. This limits insights into TTFields' potential benefits in later-line treatment.

Although the study protocol included objective criteria for defining unresectable disease, no objective criteria were defined for assessing resectability during the treatment phase. Additionally, staging laparoscopy and centralized imaging review were not mandated across all sites during screening, potentially leading to the inclusion of patients with Stage IV disease or borderline resectable cases. Similarly, during treatment, the lack of a centralized approach to evaluate response and resectability introduced variability. These limitations may affect the ability to draw definite conclusions about the impact of TTFields on resectability. Despite these challenges, resectability rates were consistent with the existing literature and there was no difference between the two treatment arms.

However, potential imbalances because of the lack of systematic centralized multidisciplinary review were mitigated by the large size of this study, which reflects real-world practice and validates the clinical significance of the survival benefit observed in the TTFields arm. While the implementation of the TTFields therapy delivery system is home based, with integrated patient support from the manufacturer, carrying the device may be an obstacle for some patients. Caregivers' assistance as well as skin prophylaxis guidelines will be essential to help patients adopt this new treatment.

In conclusion, PANOVA-3, the only phase III trial specifically in unresectable LA-PAC to show a significant OS benefit, establishes that TTFields with gemcitabine/nab-paclitaxel is an effective treatment of unresectable LA-PAC. With clinically meaningful improvements in OS, pain-free survival, and distant PFS and no exacerbation of systemic toxicity, TTFields therapy offers a potential treatment advance in the management of LA-PAC. The PANOVA-3 trial may have implications beyond LA-PAC, because it further supports the potential of concomitant use of TTFields therapy with the existing standard of care in solid tumors across a range of therapeutic settings.

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DISCLAIMER

The sponsor was involved in the study design, collection, analysis, and interpretation of data, as well as data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors

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PRIOR PRESENTATION

Presented at the ASCO Annual Meeting, Chicago, IL, May 30-June 4, 2025.

SUPPORT

Supported by Novocure Inc. H.M.B. acknowledges support under a grant awarded under the K-12 NCI grant program (K12CA090628) to study TTFields.

CLINICAL TRIAL INFORMATION

NCT03377491 PANOVA-3

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-25-00746.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-25-00746.

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ACKNOWLEDGMENT

The authors thank the patients, their families, and all investigators involved in this study. We thank Professor Daniel Von Hoff for inspiring the design of the study and supporting the development of the clinical protocol, and for serving as the first lead for the PANOVA-3 study and for pancreatic cancer research in general. We thank him for his trust and continued guidance during the entire study period. Statistical analysis was performed by sponsor-funded personnel, including Stav Edelstein, PhD; Avital Shalom, PhD; and Gitit Lavy-Shahaf, PhD; Novocure Ltd, Israel, and John Shin, MD, PhD, and Novocure Inc, USA. Medical writing support under the direction of the authors was provided by Janin Knop, PhD; Novocure GmbH, Switzerland; Chelsea Higgins, PhD, CMPP, Novocure Inc, USA; Christine Mormont, PhD; Novocure Canada Inc; Christine el Jundi, PhD; and Andrew Noble, CMPP, Bioscript Group Ltd, UK. Writing and editorial support provided by the Bioscript Group was funded by Novocure Inc and conducted according to Good Publication Practice guidelines (GPP 2022). The PANOVA-3 Study Investigators are listed in Appendix Table A1 (online only).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Tumor Treating Fields With Gemcitabine and Nab-Paclitaxel for Locally Advanced Pancreatic Adenocarcinoma: Randomized, Open-Label, Pivotal Phase III PANOVA-3 Study

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Consulting or Advisory Role: Sanofi/Aventis, Celgene, Roche, QED Therapeutics, Baxter, Incyte, Servier, Lilly, Ipsen, AstraZeneca, MSD, Eisai, Prime Oncology, Ability Pharma, Advance Medical, BioLineRX, Zymeworks, Aptitude Health, Basilea, Medscape, Novocure, Paraxel, Ellipses Pharma, Janssen, MFAR, Marketing Farmacéutico & Investigación Clínica, Amgen, Esteve, Arcus Biosciences, Boehringer Ingelheim, Taiho/Keylates, Alligator Bioscience, PEGASCY, Astellas Pharma, Revolution Medicines
Research Funding: Celgene (Inst), Agios (Inst), ASLAN Pharmaceuticals (Inst), Bayer (Inst), Roche (Inst), Genentech (Inst), AstraZeneca (Inst), Immunomedics (Inst), Lilly (Inst), Merrimack (Inst), Millennium (Inst), Novocure (Inst), Pfizer (Inst), Pharmacyclics (Inst), AbbVie (Inst), Ability Pharma (Inst), Amc Medical Research (Inst), Amgen (Inst), Armo Biosciences (Inst), Basilea Pharmaceutica International (Inst), Beigene (Inst), Keralty Group (Inst), BiolineRx (Inst), Blueprint Medicines (Inst), Boston Biomedical (Inst), Bristol Myers Squibb (BMS) (Inst), Cantargia AB (Inst), Eisai (Inst), Erytech Pharma (Inst), Fibrogen (Inst), Halozyme (Inst), Incyte (Inst), Ipsen (Inst), Loxo (Inst), Medimmune (Inst), Merck Sharp & Dohme (Inst), Nelum Corp (Inst), Novartis (Inst), OncoMed (Inst), VCN Biosciences (Inst), Zymeworks (Inst)
Travel, Accommodations, Expenses: Merck, H3 Biomedicine, Sanofi, Celgene, Servier, Prime Oncology, Incyte, AstraZeneca

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Study Sites and Principal Investigators

Site Name	Location	Principal Investigator
United States		
Tennessee Oncology	Nashville, TN	David Spigel (formerly Joanna Bendell)
Cedars Sinai	Los Angeles, CA	Arsen Osipov (formerly Andrew Hendifar)
Ochsner Clinic Foundation	New Orleans, LA	Marc Matrana
Associated Neurologists of Southern Connecticut	Fairfield, CT	Nicholas Blondin
University of Minnesota	Minneapolis, MN	Emil Lou
The University of Arizona Cancer Center	Tucson, AZ	Rachna Shroff (formerly Hani Babiker)
Texas Oncology	Dallas, TX	Douglas Orr (formerly Carlos Becerra)
Comprehensive Cancer Center of Nevada	Las Vegas, NV	Michael Anderson (formerly Fadi Braiteh)
Karmanos Cancer Center	Detroit, MI	Anthony Shields (formerly Philip Philip)
Norton Cancer Institute	Louisville, KY	John Hamm
Beth Israel Deaconess Medical Center (BIDMC)	Boston, MA	Andrea Bullock (Interim PI is Mary Peters; formerly Benjamin Schlecter)
Erlanger Health System	Chattanooga, TN	Sumana Nagireddy
West Virginia University	Morgantown, WV	Joanna Kolodney
Banner MD Anderson Cancer Center	Gilbert, AZ	Tomislav Dragovich
Seattle Cancer Care Alliance	Seattle, WA	Andrew Coveler
Pacific Cancer Medical Center	Anaheim, CA	Ajit Maniam
Virginia Mason Medical Center	Seattle, WA	Vincent Picozzi
Novant Health Oncology Specialists	Winston-Salem, NC	Judith Sears
HCA Midwest Division of Sarah Cannon Research Institute	Kansas City, MO	Joseph Stilwill (formerly Peter Van Veldhuizen, Jaswinder Singh)
Laura and Issac Perimutter Cancer Center at NYU Langone	Lake Success, NY	Francis Arena
Mount Sinai Comprehensive Cancer Center (MSCCC)	Miami Beach, FL	Mike Cusnir
Vita Medical Associates	Bethlehem, PA	Anna Niewiaroska
Loyola University Chicago	Maywood, IL	William Small
University of Kansas Cancer Center (KUCC)	Fairway, KS	Anup Kasi
Boca Raton Clinical Research Medical Center	Plantation, FL	Jason Tache
Florida Hospital Tampa	Tampa, FL	Sharona Ross (formerly Alexander Rosemurgy)
Dignity Health Cancer Institute	Carmichael, CA	Samer Shihabi
Florida Cancer Specialists	Petersburg, FL	Sunil Gandhi
Florida Cancer Specialists	Myers, FL	James Reeves
Renown Regional Medical Center	Reno, NV	Garrett Green
Piedmont Cancer Institute (PCI)	Atlanta, GA	Trevor Feinstein
Nebraska Methodist Hospital	Omaha, NE	Timothy Huyck
Geisinger Medical Center	Danville, PA	Nadia Ramdin (formerly Anand Mahadevan)
North Shore University Health	Evanston IL	Robert Marsh (formerly Marisa Hill)
University of Maryland Comprehensive Cancer Center	Baltimore, MD	Yixing Jiang
University of Oklahoma Health Sciences Center	Oklahoma City, OK	Hassan Hatoum
Arizona Oncology Associates	Tucson, AZ	Sudhir Manda
Oncology and Hematology Associates of Southwest Virginia	Roanoke, VA	Mark Kochenderfer
Texas Oncology—Bedford	Bedford, TX	Henrik Illum
Texas Oncology—Tyler	Tyler, TX	Donald Richards
Texas Oncology—El Paso Cancer	El Paso, TX	Panagiotis Valilis
Baylor, Scott and White Medical Center	Temple, TX	Lucas Wong

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TABLE A1. Study Sites and Principal Investigators (continued)

Site Name	Location	Principal Investigator
Cancer & Hematology Centers of Western Michigan	Grand Rapids, MI	Sreenivasa Chandana
Florida Hospital Cancer Institute	Orlando, FL	Herbert Newton
Houston Methodist Cancer Center and Institute of Academic Medicine	Houston, TX	Maen Abdelrahim
Cotton O'Neil Cancer Center Stormont Vail Health Care	Topeka, KS	David Einspahr
Illinois Cancer Specialist	Arlington Heights, IL	Richard Siegel
Texas Oncology—Beaumont Mamie	Beaumont, TX	Scott McKenney
Maryland Oncology Hematology	Columbia, MD	Mohit Narang
Willamette Valley Cancer Institution	Eugene, OR	Marc Uemura
NY Presbyterian Queens	Flushing, NY	Higinia Cardenes (formerly Steven DiBiase)
Infirmary Health	Mobile, AL	Kannan Thanikachalam (Formerly John Russell)
White Plains Hospital	White Plains, NY	Joshua Raff
Vista Oncology Group	Olympia, WA	Joseph Ye
Sutter Institute for Medical Research	Sacramento CA	Deepti Behl
Rush University Medical Center	Chicago, IL	Audrey Kam (formerly Ashiq Masood)
Methodist Richardson Cancer Center	Dallas, TX	Paul DeRose
Umass Memorial Hospital	Worcester, MA	Ali Tasneem (formerly Venu Bathini)
Lynn Cancer Institute, Boca Raton Regional Hospital	Boca Raton, FL	Warren Brenner
Grandview Health	Birmingham, AL	Jennifer De Los Santos
General Physician Cancer Care—Williamsville	Williamsville, NY	James Wang
Hematology Oncology Central Maine Medical Center (CMMC)	Lewiston ME	Daniel Rausch
Cancer Specialist of North Florida	Fleming Island, FL	Gaurav Trikha
Providence Medical Foundation	Fullerton, CA	David Park
Gabrail Cancer Center Research	NW Canton, OH	Nashat Gabrail
Toledo Clinic Cancer Center	Toledo, OH	Rex Mowat
OptumCare	Las Vegas, NV	Khawaja Jahangir
Tennessee Cancer Specialists	Knoxville, TN	Robert Schumaker
Princeton Radiation Oncology (Regional Cancer Care Associates LLC)	Plainsboro, NJ	Edward Soffen
Bassett Cancer Institute	Cooperstown, NY	Eric Bravin
Ridley Tree Cancer Center	Santa Barbara, CA	Mukul Gupta
Mayo Clinic Jacksonville	Jacksonville, FL	Hani Babiker
St Elizabeth Healthcare	Edgewood, KY	Ivan Bedoya-Apraez
St Helena Healthcare—Martin O'Neil Cancer Center	St Helena, FL	Tyler Kang
Canada		
Centre Hospitalier Universitaire de Sherbrooke CIUSSS de l'Estrie—CHUS	Sherbrooke, Québec	Frederic Lemay
London Health Science Center, London Regional Cancer Program	London, ON	Mark Vincent
Centre Hospitalier de l'Universite de Montreal—CHUM CIUSSS de l'Estrie—CHUS	Montreal, QC	Richard Letourneau
Germany		
Klinik München Bogenhausen	München	Martin Fuchs
Universitätsklinikum Ulm	Ulm	Thomas Theodor Werner Seufferlein
Carl-von-Basedow-Klinikum Saalekreis	Merseburg	Christine Doehring (formerly Jorn Russel)
Frau Dr med Ursula Vehling-Kaiser	Dingolfing	Mike Haberkorn
Medizinische Hochschule Hannover, Klinik fur Gastroenterologie, Hepatologie und Endokrinologie	Hannover	Arndt Vogel
Bonifatius Hospital Hematology and Oncology Lingen	Lingen (Ems)	Karen Russwurm
Klinikum Chemnitz gGmbH	Chemnitz	Jack Chater

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TABLE A1. Study Sites and Principal Investigators (continued)

Site Name	Location	Principal Investigator
Switzerland		
Fribourg Hôpital	Fribourg	Marc Küng
Winterthur Kantonsspital	Winterthur	Sabine Schacher
Israel		
Haifa Rambam Medical Center	Haifa	Maria Passhak (formerly Valeriya Semenisty)
Tel Aviv Sourasky Medical Center	Tel Aviv	Ravit Geva
Hadassah Medical Center	Jerusalem	Ayala Hubert
Rabin Medical Center	Petah Tikva	Salomon Stemmer
Sheba Pancreatic Cancer Center		Talia Golan
France		
Institut de Cancérologie de l'Ouest (ICO)	St Herblain	Hélène Senellart
Hopital Saint-Antoine	Saint-Antoine	Isabelle Trouilloud
Centre Léon Bérard	Lyon	Christelle de la Fouchardière (formerly Pauline Rochefort)
Hopital haut-Léveque CHU Bordeaux—Service d'Hépato-Gastroentérologie et d'Oncologie digestive	Bordeaux	Jean-Frederic Blan
Strasbourg Oncologie Liberale	Strasbourg	Luis-Marie Dourthe
Hospital Group Bretagne Sud	Lorient	Florence Le Roy (formerly Marie Clemence Daniel; formerly Joelle Egreteau)
Centre Armoricain d'Oncologie—CARIO	Plerin	Jerôme Martin-Babau
Centre de Lutte Contre le Cancer (CLCC)—Centre Paul Strauss	Strasbourg	Meher Ben Abdelghani
Austria		
Salzburg Uniklinik fur Innere Medizin	Salzburg	Richard Greil
Landes-Krankenhaus Steyr	Steyr	Georg Schreil
Medical University of Graz	Graz	Armin Gerger
Klinikum Klagenfurt am Wörthersee	Wörthersee	Wolfgang Eisterer
Spain		
BARCELONA: Vall d'Hebron	Barcelona	Teresa Macarulla Mercadé
Madrid, HM Hospitales CIOCC	Madrid	Antonio Cubillo
Instituto Oncologico Dr Rosell	Barcelona	Francesc Valladares Pons
Hospital Universitario Ramon Y Cajal Carretera de Colmenar Viejo	Madrid	Carmen Guillen Ponce
Hospital Regional Universitario de Málaga	Málaga	Inmaculada Ales Diaz (formerly Manuel Benavides Orgaz)
Marqués de Valdecilla University Hospital	Santander	Fernando Rivera
Elche Hospital General Universitario	Elche	Javier Gallego Plazas
Inst. Valenciano de Oncologia	Valencia	Ricardo Yaya
Pamplona Clinica Universidad de Navarra	Pamplona	Mariano Ponz Sarvise
Italy		
Università Campus Bio-Medico	Rome	Bruno Vincenzi
Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino	Torino	Mario Airoldi
Ospedale Civile Ss. Antonio e Biagio e Cesare Arrigo	Alessandria	Giovanna Bellotti
Ospedale San Giovanni	Rome	Domenico Cristiano Corsi
Azienda Ospedaliero-Universitaria Careggi	Firenze	Lorenzo Antonuzzo
Czech Republic		
Olomouc Fakultni Nemocnice	Olomouc	Bohuslav Melichar
Nemocnice Na Bulovce	Prague	Petra Holeckova

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TABLE A1. Study Sites and Principal Investigators (continued)

Site Name	Location	Principal Investigator
General University Hospital in Prague	Prague	Lubos Petruzelka
Nemocnice Novy Jicin	Novy Jicin	Rostislav Kotasek
Masaryk Institute of Oncology	Brno	Radim Nemecek
Belgium		
University of Leuven	Leuven	Eric van Cutsem
Research UZ/KU Leuven	Leuven	Jean-Luc van Laethem
Clinique Universutaire Saint Luc—Institut Roi Albert	Woluwe-Saint-Lambert	Ivan Borbath
South Korea		
Chonnam National University Hwasun Hospital	Hwasun	Jun Eul Hwang
Dong-A University Hospital	Busan	Sung Yong Oh
Gachon University Gil Hospital	Incheon	Sun Jin Sym
Inha University Hospital	Incheon	Moon Hee Lee
Keimyung University, Dongsan hospital	Daegu	Jin Young Kim
Korea University Guro Hospital	Seoul	Sang Cheul Oh
National Cancer Center	Goyang	Woo Jin Lee
Samsung Medical Center	Seoul	Joon Oh Park
Seoul National University Bundang Hospital	Seongnam-si	Jin Won Kim
The Catholic University of Korea, Seoul St Mary's Hospital	Seoul	Myung Ah Lee
Severance Hospital	Seoul	Hye Jin Choi
Ajou University Hospital	Suwon	Seok Yun Kang
CHA Bundang Medical Center	Seongnam-si	Hong Jae Chon
Poland		
WARSAW: M.Sklodowska-Curie Institute of Oncology	Warsaw	Lucjan Wyrwicz
Klinika Onkologii Uniwersytetu Medyczneg	Poznan	Rodryg Ramlau
Mrukmed Medical Center	Rzeszow	Andrzej Mruk
Uniwersytecki Szpital Kliniczny we Wrocławiu	Wroclaw	Beata Freier
Oncology and Radiotherapy Clinic University Clinical Center Non-Invasive Medicine Center	Warsaw	Ewa Kosakowska
Hungary		
Bacs-Kiskun County Teaching Hospital	Kecskemet	Judit Kocsis
Jasz-Nagykun-Szolnok Megyei Hetenyi Geza	Szolnok	Tibor Csoszi
National Institute of Oncology	Budapest	Erika Hitre
Tolna County Balassa Janos Hospital	Szekszard	Yousuf Al-Farhat
Békés Megyei Pándy Kálmán Kórháza Megyei Onkológiai Központja	Gyula	Ali Bassam
China		
Beijing Cancer Hospital	Beijing	Chunyi Hao
Jilin Guowen Hospital	Gongzhuling City, Jilin Province	Bo Liang
Henan Provincial People's Hospital	Henan	Shundong Cang
Shanghai Changhai Hospital	Shanghai	Gang Jin
Xingtai People's Hospital	Xiangtai	Changzeng Zuo
The First Affiliated Hospital of Zhengzhou University	Zhengzhou	Lijie Song
First Affiliated Hospital of Xi'an Jiaotong University	Xi'an	Zheng Wu
Beijing University People's Hospital	Beijing	Jie Gao
Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology	Wuhan	Tao Zhang
Shanxi Province Cancer Hospital	Taiyuan	Yusheng Wang
Tongji Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology	Wuhan	Xinaglin Yuan

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TABLE A1. Study Sites and Principal Investigators (continued)

Site Name	Location	Principal Investigator
Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University	Guangzhou	Zhihua Li
Guangdong Provincial People's Hospital	Guangzhou	Rufu Chen
Bethune First Hospital of Jilin University	Changchun	Wei Li
Sir Run Run Shaw Hospital affiliated to Zhejiang University School of Medicine	Hangzhou	Xiujun Cai
Linyi Cancer Hospital	Linyi	Zhizhen Zhu
Harbin Medical University Cancer Hospital	Harbin	Yuxian Bai
Beijing Union Medical College Hospital	Beijing	Chunmei Bai
Hong Kong		
Queen Mary Hospital	Hong Kong	Thomas Yau
Greenslopes Oncology	Woolloongabba	Warren Joubert
Australia		
Westmead Hospital	Westmead	Ka Yeung Mark Wong
Sydney Adventist Hospital	Wahroonga	Gavin Marx
St John of God Murdoch Hospital	Murdoch	Kynan Feeney
Monash Health	Clayton	Marion Harris
Croatia		
UHC Zagreb	Zagreb	Ana Misir (formerly Zoran Rakušić)
Brazil		
Instituto Ribeiraopretano de Combate ao Cancer	Ribeirão Preto	Adilson Faccio
Instituto Brasileiro de Controle do Cancer (IBCC)	São Paulo	Felipe Cruz
Hospital de Clínicas de Porto Alegre	Porto Alegre	Sergio De Azevedo
COI	Rio De Janeiro	Ana Paula De Souza Victorino
Ynova Pesquisa Clinica	Florianópolis	Tadeu Ferreira de Paiva Jr
Hospital de Caridade de Ijui (HCI)	Ijui	Fabio Andre Franke
Centro de Pesquisa Clínica Multidisciplinar da Santa Casa de Porto Alegre	Porto Alegre	Katsuki Arima Tiscoski
Hospital São Lucas da PUCRS	Porto Alegre	Gabriel Parolla
Oncoclinicas Rio de Janeiro S.A	Rio De Janeiro	Flora Lilno
Instituto D'Or de Pesquisa e Ensino—Matriz Rio de Janeiro	Rio De Janeiro	Mariana Bruno Siqueira
Instituto D'Or de Pesquisa e Ensino—Filial Salvador (Hospital São Rafael)	Rio De Janeiro	Marcos Lyra
Instituto D'Or de Pesquisa e Ensino	Rio De Janeiro	Paulo Hoff
Mexico		
Accelerium Clinical Research	Monterrey	Jose Luis Martinez Lira
Centro Potosino de Investigación Médica	San Luis Potosí	Dolores Mendoza Oliva
Mediadvance Clinical	Chihuahua	Arturo Vazquez
Centro de Investigación Médica Aguascalientes (CIMA)	Aguascalientes	Jesus Elvis Cabrera Luviano
FAICIC Clinical Research	Veracruz	Erika Castillo Gutierrez
Clinstile S.A de C.V	Monterrey	Vanessa Rosas Camargo
Centro de Estudios de Alta Especialidad de Sinaloa	Mazatlán	Cristian Chavez Guerra
Phylasis Clinicas Research	Izcalli	Osvaldo Hernandez Flores
Hospitales Star Medica	Izcalli	David Orta Cortez
PCR Toluca Corporativo Hospital Satelite	Toluca De Lerdo	Saul Campos
Clinica Integral Internacional de Oncologia	Puebla	Ivan Romarico González Espinoza
Hospital Angeles—Centro Medico del Potosi	Potosi	Jessica Reyes Contreras
Practice of Centro Hemato Oncologico Privado	Toluca De Lerdo	Angel Gomez Villanueva
Hospital Universitario "Dr Jose Eleuterio Gonzalez"	Monterrey	Omar Zayas Villanueva