LAPIS: A Phase III Randomized, Placebo-Controlled, Double-Blind Trial of Neoadjuvant Pamrevlumab With Chemotherapy for Patients With Locally Advanced Pancreatic Cancer

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ABSTRACT

PURPOSE Pamrevlumab demonstrated favorable safety and therapeutic potential in locally advanced pancreatic cancer (LAPC) in phase I/II trials (ClinicalTrials.gov identifiers: NCT01181245; NCT02210559). LAPIS (phase III; ClinicalTrials.gov identifier: NCT03941093) evaluated the efficacy and safety of adding pamrevlumab versus placebo to chemotherapy for patients with LAPC.

METHODS Eligible patients (randomly assigned 1:1) received investigator's choice of chemotherapy (gemcitabine plus nab-paclitaxel or folinic acid, fluorouracil, irinotecan, and oxaliplatin per the standard protocol) with either pamrevlumab (35 mg/kg every 2 weeks on days 1 and 15 before chemotherapy; additional dose on day 8 of cycle 1; arm A) or placebo (arm B) for up to six cycles. Patients were assessed for surgical eligibility based on a composite of biomarkers (carbohydrate antigen 19-9, fluorodeoxyglucose positron emission tomography [FDG-PET] imaging, RECIST v1.1 response criteria, and resectability status), guided by an independent surgical review panel. The primary end point was overall survival (OS). Treatment-emergent adverse events were monitored to evaluate safety.

RESULTS Of 284 patients, 143 and 141 were randomly assigned to arms A and B, respectively (median [range] age, 65.0 [31-90] years; 53.2% male). The median OS was 17.3 versus 17.9 months for arms A and B, respectively, and the primary end point was not met (hazard ratio [95% CI], 1.08 [0.83 to 1.41]; $P = .5487$). No appreciable increase in toxicity was noted in the pamrevlumab arm. One pamrevlumab-related death occurred in arm A.

CONCLUSION LAPIS did not meet its primary end point in this large, phase III trial featuring a design including FDG-PET imaging for response assessment, defined surgical eligibility criteria, an independent surgical review panel, and a composite event-free survival end point, collectively enhancing assessment rigor and clinical applicability and potentially establishing future standards for LAPC trials.

ACCOMPANYING CONTENT

- Data Supplement
- Protocol
- Reflexivity Statement

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INTRODUCTION

Pancreatic cancer (PC) is expected to become the second leading cause of cancer mortality in the United States by 2030.[1,2] Approximately 25% to 30% of patients with PC are diagnosed with locally advanced disease (LAPC)[3] that is considered surgically unresectable.[4] LAPC is aggressive and chemoresistant, with <15% to 20% of patients becoming eligible for curative resection after chemotherapy/radiation-based induction treatment and a median overall survival (OS) of 15 to 18 months.[4-7]

One novel therapeutic approach for LAPC is to target the tumor microenvironment (TME), which may overcome both drug and nondrug resistance mechanisms.[4,8,9] Connective tissue growth factor (CTGF), a glycoprotein that modulates tissue remodeling and fibrosis, is overexpressed in PC and contributes to tumorigenesis, and elevated CTGF correlates with worse survival outcomes for patients with LAPC.[10-13] The hypothesis that anti-CTGF therapy alters the TME in PC contrasts with the model proposed by Neesse et al, which emphasizes X-linked inhibitor of apoptosis protein (XIAP) suppression as the primary mechanism. While the exact

CONTEXT

Key Objective

LAPIS was a randomized, blinded, international, phase III trial comparing investigator's choice chemotherapy (gemcitabine/nab-paclitaxel or folinic acid, fluorouracil, irinotecan, and oxaliplatin) with or without pamrevlumab in untreated locally advanced pancreatic cancer (LAPC); overall survival (OS) was the primary end point.

Knowledge Generated

Pamrevlumab in addition to chemotherapy did not improve OS, event-free survival (EFS), progression-free survival, or objective response rate, nor did it add toxicity. LAPIS illustrated the importance of key trial design elements in LAPC, including biological response parameters (ie, carbohydrate antigen 19-9 and fluorodeoxyglucose positron emission tomography [FDG-PET] uptake), centralized radiology and surgical review panels, and EFS as an end point for future LAPC trials.

Relevance (*P.L. Kunz*)

The LAPIS study tested whether adding a new drug called pamrevlumab to standard chemotherapy could help people with LAPC live longer. Participants received either chemotherapy alone or chemotherapy plus pamrevlumab. The study found that adding pamrevlumab did not help patients live longer or delay the cancer from worsening. Although the treatment didn't show a benefit, the trial helped highlight better ways to design future studies for this stage of pancreatic cancer.*

Plain Language Summary *(P.L. Kunz)*

The LAPIS trial was an important phase III trial providing important insights for the development of future LAPC trials. While pamrevlumab did not improve outcomes when added to chemotherapy for locally advanced disease, the study underscored the value of incorporating biological markers, advanced imaging, and standardized surgical review in trial design in locally advanced PDAC.†

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pathway by which CTGF inhibition exerts its effects remains unclear, some studies suggest that it facilitates TME remodeling and may enhance the resectability of LAPC.[9,11] Conversely, other evidence, including the work by Neesse et al,[14] indicates that CTGF inhibition does not significantly disrupt the stromal barrier, but instead downregulates XIAP, thereby sensitizing tumors to gemcitabine-based chemotherapy.

Pamrevlumab, a fully human monoclonal antibody, inhibits the effects of CTGF.[15-17] It has been evaluated in clinical trials for PC and other diseases in which tissue fibrosis is a major pathogenic factor.[9,11,15-20] In preclinical work, pamrevlumab inhibited PC growth in cell cultures and KPC-engineered mice,[14,21] and in phase I (ClinicalTrials.gov identifier: NCT01181245) and phase I/II (ClinicalTrials.gov identifier: NCT02210559) clinical trials, chemotherapy plus pamrevlumab demonstrated a favorable safety profile and an encouraging therapeutic response, including increased eligibility for surgical resection, for patients with LAPC compared with historical controls.[9,11] The phase III LAPIS trial (ClinicalTrials.gov identifier: NCT03941093) evaluated the efficacy and safety of chemotherapy with or without pamrevlumab for patients with unresectable LAPC.

METHODS

Study Design and Treatment

LAPIS was a randomized, double-blind, phase III, placebo-controlled trial conducted at 72 sites in North America, Europe, and Asia. LAPIS implemented neoadjuvant treatment and evaluated surgical eligibility using protocol-specific treatment-response criteria, followed by resection when appropriate (Data Supplement, Fig S1).

Patients

Eligible patients were adults (18 years and older) with histologically/cytologically confirmed LAPC considered unresectable and central radiology panel assessment, measurable disease per RECIST v1.1, treatment-naïve status, and an Eastern Cooperative Oncology Group performance status of 0 or 1.[22] Key exclusion criteria included prior chemotherapy or radiotherapy for PC, previous (within the past 3 years) or concurrent malignancy diagnosis except nonmelanoma skin cancer and in situ carcinomas (excluding in situ breast cancer), or major surgery within 4 weeks before signing informed consent (biliary stents were permitted).

See the Data Supplement for full inclusion and exclusion criteria.

Procedures

Computed tomography (CT) scans, evaluated by central imaging, were performed at baseline to determine study eligibility and every 8 weeks during the neoadjuvant treatment period and until progressive disease (PD) was observed. Fluorodeoxyglucose positron emission tomography (FDG-PET) scans were also performed at baseline and the end of treatment to evaluate changes in maximum standardized uptake value (SUV_{max}) and metabolic tumor volume of the primary pancreatic tumor according to the central imaging protocol. During the follow-up period, CT scans were performed every 8 weeks for patients who completed treatment without evidence of PD and did not undergo surgical resection. For patients who underwent surgical resection, CT scans were performed every 4 months for up to 2 years and then every 6 months for 2-5 years.

Safety was evaluated throughout the study, on days 28 and 60 after the last chemotherapy doses, and on day 90 after surgery. An independent data monitoring committee reviewed safety data on an ongoing basis (Data Supplement, Methods).

Patients were randomly assigned 1:1 to investigator's choice of chemotherapy plus pamrevlumab (arm A) or chemotherapy plus placebo (arm B). Patients were to receive up to six cycles (28 days per cycle for a total of 24-30 weeks of treatment) of chemotherapy plus pamrevlumab or placebo, all administered by intravenous infusion. The pamrevlumab dosage (35 mg/kg every 2 weeks on days 1 and 15 before chemotherapy, with an additional dose of pamrevlumab on day 8 of cycle 1 only) and duration of treatment were selected based on the favorable efficacy and safety profile observed in previous trials,[9,11] together with exposure-response and dose-response modeling predictions. (The placebo group also received an additional dose of placebo on day 8 of cycle 1 to maintain blinding.) Pamrevlumab treatment interruptions, discontinuations, and dose modifications were not permitted. (All proposed delays or interruptions to dosing were discussed with the study's medical monitor. Adjustments to pamrevlumab administration were considered independently from chemotherapy dosing.) Investigator's choice of chemotherapy included gemcitabine 1,000 mg/m² plus nab-paclitaxel 125 mg/m² (G/NP) administered on days 1, 8, and 15 or folinic acid/leucovorin 400 mg/m² plus 5-fluorouracil 400 mg/m², 5-fluorouracil 2,400 mg/m², irinotecan 180 mg/m², and oxaliplatin 85 mg/m² (FOLFIRINOX) administered on days 1 and 15. Modified FOLFIRINOX (with an irinotecan dose reduced by 25% and the fluorouracil bolus reduced by 20%) was also permitted at the discretion of the investigators. (Initially, the study protocol only included use of G/NP as chemotherapy, but the protocol was amended on August 5, 2020, after 30 patients had been enrolled and randomly assigned, to allow investigators to choose FOLFIRINOX or G/NP per standard of care at their institutions.) These regimens were chosen at the time of protocol design and based on published trials.[23-25] Dose modifications of chemotherapy were permitted in accordance with the package inserts and/or institutional guidelines for managing toxicities.

Patients who experienced PD during the neoadjuvant treatment period discontinued the study, completed the end-of-treatment assessment, and continued into the follow-up period. All patients who completed study treatment underwent evaluation for surgical exploration. A central review panel (including radiologists, surgeons, and oncologists) assessed eligibility for surgical resection, which was defined as ≥1 of the following criteria[10]: conversion to resectable or borderline resectable status; decline in carbohydrate antigen 19-9 ≥50%; decline in FDG-PET SUV_{max} ≥30% at the end of treatment; or partial response (PR), complete response (CR), or stable disease per RECIST v1.1.[22] Contraindications for surgery included development of distant metastases, local progression per RECIST v1.1, Karnofsky score ≤50, non-reconstructible vascular involvement per central surgical panel review, or other conditions that according to the investigator or site surgeon would contraindicate surgery. The central review panel provided a determination of surgical eligibility, but the final decision as to whether a patient underwent surgery was made by the principal surgeon investigator at the study site.

For eligible patients, surgery was performed 4-8 weeks after the last dose of study treatment. All patients were followed for PD or recurrence (local or distant), survival, and additional anticancer therapy during the follow-up period for approximately 18 months after the last dose. Patients considered ineligible for surgery continued into the follow-up period. At the discretion of the investigator, ineligible patients were allowed to continue chemotherapy beyond 6 months and/or receive radiation therapy or other local therapy as per standard of care at their institution.

Outcomes

The primary end point was OS, defined as the time from random assignment to death from any cause. Secondary end points included event-free survival (EFS), defined as the time to "treatment failure" based on earliest occurrence of failure to achieve local disease-free status at the end of treatment and/or after surgery, local or distant recurrence, or death; progression-free survival (PFS), defined as the time from random assignment until disease progression or death from any cause (whichever occurred first); and objective response rate (ORR; CR or PR per RECIST v1.1; Data Supplement, Methods).[26]

Resection eligibility and outcomes were exploratory end points. An outcome of R0 or R1 was considered resection achieved, whereas an outcome of R2 or partial resection was considered resection not achieved, as determined by a central pathology review.

Safety analyses included frequency and severity of treatment-emergent adverse events (TEAEs)[27] and the relationship of any TEAE to study treatment. Surgical complications were also recorded.[28]

Statistical Analysis

A sample size of 280 patients was planned to provide a ≥80% power (approximately 233 deaths by the end of the follow-up period) to demonstrate a hazard ratio (HR) of 0.68 (using a two-sided significance level of 5%) between pamrevlumab and placebo arms with the assumption of the median OS of 24 and 16.3 months, respectively, based on previous trials.[10] For the assessment of EFS, 161 events were required to provide a 75% power to demonstrate a HR of 0.60 (using a one-sided false-positive error rate of 0.005). A description of the preplanned interim analysis is provided in the Data Supplement.

Efficacy outcomes are reported using the intent-to-treat (ITT) population, comprising all randomly assigned patients. OS, EFS, and PFS were summarized using the Kaplan-Meier method; follow-up time was calculated using the reverse Kaplan-Meier method. The stratified Cox proportional hazards model including treatment and stratification factors (chemotherapy regimen, nonreconstructible disease, geographic region, and superior mesenteric artery encasement) was used to compare the treatment arms and estimate the HR and corresponding 95% CI. ORR and exact 95% CI were summarized using a normal approximation method. Safety was assessed for all randomly assigned patients who received at least one dose of treatment. Analyses were performed using SAS version 9.3 or higher. The primary analysis data cutoff date was July 19, 2024.

The study was conducted in accordance with the International Conference on Harmonization E6 R2 Guideline for Good Clinical Practice, the Declaration of Helsinki, any other applicable regulatory requirements, and institutional review board or independent ethics committee requirements. Patients provided written informed consent before study participation.

RESULTS

Patients, Disposition, and Exposure

LAPIS enrolled and randomly assigned 284 patients (Fig 1; arm A [chemotherapy plus pamrevlumab], 143 patients; arm B [chemotherapy plus placebo], 141 patients). The safety population excluded one patient in arm A who did not receive treatment. More patients received G/NP than FOLFIRINOX as backbone chemotherapy with pamrevlumab or placebo (G/NP: arm A, 114 [79.7%]; arm B, 112 [79.4%]; FOLFIRINOX: arm A, 28 [19.6%]; arm B, 29 [20.6%]).

Patient demographics and baseline clinical characteristics are listed in Table 1. The population included slightly more

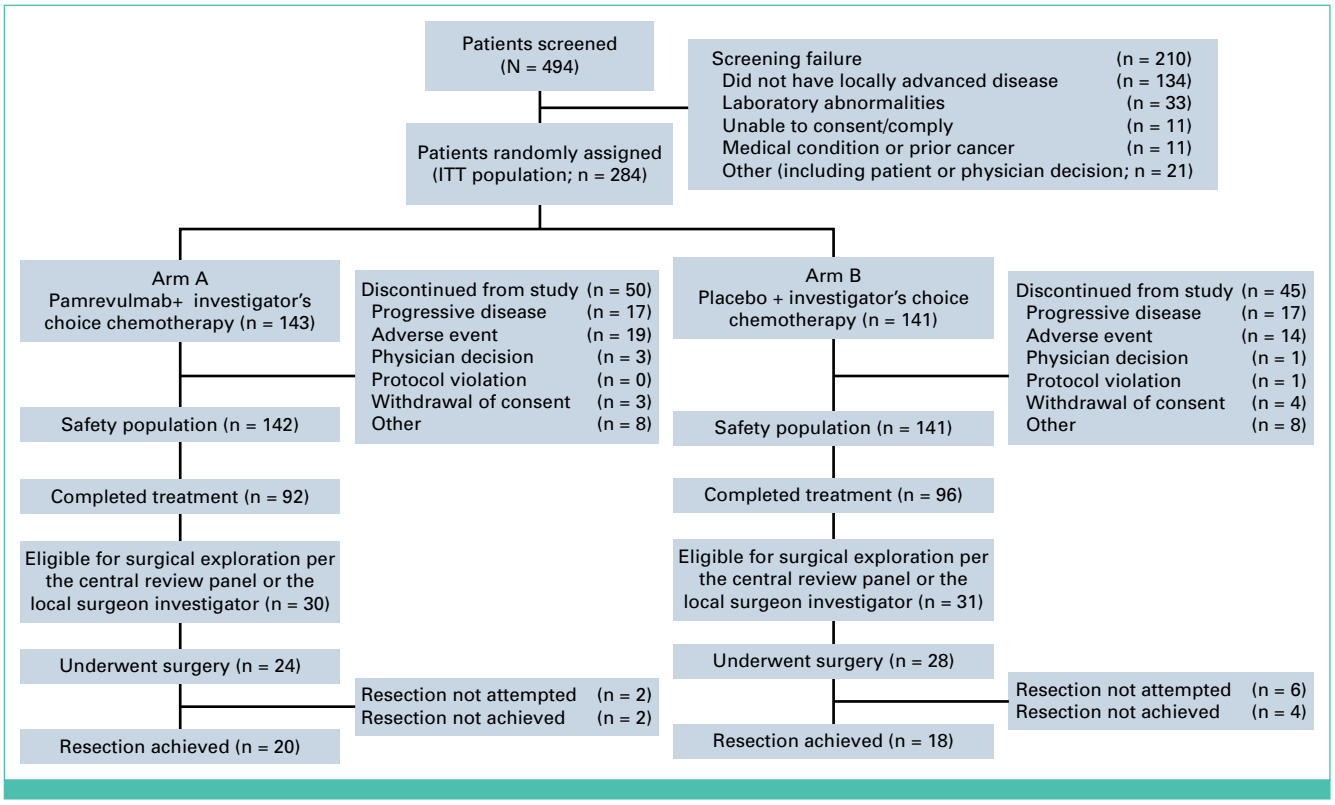

FIG 1. CONSORT diagram. ITT, intent to treat.

TABLE 1. Demographics and Baseline Clinical Characteristics

Characteristic	Arm A Pamrevlumab + Investigator's Choice Chemotherapy (n = 143)		Arm B Placebo + Investigator's Choice Chemotherapy (n = 141)		Total (N = 284)
	Pamrevlumab + FOLFIRINOX (n = 28)	Pamrevlumab + G/NP (n = 114)	Placebo + FOLFIRINOX (n = 29)	Placebo + G/NP (n = 112)	
Age, years					
Mean (SD)	64.5 (9.54)		64.5 (9.60)		64.5 (9.56)
	62.4 (9.36)	64.9 (9.50)	63.5 (7.70)	64.7 (10.05)	
Median (range)	64.0 (31-90)		65.0 (38-82)		65.0 (31-90)
	62.0 (40-77)	64.5 (31-90)	64.0 (46-80)	66.0 (38-82)	
Sex, No. (%)					
Male	82 (57.3)		69 (48.9)		151 (53.2)
	15 (53.6)	66 (57.9)	13 (44.8)	56 (50.0)	
Female	61 (42.7)		72 (51.1)		133 (46.8)
	13 (46.4)	48 (42.1)	16 (55.2)	56 (50.0)	
Race, No. (%)					
White	96 (67.1)		79 (56.0)		175 (61.6)
	21 (75.0)	75 (65.8)	12 (41.4)	67 (59.8)	
Asian	25 (17.5)		35 (24.8)		60 (21.1)
	2 (7.1)	23 (20.2)	7 (24.1)	28 (25.0)	
Black/African American	5 (3.5)		5 (3.5)		10 (3.5)
	1 (3.6)	4 (3.5)	2 (6.9)	3 (2.7)	
American Indian/Alaskan Native/other	5 (3.5)		9 (6.4)		14 (4.9)
	0	4 (3.5)	3 (10.3)	6 (5.4)	
Not reported	12 (8.4)		13 (9.2)		25 (8.8)
	4 (14.3)	8 (7.0)	5 (17.2)	8 (7.1)	
Ethnicity, No. (%)					
Not Hispanic or Latino	122 (85.3)		124 (87.9)		246 (86.6)
	24 (85.7)	97 (85.1)	23 (79.3)	101 (90.2)	
Hispanic or Latin	10 (7.0)		2 (1.4)		12 (4.2)
	0	10 (8.8)	0	2 (1.8)	
Not reported	9 (6.3)		13 (9.2)		22 (7.7)
	4 (14.3)	5 (4.4)	6 (20.7)	7 (6.3)	
Unknown	2 (1.4)		2 (1.4)		4 (1.4)
	0	2 (1.8)	0	2 (1.8)	
Geographic region, No. (%)					
North America/Europe	119 (83.2)		112 (79.4)		231 (81.3)
	26 (92.9)	93 (80.9)	25 (86.2)	87 (77.7)	
Asia Pacific	24 (16.8)		29 (20.6)		53 (18.7)
	2 (7.1)	22 (19.1)	4 (13.8)	25 (22.3)	
ECOG performance status, No. (%)					
0	68 (47.6)		58 (41.1)		126 (44.4)
	17 (60.7)	51 (44.3)	13 (44.8)	45 (40.2)	
1	75 (52.4)		83 (58.9)		158 (55.6)
	11 (39.3)	64 (55.7)	16 (55.2)	67 (59.8)	
Nonreconstructible disease,[a] No. (%)					
Yes	109 (76.2)		106 (75.2)		215 (75.7)
	21 (75.0)	88 (76.5)	22 (75.9)	84 (75.0)	
No	34 (23.8)		35 (24.8)		69 (24.3)
	7 (25.0)	27 (23.5)	7 (24.1)	28 (25.0)	

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TABLE 1. Demographics and Baseline Clinical Characteristics (continued)

Characteristic	Arm A Pamrevlumab + Investigator's Choice Chemotherapy (n = 143)		Arm B Placebo + Investigator's Choice Chemotherapy (n = 141)		Total (N = 284)
	Pamrevlumab + FOLFIRINOX (n = 28)	Pamrevlumab + G/NP (n = 114)	Placebo + FOLFIRINOX (n = 29)	Placebo + G/NP (n = 112)	
TNM stage, No. (%)					
Stage T					
TX	3 (2.1)		1 (0.7)		4 (1.4)
	1 (3.6)	2 (1.7)	1 (3.4)	0	
T0	0		0		0
	0	0	0	0	
Tis	0		0		0
	0	0	0	0	
T1	2 (1.4)		2 (1.4)		4 (1.4)
	1 (3.6)	1 (0.9)	0	2 (1.8)	
T2	13 (9.1)		14 (9.9)		27 (9.5)
	4 (14.3)	9 (7.8)	4 (13.8)	10 (8.9)	
T3	20 (14.0)		14 (9.9)		34 (12.0)
	3 (10.7)	17 (14.8)	1 (3.4)	13 (11.6)	
T4	102 (71.3)		110 (78.0)		212 (74.6)
	18 (64.3)	84 (73.0)	23 (79.3)	87 (77.7)	
Missing	3 (2.1)		0		3 (1.1)
	1 (3.6)	2 (1.7)	0	0	
Stage N					
NX	21 (14.7)		15 (10.6)		36 (12.7)
	1 (3.6)	20 (17.4)	3 (10.3)	12 (10.7)	
N0	69 (48.3)		63 (44.7)		132 (46.5)
	15 (53.6)	54 (47.0)	15 (51.7)	48 (42.9)	
N1	45 (31.5)		56 (39.7)		101 (35.6)
	10 (35.7)	35 (30.4)	11 (37.9)	45 (40.2)	
N2	5 (3.5)		7 (5.0)		12 (4.2)
	1 (3.6)	4 (3.5)	0	7 (6.3)	
Missing	3 (2.1)		0		3 (1.1)
	1 (3.6)	2 (1.7)	0	0	
Stage M					
MX	4 (2.8)		8 (5.7)		12 (4.2)
	2 (7.1)	2 (1.7)	2 (6.9)	6 (5.4)	
M0	136 (95.1)		133 (94.3)		269 (94.7)
	25 (89.3)	111 (96.5)	27 (93.1)	106 (94.6)	
M1	0		0		0
	0	0	0	0	
Missing	3 (2.1)		0		3 (1.1)
	1 (3.6)	2 (1.7)	0	0	
Location of the tumor in the pancreas, No. (%)					
Head	89 (62.2)		96 (68.1)		185 (65.1)
	20 (71.4)	69 (60.0)	21 (72.4)	75 (67.0)	
Body	46 (32.2)		43 (30.5)		89 (31.3)
	7 (25.0)	39 (33.9)	8 (27.6)	35 (31.3)	

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TABLE 1. Demographics and Baseline Clinical Characteristics (continued)

Characteristic	Arm A Pamrevlumab + Investigator's Choice Chemotherapy (n = 143)		Arm B Placebo + Investigator's Choice Chemotherapy (n = 141)		Total (N = 284)
	Pamrevlumab + FOLFIRINOX (n = 28)	Pamrevlumab + G/NP (n = 114)	Placebo + FOLFIRINOX (n = 29)	Placebo + G/NP (n = 112)	
Tail	5 (3.5)		2 (1.4)		7 (2.5)
	0	5 (4.3)	0	2 (1.8)	
Missing	3 (2.1)		0		3 (1.1)
	1 (3.6)	2 (1.7)	0	0	
FDG-PET SUV_{max}					
No.	28	103	25	108	
Mean (SD)	7.4 (4.070)	7.36 (3.576)	7.42 (4.516)	7.39 (3.959)	
Median (range)	6.20 (2.2-21.3)	6.90 (2.2-24.2)	6.60 (0.1-24.3)	6.55 (2-22.3)	
CA19-9, U/mL					
No.	27	110	28	109	
Mean (SD)	5,500.841 (14,733.2594)	4,120.885 (14,511.2646)	1,125.349 (1,491.5689)	2,827.202 (11,774.2497)	
Median (range)	195.870 (1-73,050.3)	360.360 (2-120,000)	417.500 (2-5,989.31)	292.580 (2-120,000)	

NOTE. ITT population (all randomly assigned patients).
Abbreviations: CA19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group; FDG-PET, fluorodeoxyglucose positron emission tomography; FOLFIRINOX, folinic acid/leucovorin 400 mg/m^2 plus 5-fluorouracil 400 mg/m^2, 5-fluorouracil 2,400 mg/m^2, irinotecan 180 mg/m^2, and oxaliplatin 85 mg/m^2 administered on days 1 and 15; G/NP, gemcitabine 1,000 mg/m^2 plus nab-paclitaxel 125 mg/m^2 administered on days 1, 8, and 15; ITT, intent to treat; SD, standard deviation; SUV_{max}, maximum standardized uptake value.
[a]According to central radiology panel assessment.[22]

men (151 [53.2%]) than women, and the median (range) age was 65.0 (31-90) years. Most patients (231 [81.3%]) were from North America or Europe. Slightly more than half patients (158 [55.6%]) had a performance status of 1, and most (215 [75.7%]) had nonreconstructible disease at enrollment, according to the central review panel.

Nearly two thirds of patients completed treatment (arm A, 92 [64.8%]; arm B, 96 [68.1%]; Fig 1). More than three quarters of patients died during the study (arm A, 118 [82.5%]; arm B, 112 [79.4%]). The median (range) treatment duration and median (95% CI) duration of follow-up were similar in both groups (arm A, 5.2 [95% CI, 0.03 to 8.7] months; arm B, 5.2 [95% CI, 0.03 to 7.0] months; and arm A, 38.18 [95% CI, 33.84 to 39.79] months; arm B, 38.67 [95% CI, 34.66 to 40.74] months, respectively).

Efficacy

Results of the interim analysis of EFS are reported in the Data Supplement (Table S1).

In the primary analysis, OS was similar between groups (median [95% CI]: arm A, 17.3 [95% CI, 15.5 to 18.9] months; arm B, 17.9 [95% CI, 14.6 to 20.3] months), and the primary end point was not met (HR [95% CI], 1.08 [95% CI, 0.83 to 1.41]; P = .5487; Fig 2). Subgroup analyses revealed no significant differences in OS between treatment arms or chemotherapy regimens (Data Supplement, Table S2, Fig S2).

EFS and PFS were also similar between groups. The median (95% CI) EFS was 5.7 (95% CI, 5.6 to 6.0) months in arm A and 5.8 (95% CI, 5.6 to 6.4) months in arm B (HR [95% CI], 1.05 [95% CI, 0.78 to 1.39]; P = .7738; Fig 3A). In arm A, 99 patients (69.2%) experienced an event, and 102 (72.3%) in arm B experienced an event. Surgery-related events (surgery not performed, surgery canceled, or surgery not achieved or attempted) were the most common events in both groups (arm A, 66 [46.2%]; arm B, 74 [52.5%]), followed by radiologic progression (arm A, 25 [17.5%]; arm B, 18 [12.8%]). Median (95% CI) follow-up times were similar (arm A, 9.43 [95% CI, 7.75 to 25.92] months; arm B, 11.89 [95% CI, 8.90 to 29.14] months).

The median (95% CI) PFS was 9.4 (95% CI, 7.8 to 11.8) months in arm A and 9.4 (95% CI, 7.7 to 10.8) months in arm B (HR [95% CI], 1.01 [95% CI, 0.65 to 1.56]; P = .9731; Fig 3B). In arm A, 48 patients (33.6%) experienced an event (PD, 42 [29.4%]; death, 6 [4.2%]), and 44 (31.2%) in arm B experienced an event (PD, 32 [22.7%]; death, 12 [8.5%]). Among patients who were censored (arm A, 95 [66.4%]; arm B, 97 [68.8%]), the most common reason for censoring was the start of a new anticancer treatment (arm A, 78 [54.5%]; arm B, 82 [58.2%]). Median (95% CI) follow-up times were similar (arm A, 5.78 [95% CI, 5.55 to 6.11] months; arm B, 5.82 [95% CI, 5.59 to 6.51] months). Subgroup analyses revealed no significant differences in EFS or PFS (Data Supplement, Table S2).

ORR was lower in arm A compared with arm B. Fewer patients in arm A achieved PR than in arm B (arm A, 43 [30.1%]; arm

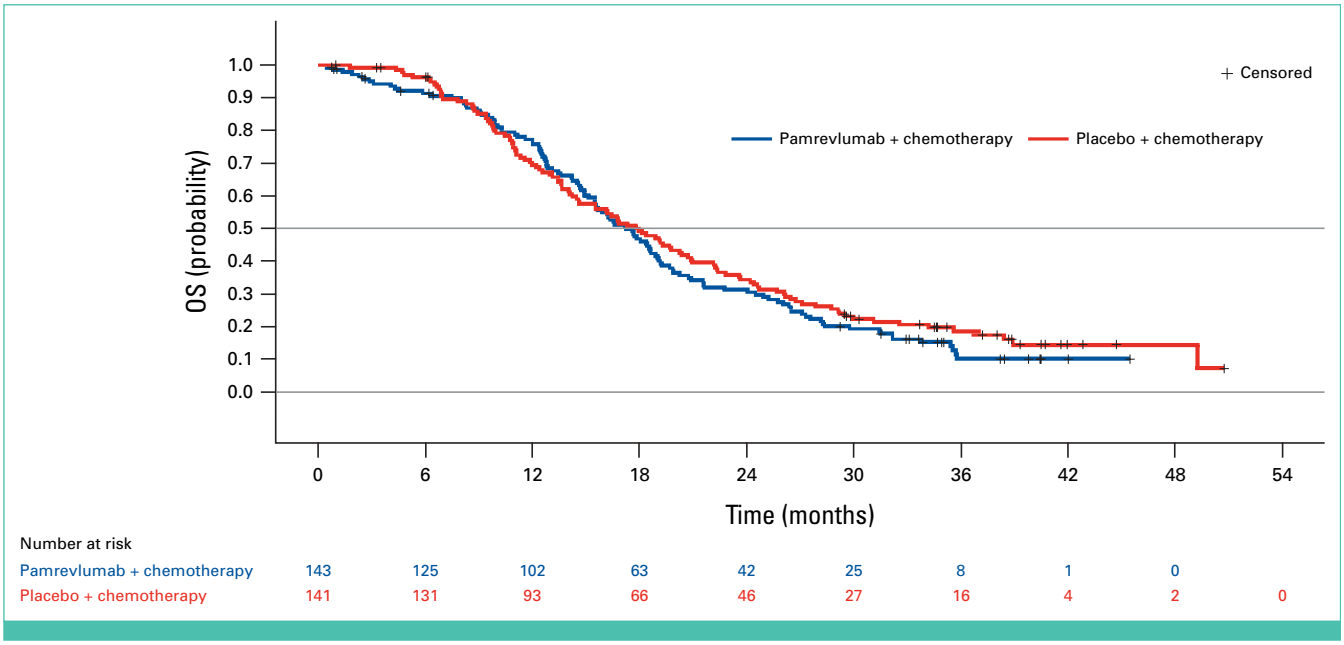

FIG 2. Kaplan-Meier plot of OS[a] in the ITT population. [a]OS was defined as the time from random assignment to death from any cause. ITT, intent to treat; OS, overall survival.

B, 64 [45.4%]; odds ratio [OR], 0.50 [95% CI, 0.31 to 0.82]; P = .0054). No patient in either group achieved CR (Data Supplement, Table S3). The response rates were similar among patients who received FOLFIRINOX and those who received G/NP although the percentage of patients who received FOLFIRINOX was much smaller than the percentage who received G/NP (20% *v* 80%), making statistical analysis difficult.

From the total population of 284 patients, 188 (66.2%) completed 6 months of therapy and were considered for surgery. Of these, 61 (21.5%) patients were recommended for surgery: 22 (7.7%) by the central review panel and an additional 39 (13.7%) by the site surgeon investigators (Table 2). Changes in CA19-9 and SUV_{max} at the end of treatment for these 61 patients are listed in the Data Supplement (Table S4). There was concordance of recommendation between the surgeons and the review panel for 150 of 188 (79.8%) patients. Fifty-two of the 61 patients underwent surgery, and 38 (13.4%) patients in the entire ITT population achieved resection as defined by the protocol (R0 or R1).

Postneoadjuvant anticancer medications and procedures are listed in the Data Supplement (Table S5). Surgical safety outcomes are listed in the Data Supplement (Table S6).

Safety

Nearly all patients experienced a TEAE (arm A, 142 [100.0%]; arm B, 140 [99.3%]). Most TEAEs were grade 3 or higher (arm A, 123 [86.6%]; arm B, 118 [83.7%]; Data Supplement, Table S7). The most common treatment-related TEAEs across arms were fatigue, diarrhea, nausea, and anemia. Overall, pamrevlumab did not add toxicity compared with the expected safety profile of the chemotherapy regimens. TEAEs (according to the System Organ Class) that occurred at least 10% more frequently with pamrevlumab/FOLFIRINOX than with placebo/FOLFIRINOX were respiratory, thoracic, and mediastinal disorders (39.3% *v* 27.6%) and skin and subcutaneous tissue disorders (53.6% *v* 37.9%; Data Supplement, Table S8). No TEAEs occurred more than 10% more frequently with pamrevlumab/G/NP compared with placebo/G/NP.

TEAEs leading to death occurred in seven patients (4.9%) in arm A and 5 (3.5%) in arm B. In arm A, 1 death (0.7%; pneumonia) was considered related to pamrevlumab and 3 deaths (2.1%) were related to either FOLFIRINOX or G/NP; no deaths in arm B were considered related to treatment.

DISCUSSION

The LAPIS trial enrolled one of the largest patient cohorts in an LAPC trial to date and conducted rigorous assessments across 72 centers worldwide. Previous trials in LAPC reported R0 resection rates of 14%-31% and a median OS of 18-20 months,[29-32] and LAPIS results were consistent with these findings. However, LAPIS did not demonstrate improvement in its primary end point of OS or secondary end points of EFS, PFS, and OR with the addition of pamrevlumab to standard chemotherapy. Pamrevlumab was not associated with additional toxicity compared with standard chemotherapy regimens.

The LAPIS protocol included prespecified objective resection criteria including biological parameters, CA19-9, and FDG-

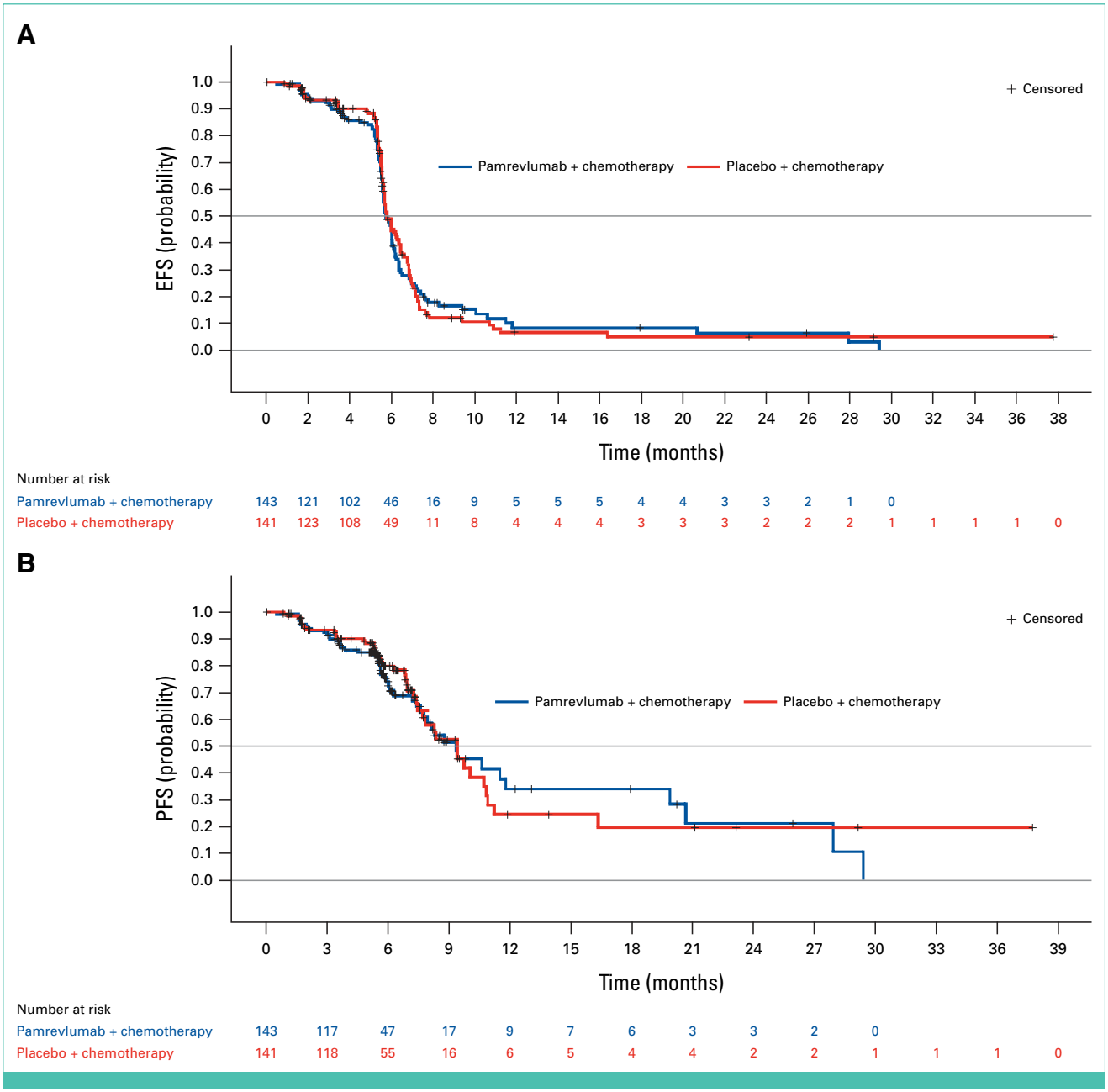

FIG 3. Secondary efficacy outcomes in the ITT population. (A) Kaplan-Meier plot of EFS.[a] (B) Kaplan-Meier plot of PFS.[b] [a]EFS was defined as the time to treatment failure based on earliest occurrence of failure to achieve local disease-free status at the end of treatment and/or after surgery, local or distant recurrence, or death.[21] [b]PFS was defined as the time from random assignment until disease progression or death. EFS, event-free survival; ITT, intent to treat; PFS, progression-free survival.

PET uptake, along with radiographic conversion to guide the decision for surgical resection. Furthermore, LAPIS used centralized radiology and surgical review panels to validate eligibility, standardize resection decisions, and ensure uniform pathologic assessments, promoting adherence to high standards across diverse clinical sites. Although there was an approximate 80% concordance between the central review panel and the site surgeon investigators, the latter group was actually much more successful in identifying candidates for potentially successful surgical resection. The reasons for this require further exploration.

The ultimate therapeutic goals for LAPC are both prolonging OS and increasing the percentage of patients treated with curative surgical resection. Therefore, the concept of EFS as a central end point for the interim analysis was introduced in LAPIS. EFS was aimed at comprehensively capturing the latter outcome by measuring survival until curative surgery was no longer feasible. EFS integrates disease progression, patient morbidity, and surgical outcomes into a single measure, providing a comprehensive view of therapeutic impact and addressing both OS and frequency of treatment with curative intent. This

TABLE 2. Surgical Eligibility Decisions and Outcomes

Treatment Group				Was Surgery Recommended by the Review Panel? No.	Did Site Surgeon Investigators Agree With Recommendation? No.	Did Patient Undergo Surgery? No.	Was Resection Achieved? No.
Arm A Pamrevlumab + investigator's choice chemotherapy (n = 143)	Pamrevlumab + FOLFIRINOX (n = 28)	Reconstructible disease at baseline (n = 7)	Completed study treatment and eligible for evaluation for surgical exploration (n = 5)	Yes, 1	Yes, 0	Yes, 0	
						No, 0	
					No, 1	Yes, 0	
						No, 1	
				No, 4	Yes, 2	Yes, 0	
						No, 2	
					No, 2	Yes, 1	Yes, 1
							No, 0
						No, 1	
		Nonreconstructible disease at baseline (n = 21)	Completed study treatment and eligible for evaluation for surgical exploration (n = 13)	Yes, 2	Yes, 2	Yes, 2	Yes, 2
							No, 0
						No, 0	
					No, 0	Yes, 0	
						No, 0	
				No, 11	Yes, 5	Yes, 0	
						No, 5	
					No, 6	Yes, 6	Yes, 6
							No, 0
						No, 0	
	Pamrevlumab + G/NP (n = 115)	Reconstructible disease at baseline (n = 27)	Completed study treatment and eligible for evaluation for surgical exploration (n = 19)	Yes, 4	Yes, 4	Yes, 4	Yes, 3
							No, 1
						No, 0	
					No, 0	Yes, 0	
						No, 0	
				No, 14	Yes, 12	Yes, 0	
						No, 12	
					No, 2	Yes, 2	Yes, 1
							No, 1
						No, 0	
				Not evaluated, 1			
		Nonreconstructible disease at baseline (n = 88)	Completed study treatment and eligible for evaluation for surgical exploration (n = 63)	Yes, 5	Yes, 3	Yes, 3	Yes, 2
							No, 1
						No, 0	
					No, 2	Yes, 0	
						No, 2	
				No, 52	Yes, 44	Yes, 0	
						No, 44	
					No, 8	Yes, 6	Yes, 5
							No, 1
						No, 2	
				Not evaluated, 6			

(continued on following page)

TABLE 2. Surgical Eligibility Decisions and Outcomes (continued)

Treatment Group				Was Surgery Recommended by the Review Panel? No.	Did Site Surgeon Investigators Agree With Recommendation? No.	Did Patient Undergo Surgery? No.	Was Resection Achieved? No.
Arm B Placebo + investigator's choice chemotherapy (n = 141)	Placebo + FOLFIRINOX (n = 29)	Reconstructible disease at baseline (n = 7)	Completed study treatment and eligible for evaluation for surgical exploration (n = 5)	Yes, 2	Yes, 2	Yes, 2	Yes, 2
							No, 0
						No, 0	
					No, 0	Yes, 0	
						No, 1	
				No, 3	Yes, 1	Yes, 0	
						No, 1	
					No, 2	Yes, 2	Yes, 1
							No, 1
						No, 0	
		Nonreconstructible disease at baseline (n = 22)	Completed study treatment and eligible for evaluation for surgical exploration (n = 17)	Yes, 1	Yes, 1	Yes, 1	Yes, 1
							No, 0
						No, 0	
					No, 0	Yes, 0	
						No, 0	
				No, 16	Yes, 13	Yes, 0	
						No, 13	
					No, 3	Yes, 3	Yes, 2
							No, 1
						No, 0	
	Placebo + G/NP (n = 112)	Reconstructible disease at baseline (n = 28)	Completed study treatment and eligible for evaluation for surgical exploration (n = 19)	Yes, 5	Yes, 5	Yes, 4	Yes, 1
							No, 3
						No, 1	
					No, 0	Yes, 0	
						No, 0	
				No, 14	Yes, 10	Yes, 0	
						No, 10	
					No, 4	Yes, 3	Yes, 2
							No, 1
						No, 1	
		Nonreconstructible disease at baseline (n = 84)	Completed study treatment and eligible for evaluation for surgical exploration (n = 66)	Yes, 2	Yes, 2	Yes, 2	Yes, 2
							No, 0
						No, 0	
					No, 0	Yes, 0	
						No, 2	
				No, 56	Yes, 44	Yes, 0	
						No, 44	
					No, 12	Yes, 11	Yes, 7
							No, 4
						No, 1	
				Not evaluated, 8			

Abbreviations: FOLFIRINOX, folinic acid/leucovorin 400 mg/m^2 plus 5-fluorouracil 400 mg/m^2, 5-fluorouracil 2,400 mg/m^2, irinotecan 180 mg/m^2, and oxaliplatin 85 mg/m^2 administered on days 1 and 15; G/NP, gemcitabine 1,000 mg/m^2 plus nab-paclitaxel 125 mg/m^2 administered on days 1, 8, and 15.

multidimensional end point may serve as a model for future studies, emphasizing the need for outcome metrics that go beyond OS alone for LAPC trials.

Therapeutic advances in LAPC require consideration of enhanced disease control both locally and systemically. With respect to local control, the ability of surgery to eradicate

locally advanced disease may be approaching its asymptote.[33] Consequently, the development of a broader array of local therapies (such as dose-intensified radiotherapy,[34,35] electrical tumor-treating fields,[36,37] or selective catheter-directed infusions of therapeutic agents[38,39]), either individually or in conjunction with surgery, may be necessary. With respect to systemic disease, antistromal agents might have a greater impact on macro- rather than micrometastatic disease sites. Future efforts may focus on combination therapies[40] targeting not only the tumor cells but also the tumor stroma, immune microenvironment, and perfusion, which are critical aspects of LAPC biology. In addition, evolving approaches such as KRAS inhibitors[41-43] and antimetabolic strategies[44,45] may offer new approaches for improving outcomes in LAPC.

Eligibility for surgical resection in LAPIS was based on criteria from the prior phase I/II trial,[9] and the same objective resectability criteria were adopted to ensure consistency and reduce subjectivity in surgical decisions. However, these criteria are not universally accepted as the standard of care as resectability assessments vary across institutions.

Unlike the earlier phase I/II trial,[9] patients with nonreconstructible disease were included in the LAPIS trial as they represent a significant portion of the overall LAPC population. Excluding them would have introduced bias into the trial design. Although the likelihood of curative resection—and therefore impact on OS—is limited in this group, their inclusion was essential to assess OS in the overall population. The phase I/II trial was a smaller US-based study and included approximately 30% of unresectable patients, compared with approximately 70% in the global phase III LAPIS trial—a key distinction likely contributing to differing outcomes. The trials also differed qualitatively: LAPIS included more nonresectable patients, mandated no staging laparoscopy, allowed multiple chemotherapy regimens, and incorporated formal surgical oversight. Quantitative differences included sample size, patient demographics, and institutional scope. In addition, LAPIS was conducted during the COVID-19 pandemic, which might have further affected trial outcomes.

While LAPIS did not show a survival benefit, it stands out for its scale, rigorous design, and execution in LAPC. It establishes benchmark survival and response rates for FOLFIRINOX and G/NP, providing a reference for future trials. LAPIS highlights the therapeutic challenges in LAPC and may inform more efficient, focused trial designs going forward.

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DATA SHARING STATEMENT

FibroGen, Inc, is committed to data sharing and to furthering medical research and patient care. Based on scientific merit, requests from qualified external researchers for anonymized patient-level and study-level clinical trial data (including redacted clinical study reports) for medicines and indications approved in the United States and Europe will be considered after the respective primary study is accepted for publication. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. Deidentified individual patient data will not be shared.

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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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