Randomized Phase II Study of Nab-Paclitaxel and Gemcitabine With or Without Tocilizumab as First-Line Treatment in Advanced Pancreatic Cancer: Survival and Cachexia

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ABSTRACT

PURPOSE This randomized phase-II trial (ClinicalTrials.gov identifier: NCT02767557) compared efficacy of gemcitabine/nab-paclitaxel (Gem/Nab) with or without the anti–interleukin-6 (IL-6) receptor antibody tocilizumab (Toc) for advanced pancreatic cancer (PC).

METHODS A safety cohort received Gem 1,000 mg/m² and Nab 125 mg/m² on days 1, 8, and 15, and Toc 8 mg/kg on day 1 for each 28-day cycle. Participants with modified Glasgow prognostic scores of 1 or 2 were randomly assigned 1:1 to receive Gem/Nab/Toc or Gem/Nab. The primary end point was the overall survival (OS) rate at 6 months (OS6). Secondary end points were progression-free survival (PFS), overall response rate (ORR), and safety. Exploratory end points were cachexia, quality of life, and biomarkers, including the cachexia-promoting protein, growth differentiation factor 15 (GDF15).

RESULTS Overall, 147 patients were treated, including six safety cohort participants. The median follow-up period was 8.1 months (IQR, 4.2-13.9). OS6 was 68.6% (95% CI, 56.3 to 78.1) for the Gem/Nab/Toc group and 62.0% (49.6-72.1) for the Gem/Nab group (P = .409). OS for Gem/Nab/Toc versus Gem/Nab improved at 18 months (27.1% *v* 7.0%, P = .001). No differences in median OS, PFS, or ORR were observed. Incidence of grade-3+ treatment-related adverse events (TrAEs) was 88.1% for Gem/Nab/Toc and 63.4% for Gem/Nab (P < .001). Gem/Nab/Toc decreased muscle loss versus Gem/Nab, with median change +0.1013% versus −3.430% (P = .0012) at 2 months and +0.7044 versus −3.353% (P = .036) at 4 months. Incidence of muscle loss was 43.48% on Gem/Nab/Toc versus 73.52% on Gem/Nab at 2 months (P = .0045) and 41.82% versus 68.75% (P = .0062) at 4 months. GDF15 was not changed by Gem/Nab or Gem/Nab/Toc.

CONCLUSION Although the primary end point was not met and TrAEs were increased by Toc, increased survival at 18 months and reduced muscle wasting support an anticachexia effect of IL-6 blockade independent of GDF15. Further studies could leverage these findings for precision anticachexia therapy.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Pancreatic ductal adenocarcinoma is among the most aggressive and drug-resistant cancers.[1,2] Although gemcitabine/nab-paclitaxel (Gem/Nab) and leucovorin calcium, fluorouracil, irinotecan, and oxaliplatin have improved overall survival (OS) in metastatic pancreatic cancer (PC), many tumors remain chemoresistant and most patients experience progressive disease (PD) within a year of diagnosis.[3,4] Moreover, patients often suffer severe cachexia—a syndrome of dysmetabolism and inflammation leading to weight loss and tissue wasting—resulting in increased treatment toxicity, reduced response, lower quality of life (QoL), and decreased survival.[5,6] There are no approved therapies for cachexia, despite off-label use of olanzapine and a recent encouraging phase II trial of the anti–growth

CONTEXT

Key Objective

To our knowledge, this is the first prospective randomized, phase II study to evaluate the efficacy of gemcitabine/nab-paclitaxel with or without tocilizumab (Toc; anti–interleukin-6 [IL-6] receptor antibody) as a first-line treatment in patients with advanced pancreatic cancer (PC).

Knowledge Generated

In this study of 147 patients with advanced PC, the addition of Toc to chemotherapy did not significantly improve 6-month survival versus chemotherapy alone. At 18 months, the addition of Toc reduced incidence and severity of muscle wasting, suggesting an anticachexia effect of neutralizing IL-6 signaling.

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

The topic of mitigating cachexia is a highly topical one. This randomized phase II study, albeit negative for primary end point, provides some insights for the field and an avenue for further investigation.*

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

differentiation factor 15 (GDF15) antibody ponsegromab.[7] These factors contribute to the poor 5-year survival rate of 13% for PC.[8]

Interleukin-6 (IL-6), a proinflammatory cytokine, modulates the tumor microenvironment and host response to tumor in PC.[9,10] It activates innate immunity, promoting inflammation, immune suppression, tumor growth, metastasis, and chemotherapy resistance.[10-18] IL-6 is also linked to cachexia, fatigue, anemia, and pain.[19-22] Elevated circulating IL-6 is observed in 60% of patients with PC, correlating with poor outcomes.[23,24] As a major inducer of the hepatic acute phase response, IL-6 triggers C-reactive protein (CRP) while suppressing albumin production, making CRP and the modified Glasgow Prognostic Score (mGPS) reasonable surrogate markers of IL-6 activity and predictors of cachexia, morbidity, and mortality.[25-27]

Tocilizumab (Toc), a humanized anti–IL-6 receptor (IL-6R) antibody, inhibits IL-6 signaling by blocking its binding to both soluble and membrane-resident IL-6R, JAK/STAT3 pathway activation and subsequent inflammation.[28] In mouse models, IL-6R neutralization has resulted in reduced tumor growth, metastases, recurrence, and cachexia, and improved chemotherapy response.[19,29-31] These findings suggest that Toc may have both antitumor and anticachexia activity.

In a phase I study including 10 patients with metastatic PC resistant to Gem/Nab, combining Toc with Gem/Nab-rechallenge achieved an 80% disease control rate (DCR) and tumor shrinkage in four patients.[32] Toc also enhanced drug delivery to tumors, overcoming chemoresistance. Toc was reported to reduce inflammation and weight loss in lung cancer cachexia.[33,34] Moreover, a phase II study showed the anti–IL-6 antibody ALD518 reduced muscle loss and anemia in patients with lung cancer.[35] This study aimed to evaluate whether survival, treatment response, and cachexia could be improved by adding Toc to first-line Gem/Nab in advanced PC.

METHODS

Patient Population

Eligible patients had histologically-confirmed, treatment-naïve, locally advanced or metastatic PC, an Eastern Cooperative Oncology Group performance status (PS) of 0-1, an mGPS of 1 or 2 within 14 days of random assignment (mGPS of 0: CRP ≤10 mg/L and albumin ≥35 g/L; mGPS of 1: CRP >10 mg/L and albumin ≥35 g/L; mGPS of 2: CRP >10 mg/L and albumin <35 g/L), and measurable disease per RECIST 1.1 criteria.[36] All provided signed informed consent for the Danish BIOPAC (BIOmarkers in patients with PAncreatic Cancer) study (ClinicalTrials.gov identifier: NCT03311776).[37]

Study Design

This was an open-label randomized phase II trial conducted at Copenhagen University Hospital, Herlev, Denmark, and Oslo University Hospital, Oslo, Norway. The study protocol and informed consent form were approved by independent ethics committees (H-16034901: September 22, 2016, and 25,297: December 23, 2019, respectively, for the two departments) before the study commenced. All the participants provided written informed consent. This study followed the CONSORT reporting guidelines (Data Supplement, Table S1, online only).

Patients were assigned (1:1) to receive Gem (1,000 mg/m^2) and Nab (125 mg/m^2) on days 1, 8, and 15, and Toc

(8 mg/kg) on day 1 once every 4 weeks, or Gem (1,000 mg/m²) and Nab (125 mg/m²) on days 1, 8, and 15 once every 4 weeks (Data Supplement, Fig S1). Random assignments were performed online using a stratified balanced allocation model, stratified according to PS (0 *v* 1) and stage (locally advanced *v* metastatic). Treatment was continued until PD, unacceptable toxicity, withdrawal of consent, or clear clinical deterioration according to the investigator's judgment. A safety phase involving a run-in assessment of 3 + 3 patients receiving Gem/Nab/Toc was performed (Data Supplement).

Study End Points and Assessments

The primary end point was the 6-months OS rate (OS6). Secondary end points included progression-free survival (PFS), OS, overall response rate (ORR), DCR, safety, PS at 3 and 6 months, assessed by the investigator and patient, and QoL. Additional end points involved cachexia-related metrics, including body weight and composition from computed tomography (CT) scans at baseline, 2 months, and 4 months, and biomarker analysis of circulating carbohydrate antigen (CA) 19-9, IL-6, IL-8, CD163, YKL-40, GDF15, and survival-related genes.

Tumor response was assessed once every 8 weeks using RECISTv.1.1. Follow-up assessments were scheduled until PD if the patient discontinued treatment for reasons other than PD. CA 19-9 and CRP levels were measured at once every 4 weeks. Adverse events (AEs), including treatment-related adverse events (TrAEs), were recorded at every visit from baseline throughout treatment and for 30 days after treatment discontinuation and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0.[38] QoL was assessed once every 8 weeks by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), Version 3.0.

Body Composition Measurements

Skeletal muscle and adipose tissue were measured at the level of the third lumbar vertebra from CT scans taken at baseline, 2 months, and 4 months using Data Analysis Facilitation Suite by Voronoi Health Analytics, Inc and differences analyzed by investigators blinded to treatment arm. Tissue compartment Z-scores were calculated as reported.[39] Details are provided in the Data Supplement.

Blood Sample Collection and Biomarker Analysis

Details on the methods for the determination of CRP, IL-6, IL-8, CD163, YKL-40. GDF15, and CA 19-9 levels are provided in the Data Supplement. From September 10, 2018, onward, gene sequencing was performed using the FoundationOne Liquid CDx assay in 84 patients.

Statistical Analyses

The clinical cutoff date was January 9, 2023. Assuming an OS6 rate of 67% in the reference arm and an improvement of at least 20% by the intervention corresponding to OS6 of 80%, a total of 140 patients were required (1:1 allocation) to obtain a statistical power of 80% with a significance level of 5% using a two-sided test. To detect differences of this magnitude with the log-rank test, the study was required to observe 95 events. OS6 and time-to-event end points were estimated using the Kaplan-Meier method, and differences in time-to-event were analyzed using the log-rank test. Effects are presented as hazard ratios (HRs) with corresponding 95% CIs. Subgroup analysis was performed using the Cox proportional hazards model with the relevant interaction term included. The treatment effect within each subgroup was extracted and presented as a HR. To detect differences in ORR and DCR, χ^2 and Fisher's exact tests were used.

Details of the statistical analyses of the body weight, body composition, and circulating biomarkers are described in the Data Supplement.

Descriptive analyses were used to report AEs, drug exposure, PS, EORTC QLQ-C30 score, and changes from baseline. A 10-point change in the EORTC QLQ-C30 was considered clinically meaningful (Data Supplement).[40] All outcome analyses were performed in a modified intention-to-treat population comprising randomly assigned patients who received at least one treatment. $P < .05$ was considered significant.

RESULTS

Patients

A total of 147 patients were enrolled and treated between January 31, 2017, and July 1, 2021 (Fig 1). Among them, six patients were treated with Gem/Nab/Toc as a safety run-in, while 141 were randomly assigned to receive Gem/Nab/Toc (n = 70) or Gem/Nab (n = 71). With all patients deceased as of January 9, 2023, the median follow-up was 8.1 months (IQR, 4.2-13.9). The baseline characteristics were generally similar between groups, except for head tumors (65.7% *v* 47.9%) and biliary tract stents (44.3% *v* 25.4%), which were more common in the Gem/Nab/Toc group (Table 1). Both groups had a similar distribution of patients with stage III and IV disease. The median CRP levels were 29 and 25 mg/L in the Gem/Nab/Toc and Gem/Nab groups, respectively.

Efficacy

OS6 was 68.6% (95% CI, 56.3 to 78.1) and 62.0% (95% CI, 49.6 to 72.1) in the Gem/Nab and Gem/Nab/Toc groups ($P = .409$) (Table 2), respectively. The median OS did not

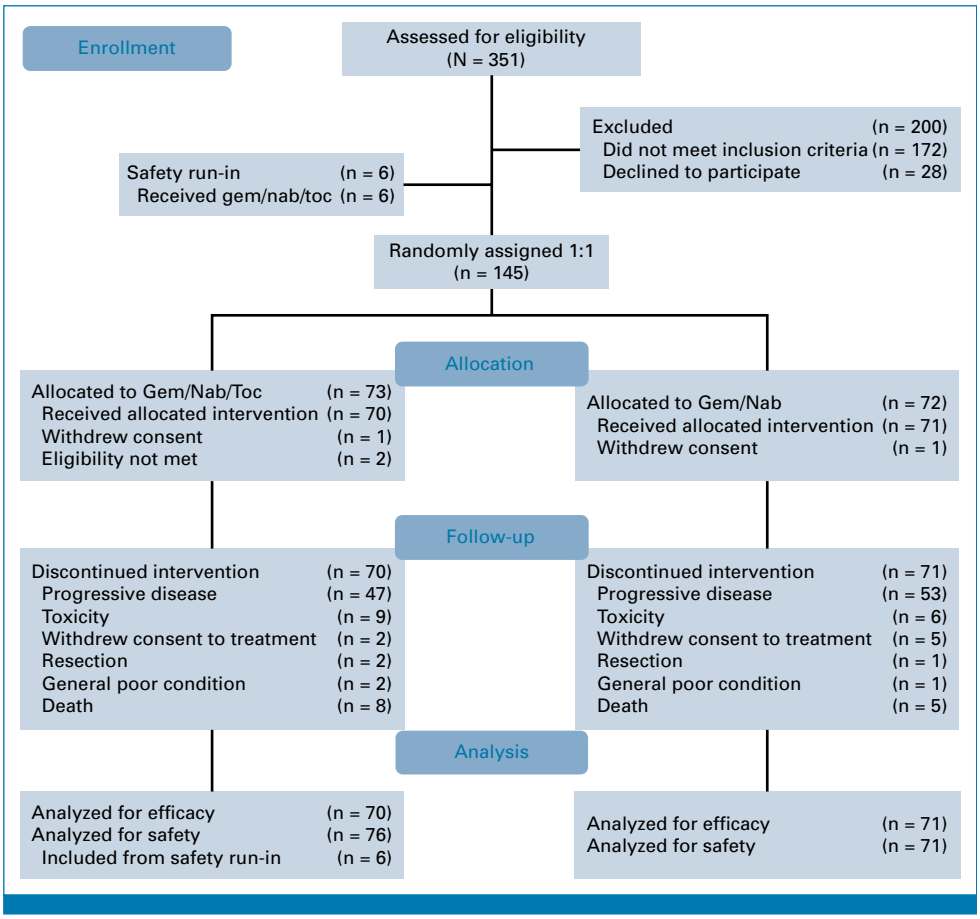

FIG 1. CONSORT diagram. Gem, gemcitabine; Nab, nab-paclitaxel; Toc, tocilizumab.

differ significantly between the groups (Fig 2A) and was 8.4 months in Gem/Nab/Toc group and 8.0 months in Gem/Nab group (HR, 0.75 [95% CI, 0.54 to 1.05]; $P = .0.096$). The 12-, 18-, and 24-month OS rates were 37.1% (95% CI, 26.0% to 48.3%), 27.1% (95% CI, 17.4% to 37.8%), and 10% (95% CI, 4.4% to 18.3%) for Gem/Nab/Toc and 28.2% (95% CI, 18.3% to 38.9%), 7.0% (95% CI, 2.6% to 14.5%), and 2.8% (95% CI, 0.5% to 8.8%) for Gem/Nab groups ($P = .254$, .001, and 0.079, respectively). Three patients without PD were censored for PFS during treatment initiation. The median PFS was similar between groups; 5.6 in the Gem/Nab/Toc group and 5.5 months in the Gem/Nab group (HR, 0.85 [95% CI, 0.60 to 1.19]; $P = .339$; Fig 2B). The ORR was 37.1% (95% CI, 25.9% to 49.5%) for the Gem/Nab/Toc group compared with 35.2% (95% CI, 24.2% to 47.5%) in the Gem/Nab group. No complete responses were observed in either treatment group. The DCR was similar between the two groups. Two patients in the Gem/Nab/Toc group were classified as having PD on the first CT scan and continued treatment for 13 and 11 months, respectively. Subsequent CT scans revealed tumor regression. Despite numerical imbalances in patients who had PS deterioration, as assessed by both investigators and patients at 3 and 6 months, in the Gem/Nab/Toc group compared with the Gem/Nab group (Table 2, Data Supplement, Fig S2), the differences between the treatment groups were not significant. In the subgroup analysis, OS and PFS across subgroups were consistent with the overall population, with an expected range of variability observed, except for the neutrophil-to-lymphocyte ratio (NLR; Data Supplement, Fig S3). Although there was no survival difference between treatment groups in patents with NLR <5, the addition of Toc resulted in significantly better PFS in patients with NLR ≥5.

Treatment Exposure

The median number of both Gem and Nab cycles in the Gem/Nab/Toc group was five. Details are provided in the Data Supplement (Tables S2 and S3).

Safety

Incidence of ≥grade 3 TrAEs was 88.1% in the Gem/Nab/Toc group and 63.4% in the Gem/Nab group ($P < .001$; Fig 3, Data Supplement, Table S4). Two treatment-related deaths occurred in the Gem/Nab/Toc group and one due to septic shock in the Gem/Nab group. Neutropenia, thrombocytopenia, nausea, and elevated alanine aminotransferase levels

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	Gem/Nab/Toc (n = 70)	Gem/Nab (n = 71)	*P*
Median age, years (range)	68 (34-84)	67 (36-84)	
Sex, No. (%)			.6798
Female	30 (43)	28 (39)	
Male	40 (57)	43 (61)	
ECOG PS, No. (%)			.9136
0	26 (37)	27 (38)	
1[a]	44 (63)	44 (62)	
Weight loss before diagnosis, No. (%)			.2171
<5%	24 (34)	18 (25)	
≥5%	42 (60)	50 (70)	
Location of primary tumor, No. (%)			.03266
Head	46 (66)	34 (48)	
Other[b]	24 (34)	37 (52)	
Body mass index, median (IQR)	24.7 (21.9-27.5)	24.5 (22.3-27.6)	.734
Disease stage, No. (%)			.7722
Locally advanced	5 (7)	6 (8)	
Metastatic[c]	65 (93)	65 (92)	
No. of metastatic sites, No. (%)			.9208
0	5 (7)	6 (8)	
1	27 (38)	24 (34)	
2	18 (26)	21 (30)	
≥3	20 (29)	20 (28)	
Sites of metastasis, No. (%)			.1151
Liver	52 (74)	49 (69)	
Lung	10 (14)	20 (28)	
Peritoneum	14 (20)	21 (30)	
Lymph nodes	34 (49)	22 (31)	
Other	15 (21)	14 (20)	
Previous resection, No. (%)			.6196
Yes	2 (3)	1 (1)	
No	68 (97)	70 (99)	
Biliary stent, No. (%)			.01824
Yes	31 (44)	18 (25)	
No	39 (56)	53 (75)	
Median time from diagnosis to random assignment, weeks (range)	3 (1-20)	3 (1-75)	.763
CA19-9, kU/L, median (IQR)	1,990 (218-9,973)	2270 (76-17,400)	.782
NLR, median (IQR)[d]	4 (3-7)	5 (3-9)	.226
Albumin, g/L, median (IQR)[e]	37 (33-42)	39 (34-43)	.158
CRP, mg/L, median (IQR)	29 (16-63)	25 (15-61)	.376
mGPS, No. (%)[f]			.4784
0	4 (6)	7 (10)	
1	42 (60)	44 (62)	
2	23 (33)	18 (25)	

(continued in next column)

TABLE 1. Patient Demographics and Baseline Characteristics (continued)

NOTE. Data are presented as No. (%) unless otherwise indicated. Columns can add up to >100% since some patients are listed in more than one group.

Abbreviations: CA19-9, carbohydrate antigen19-9; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Gem, gemcitabine; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil-to-lymphocyte ratio; Toc, tocilizumab.

[a]For one patient, ECOG 0 was reconsidered as ECOG 1 after random assignment.

[b]Body, tail, or known location.

[c]For three patients, the disease stage was reconsidered as metastatic after random assignment.

[d]One patient from both the Gem/Nab/Toc and Gem/Nab groups had missing baseline NLR values.

[e]One patient from the Gem/Nab/Toc group and three patients from the Gem/Nab group had missing baseline albumin values.

[f]One patient from the Gem/Nab/Toc and two patients from the Gem/Nab group had missing baseline mGPS values.

differed significantly between the groups. The most common grade 3 to 4 AEs that occurred in at least 5% of patients were neutropenia (55.3%), thrombocytopenia (40.8%), infection (19.7%), elevated alanine aminotransferase (18.4%), and diarrhea (17.1%) in the Gem/Nab/Toc group, and infection (21.1%), fatigue (18.3%), and neutropenia (16.9%) in the Gem/Nab group.

Cachexia End Points

Body weight and body composition from CT scans were assessed at baseline, 2 months, and 4 months after treatment onset. Patients in both Gem/Nab and Gem/Nab/Toc groups demonstrated weight loss and had low muscle mass by Z-score at random assignment, although these were not different by group (Figs 4A and 4B). Weight change (Fig 4C) at 2 and 4 months was not different between groups. However, Gem/Nab/Toc decreased muscle loss versus Gem/Nab, with median change +0.101% versus −3.43% ($P = .001$) at 2 months and +0.704 versus −3.35 ($P = .036$) at 4 months (Fig 4D). Incidence of muscle loss was also less, with 43.48% of patients on Gem/Nab/Toc losing muscle versus 73.52% of those on Gem/Nab at 2 months ($P = .0075$), and 41.8% versus 68.8% ($P = .01$) at 4 months (Figs 4E, Data Supplement, Fig S4). Skeletal muscle change at 4 months associated positively with OS for Gem/Nab/Toc (r = 0.418, $P = .001$) but not

for Gem/Nab (r = 0.207, P = .159; Fig 4F); similar results were observed at 2 months (Data Supplement, Fig S4D). Skeletal muscle radiodensity was not different between groups at any point—baseline, 2 months, or 4 months (Data Supplement, Fig S4E). Changes in adipose tissue were not significantly different between groups and tended to be associated with OS only in the Gem/Nab/Toc group (Data Supplement, Figs S5 and S6).

Quality of Life

The global health status worsened in fewer patients in the Gem/Nab/Toc group than in the Gem/Nab group at week 24 (39% *v* 46%; Data Supplement, Fig S7). Details are provided in the Data Supplement (Table S5, and Figures S7 and S8).

Circulating Biomarkers

GDF15 levels were not different between groups at baseline and were not changed after the first round of chemotherapy, either Gem/Nab or Gem/Nab/Toc (Fig 4H). Circulating biomarkers CRP, IL-6, IL-8, sCD163, YKL-40, and CA 19-9 are presented in the Data Supplement (Table S6 and Figs S9-S12). Briefly, CRP declined, and IL-6 increased in the Gem/Nab/Toc group—consistent with known effects of Toc.

TABLE 2. Overall Survival, Progression-Free Survival, and Response Rate Performance Status by Treatment Group in the Modified Intention-To-Treat Population

Efficacy Variable	Gem/Nab/Toc, n = 70	Gem/Nab, n = 71	HR or Response Rate Ratio (95% CI)[a]	*P*
OS				
Median OS, months (95% CI)	8.4 (6.7 to 11.4)	8.0 (5.9 to 9.8)	0.75 (0.54 to 1.05)	.096
OS rate, % (95% CI)				
6 months	68.6 (56.3 to 78.1)	62.0 (49.6 to 72.1)		.409
12 months	37.1 (26.0 to 48.3)	28.2 (18.3 to 38.9)		.254
18 months	27.1 (17.4 to 37.8)	7.0% (2.6 to 14.5)		.001
24 months	10.0 (4.4 to 18.3)	2.8 (0.5 to 8.8)		.079
PFS				
Median PFS, months (95% CI)	5.6 (3.9 to 7.4)	5.5 (3.5 to 7.0)	0.85 (0.60 to 1.19)	.339
PFS rate, % (95% CI)				
6 months	43.3 (31.3 to 54.6)	43.1 (31.4 to 54.3)		.989
12 months	11.9 (5.6 to 20.9)	8.6 (3.5 to 16.6)		.524
Response				
Overall response rate, % (95% CI)	37.1 (25.9 to 49.5)	35.2 (24.2 to 47.5)	1.05 (0.68 to 1.64)	.95
Best overall response, No. (%)				
Complete response	0	0		
Partial response	26 (37.1)	25 (35.2)		
Stable disease	25 (35.7)	23(32.4)		
Progressive disease[b]	11 (15.7)	14 (19.7)		
Not evaluable[c]	8 (11.4)	9 (12.7)		
ECOG PS				
Investigator assessment				
PS deterioration at 3 months, % (95% CI)	25.7 (16.0 to 37.6)	39.4 (28.0 to 51.7)		.119
PS deterioration at 6 months, % (95% CI)	41.4 (29.8 to 53.8)	49.3 (37.2 to 61.4)		.442
Patient assessment				
PS deterioration at 3 months, % (95% CI)	32.9 (22.1 to 45.1)	39.4 (28.0 to 51.7)		.524
PS deterioration at 6 months, % (95% CI)	38.6 (27.1 to 51.0)	45.1 (33.2 to 57.3)		.541

Abbreviations: CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Gem, gemcitabine; HR, hazard ratio; Nab, nab-paclitaxel; OS, overall survival; PFS, progression-free survival; Toc, tocilizumab.

[a]The HR for death is provided for OS, and the hazard ratio for progression or death is provided for PFS, with a hazard ratio of <1 favoring the Gem/Nab/Toc group. Response rate ratios were provided, with a response rate ratio of more than 1 favoring the Gem/Nab/Toc group. The 95% CI for response rate ratios was calculated according to the asymptotic 95% CI of the relative risk in the Gem/Nab/Toc group, compared with the Gem/Nab group.

[b]Two patients from the Gem/Nab/Toc group with progressive disease on the first postbaseline assessment had a partial response on the following CT scans.

[c]Patients who did not undergo a postbaseline tumor assessment or postbaseline assessment were not evaluable.

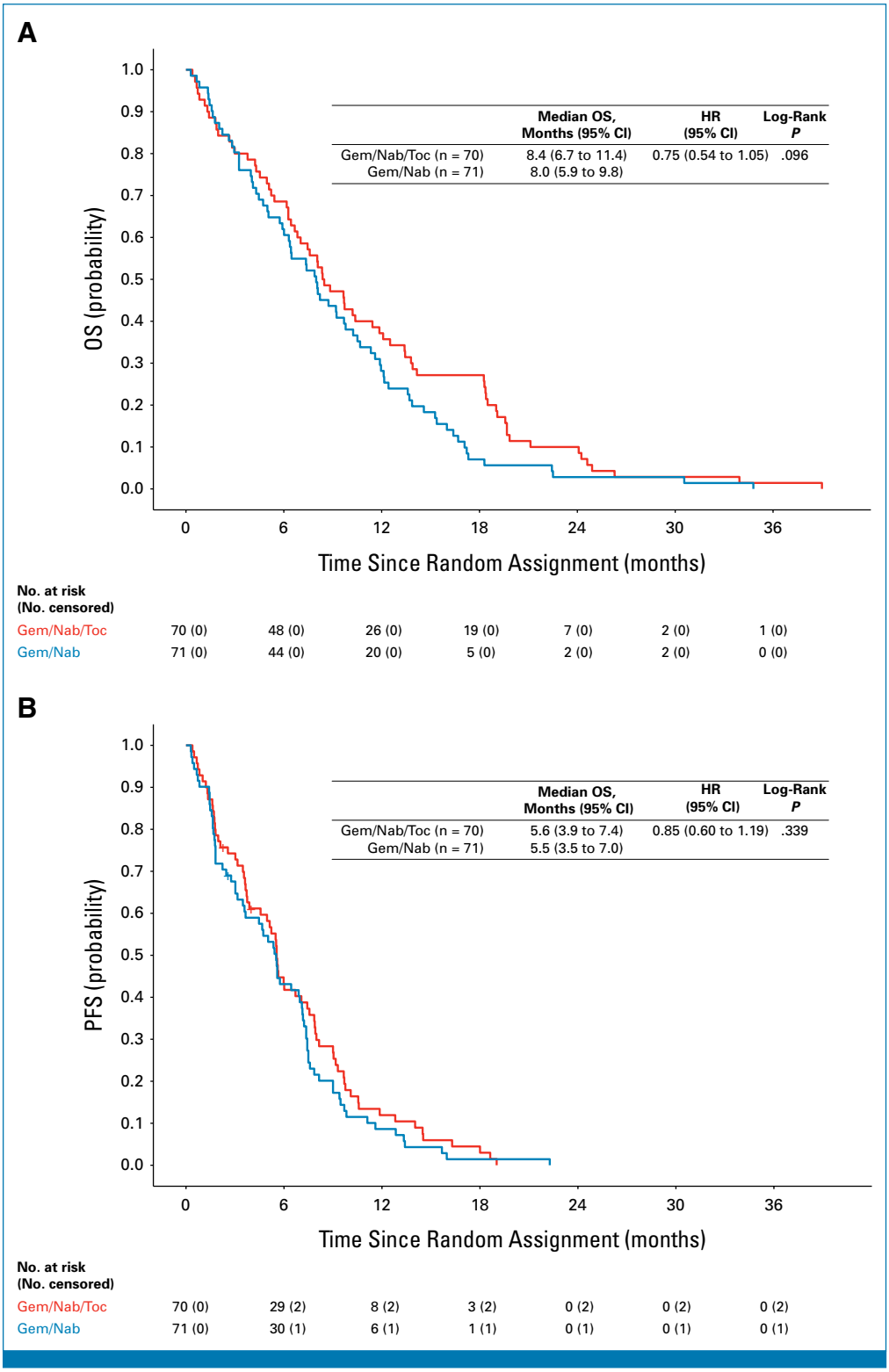

FIG 2. Kaplan-Meier curves for (A) OS and (B) PFS. Gem, gemcitabine; HR, hazard ratio; Nab, nab-paclitaxel; OS, overall survival; PFS, progression-free survival; Toc, tocilizumab.

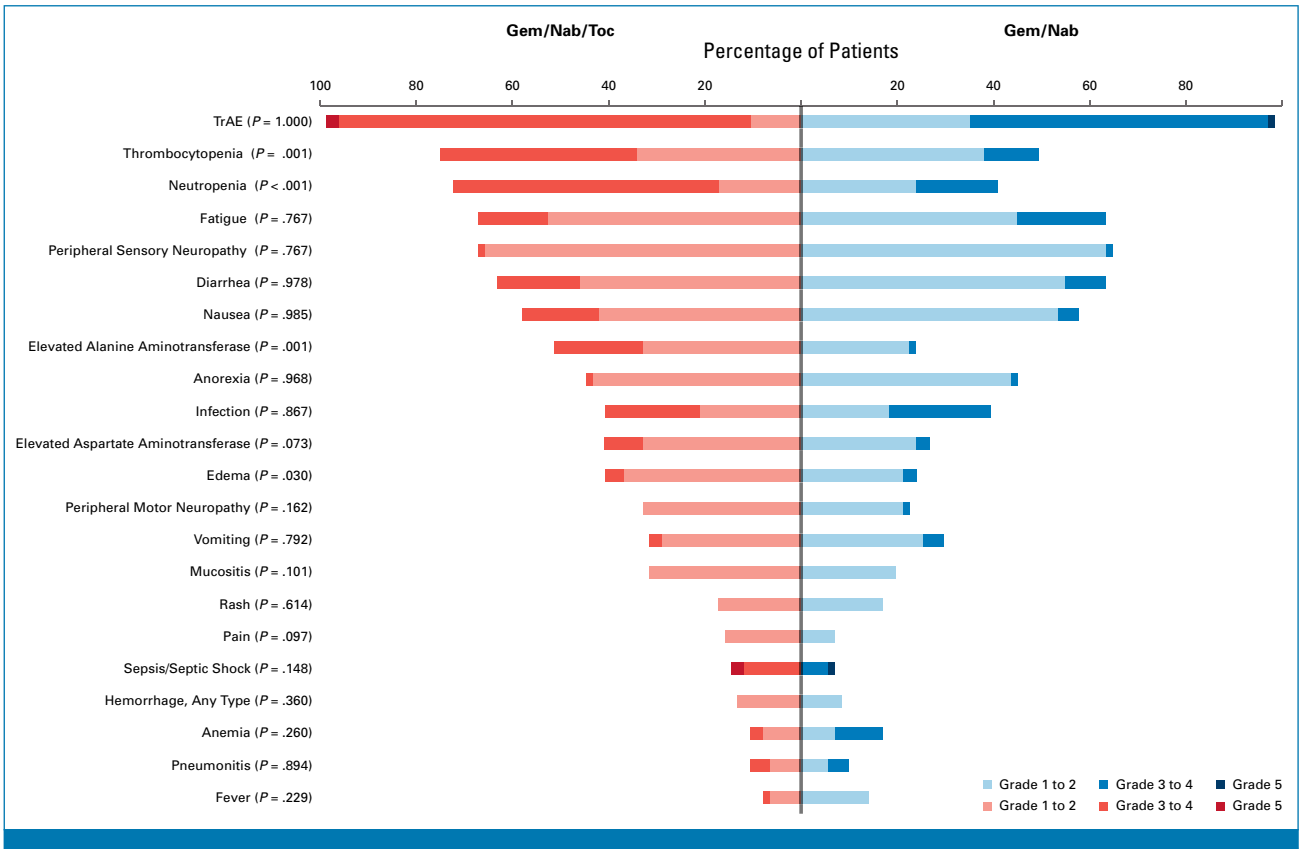

FIG 3. Summary of TrAEs that occurred in at least 10% of all treated patients. The *P* value is provided for ≥grade 3 adverse events. Gem, gemcitabine; Nab, nab-paclitaxel; Toc, tocilizumab; TrAEs, treatment-related adverse events.

Genomic Analysis

Sequencing results were obtained from 75 patients. Details are provided in the Data Supplement (Table S7, and Figs S13-S15).

DISCUSSION

To our knowledge, this is the first randomized study to compare Toc combined with Gem/Nab with Gem/Nab alone in treatment-naïve patients with advanced PC. Adding Toc to Gem/Nab did not improve the OS6 or median OS in patients with advanced PC, although more patients in the Toc group survived at 18 months and survival trended higher at 24 months. No differences were observed in ORR, suggesting no effect of Toc on tumor control. Less muscle wasting was noted in the Toc-treated patients and muscle preservation associated positively with OS, suggesting that IL-6 neutralization might promote survival through anticachexia effects.

We selected patients with high CRP concentrations (>10 mg/L) as a surrogate marker of the IL-6 pathway activity. Given the in vitro data that CRP suppresses T-cell reactivity, a decrease in CRP by Toc could be beneficial for anticancer efficacy.[41] Furthermore, previous studies suggest that IL-6 inhibition would promote chemoresponse. The majority of patients with metastatic PC included in a nonrandomized early-phase study achieved disease control after Toc combined with a Gem/Nab-rechallenge.[32] Analyses of paired biopsies showed increased cleaved poly (ADP-ribose) polymerase in tumor nuclei, decreased proliferation of cancer-associated fibroblasts, and decreased phosphorylation of the IL-6 pathway mediator, STAT3, along with increased drug infiltration. In another study, IL-6 promoted chemoresistance and compromised chemotherapy-induced anticancer immune responses.[18] Circulating levels of IL-6 predict the efficacy of Gem. Moreover, high IL-6 levels are associated with poor prognosis in patients with advanced PC receiving systemic therapy.[23,24,42] Because of T-cell responses to IL-6 signaling and preclinical evidence of enhanced immunotherapy response with IL6 inhibition, several ongoing clinical trials are testing the efficacy of IL-6 blockade combined with checkpoint inhibitors in cancer (ClinicalTrials.gov identifiers: NCT04940299, NCT04691817, and NCT03999749).[10-17] Consistent with a role for IL-6 in poor outcomes in PC, in our study, a high level of IL-6 was associated with worse survival in both groups. For patients with IL-6 levels higher than the 95th percentile in healthy blood donors (>4.92 pg/mL), survival was slightly longer in the Gem/Nab/Toc group. When grouping patients by the median IL-6 level in the study cohort (ie, >8.7 pg/mL), the addition of Toc tended to prolong survival in patients with low IL-6 levels. The median pretreatment

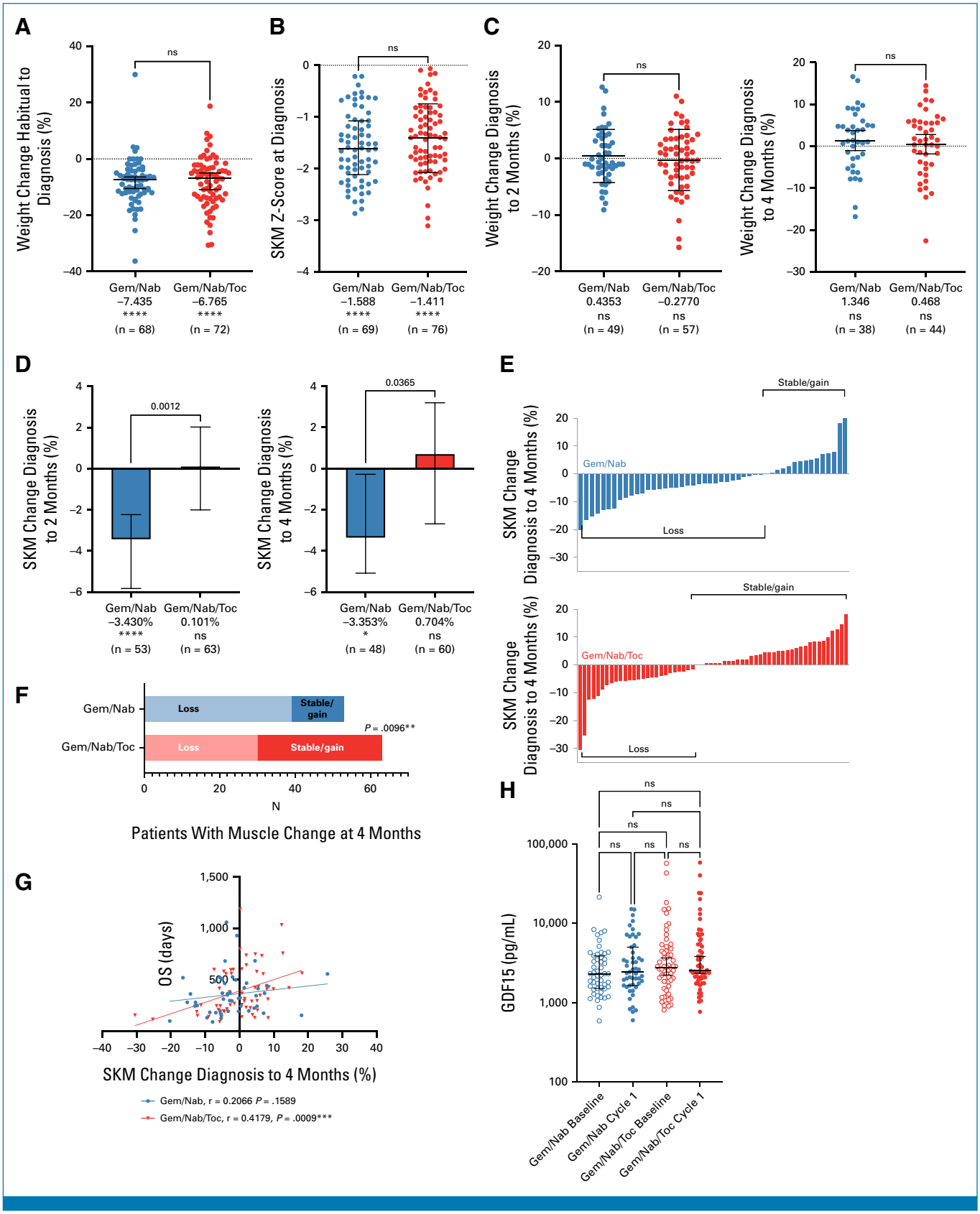

FIG 4. Cachexia phenotypes at baseline, 2 months, and 4 months after treatment initiation. (A) Body weight change from patient-reported habitual weight to baseline. (B) SKM mass by age-, race-, and sex-adjusted Z-score. (C) Weight change from baseline to 2 months or 4 months of treatment. (D) SKM change from diagnosis to 2 months or 4 months. (E) Waterfall plot of SKM change from baseline to 4 months. (F) Proportions of patients with loss versus stable/gain SKM at 4 months. (G) SKM change at 4 months versus OS. (H) Plasma GDF15 levels at baseline and after cycle 1. Statistics: (A, C, D) Wilcoxon signed rank test versus 0; Mann-Whitney test between groups. (continued on following page)

FIG 4. (Continued). (B) One sample *t*-test versus 0. Unpaired *t* test between groups. (F) Fisher's two-sided exact test. (G) Pearson correlation. (H) Grouped two-way ANOVA for time and treatment. *P < .05, **P < .01, ***P < .001, ****P < .0001. Shown are median ±95% CI. ANOVA, analysis of variance; GDF15, growth differentiation factor 15; OS, overall survival; SKM, Skeletal muscle.

IL-6 level in the patients was much higher than the 95th percentile in healthy blood donors, presumably implying aggressive pathophysiology, a much worse prognosis for these patients, and complex mechanisms underlying IL-6 pathway activation.

Gem/Nab had a better safety profile than Gem/Nab/Toc, with the overall profiles consistent with those previously observed. The frequency of ≥grade 3 TrAEs was higher with Toc combined with chemotherapy than with Gem/Nab alone, resulting in a compromised chemotherapy dose intensity in the Gem/Nab/Toc group. This raises the question of whether a higher chemotherapy exposure in the Gem/Nab/Toc group would have influenced survival. However, most patients in both treatment groups discontinued chemotherapy because of PD.

Consistent with abundant functional data in preclinical models and associative data in patient populations linking IL-6 to muscle wasting and cachexia, patients treated with Toc experienced less muscle wasting. Muscle change in the Gem/Nab group was −3.43% at 2 months and −3.36% at 4 months, approximately half the average muscle loss observed from treatment initiation to last visit in our retrospective study of 125 patients treated with first-line Gem/Nab.[43] Average muscle change in the Gem/Nab/Toc group was not significantly different from 0 at either time point. Thus, there appears to be a biologically meaningful, muscle-preserving effect of Toc. Effects in adipose were not discernible because of high variability of response. Although not all patients showed muscle protection, the data confirm a causal role for IL-6–mediated wasting in at least a subset of patients with PC.

Cachexia in PC is likely multifactorial. GDF15 produces nausea, vomiting, anorexia, and cachexia.[44] Ponsegromab, a monoclonal antibody that targets circulating GDF15, promoted dose-dependent weight gain in a recent Phase II trial of advanced cancer patients with cachexia, including patients with PC.[7] Nearly all patients in our study had sufficient GDF15 (>1,500 pg/mL) to qualify for the ponsegromab trial. Unlike cisplatin-based chemotherapy regimens, Gem/Nab and Gem/Nab/Toc did not change GDF15 levels, consistent with preclinical data showing low/no cachexia-inducing effects of Gem/Nab.[45] Furthermore, these results indicate that GDF15 is either upstream or independent of IL-6. Thus, combination therapy against both targets might be more effective than inhibition of one or the other. Further studies will interrogate additional cachexia mediators to determine whether approaches stratifying patients by biomarkers might define a new precision approach to cachexia therapy in PC.

Our study had limitations. First, CRP levels generally declined with Toc, but not in all patients, so the use of CRP or its cutoff value as a surrogate marker for IL-6 bioactivity or Toc efficacy remains unclear. Additionally, given the variability in Toc's half-life on the basis of concentration, tissue, and disease-specific factors, and the fact that the dosing and scheduling in our study were based on recommendations in other contexts, the optimal dosing regimen for Toc in patients with cancer—particularly those with PC—remains uncertain, as the pharmacokinetics and pharmacodynamics in this population may differ from other settings. Indeed, cachexia associates to more rapid antibody clearance, potentially affecting IL-6 suppression by Toc.[46] Second, although survival rates at later time points were numerically higher in the Gem/Nab/Toc group, the small sample size limits definitive conclusions. Third, Toc suppresses markers of infection, such as CRP and fever, complicating its use in immunocompromised patients with cancer because of increased risk of infection. In this study, although the proportion was low overall, two patients among 76 (2.6%) in the Gem/Nab/Toc group and one of 71 (1.4%) in the Gem/Nab group had fatal treatment-related toxicities. Additionally, IL-6 inhibition may affect hematopoiesis, underscoring the importance of closely monitoring hematologic parameters during treatment to minimize on-target toxicities while maintaining therapeutic efficacy. Fourth, the open-label study design and imbalances of head tumors and biliary stents between groups may have confounded toxicity and outcome data. For future trials, OS and PFS, which are less susceptible to data collection variability, may be more reliable end points than OS6, whose limitations—particularly in the context of immune-oncology agents and the potential for pseudoprogression—underscore the need to prioritize these alternative end points for robust treatment efficacy assessment. Fifth, although body composition changes suggested a protective effect of Toc on muscle, functional end points such as strength or gait speed were not measured. Additionally, edema, observed more frequently in the Gem/Nab/Toc group, might have confounded measurements of weight and muscle mass. However, skeletal muscle radiodensity was unchanged and thus edema specific to Toc is not likely an explanation for the increased muscle area. Sixth, QoL improvements in the Gem/Nab/Toc should be cautiously interpreted because of declining availability of self-reported data over time. Similarly, we acknowledge the need for caution when interpreting

findings from post hoc analyses or multiple statistical tests, as these are exploratory in nature and carry an increased risk of bias. Finally, the aggressive course of the disease and rapid patient deterioration posed challenges.

In conclusion, the results of our exploratory analyses showing survival variations dependent on circulating IL-6 levels, a protective effect of Toc on cachexia-related end points independent of GDF15, and a correlation between muscle preservation and survival imply a causal role for IL-6 in PC morbidity and mortality that warrants further evaluation. Therefore, future studies should focus on identifying subsets of patients who could benefit from the addition of Toc to their treatment regimen.

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Randomized Phase II Study of Nab-Paclitaxel and Gemcitabine With or Without Tocilizumab as First-Line Treatment in Advanced Pancreatic Cancer: Survival and Cachexia

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