SWOG S1815: A Phase III Randomized Trial of Gemcitabine, Cisplatin, and Nab-Paclitaxel Versus Gemcitabine and Cisplatin in Newly Diagnosed, Advanced Biliary Tract Cancers

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ABSTRACT

PURPOSE SWOG S1815 was a randomized, open label phase III trial, evaluating gemcitabine, nab-paclitaxel, and cisplatin (GAP) versus gemcitabine and cisplatin (GC) in patients with newly diagnosed advanced biliary tract cancers (BTCs).

METHODS Patients with newly diagnosed locally advanced unresectable or metastatic BTC, including intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) and gallbladder carcinoma (GBC), were randomly assigned 2:1 to either GAP (gemcitabine 800 mg/m^2, cisplatin 25 mg/m^2, and nab-paclitaxel 100 mg/m^2 intravenously once per day on days 1 and 8 of a 21-day cycle) or GC (gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2 intravenously once per day on days 1 and 8 of a 21-day cycle).

RESULTS Among 452 randomly assigned participants, 441 were eligible and analyzable, 67% with ICC, 16% with GBC, and 17% with ECC. There was no significant difference in overall survival (OS) between GAP versus GC. Median OS with GAP was 14.0 months (95% CI, 12.4 to 16.1) and 13.6 months with GC (95% CI, 9.7 to 16.6); hazard ratio (HR), 0.91 (95% CI, 0.72 to 1.14); $P = .41$. Median progression-free survival (PFS) was similar between groups with median PFS for GAP being 7.5 months (95% CI, 6.4 to 8.5) versus 6.3 months for GC (95% CI, 4.4 to 8.2); HR, 0.89 (95% CI, 0.71 to 1.12); $P = .32$. In exploratory subset analyses, the OS and PFS benefits of GAP versus GC treatment were greater in locally advanced disease compared with metastatic disease, although not statistically significant (interaction $P = .14$ for OS and $P = .17$ for PFS). Moreover, GAP versus GC showed greater improvement in PFS among participants with GBC than those with ICC or ECC (interaction $P = .01$), but not OS (interaction $P = .28$).

CONCLUSION The addition of a taxane in the GAP regimen to the standard gemcitabine-cisplatin regimen did not improve OS in newly diagnosed BTC. More toxicity was encountered with GAP versus GC.

ACCOMPANYING CONTENT

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Appendix

Protocol

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INTRODUCTION

Biliary tract cancers (BTCs) are a heterogeneous group of malignancies including intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), and gallbladder carcinoma (GBC). Patients typically present with advanced disease where potentially curative surgical resection is not an option.[1] The therapeutic landscape for BTC has expanded significantly over recent years largely because of advances in molecularly targeted therapies and immunotherapies.[1-3] However, the survival benefit of adding immune checkpoint inhibitors (ICIs) to frontline gemcitabine and cisplatin (GC) chemotherapy for advanced disease is modest, averaging a 1.5-month improvement in median overall survival (OS).[2,3]

Preclinical data suggest that stroma-remodeling nanoparticles enhance the delivery of chemotherapeutic agents into desmoplastic tumors such as pancreatic cancer and cholangiocarcinoma.[4,5] A single-arm phase II study evaluated the combination of gemcitabine, nab-paclitaxel, and cisplatin (GAP) in patients with advanced BTC and demonstrated encouraging clinical activity, including a median progression free-survival (PFS) of 11.8 months, overall response rate

CONTEXT

Key Objective

This study evaluated the benefit of gemcitabine, nab-paclitaxel, and cisplatin (GAP) versus gemcitabine and cisplatin (GC) alone for untreated advanced biliary tract cancer (BTC).

Knowledge Generated

Treatment with GAP chemotherapy did not result in improved median overall survival over standard GC chemotherapy for the treatment of advanced BTC. Triplet chemotherapy with GAP was also more toxic than GC, resulting in more hematologic and nonhematologic grade 3 or higher treatment-related adverse events.

Relevance *(A.H. Ko)*

Triplet chemotherapy should not routinely be offered to patients with advanced BTC.*

*Relevance section written by *JCO* Associate Editor Andrew H. Ko, MD, FASCO.

(ORR) of 45%, disease control rate (DCR) of 84%, and median OS of 19.2 months.[6] These results were favorable in the context of outcomes with GC in the ABC-02 trial. We therefore designed a randomized phase III study comparing the taxane-containing triplet, GAP, to a standard GC doublet in newly diagnosed locally advanced and metastatic BTCs.[6,7]

METHODS

Study Design

SWOG S1815 was a randomized, open-label, phase III trial, comparing GAP with GC in newly diagnosed advanced BTCs (ClinicalTrials.gov identifier: NCT03768414). The primary objective was to test the superiority of GAP over GC with respect to OS. This study was conducted by the SWOG Cancer Research Network, as funded by the National Cancer Institute (NCI) National Clinical Trials Network, with 151 participating institutions. The applicable regulations and guidelines governing clinical study conduct were followed and the study was performed in compliance with the Declaration of Helsinki. Study participants were randomly assigned to the treatment arms in a 2:1 ratio (GAP:GC) using a dynamic balancing algorithm with stratification by disease site (ICC *v* ECC *v* GBC), disease stage (locally advanced *v* metastatic), and Zubrod performance status (0 *v* 1). The trial was approved by the NCI Central Institutional Review Board; all participants provided informed consent.

Patients

Patients were required to have histologically or cytologically confirmed ICC, ECC, or GBC that was either metastatic, or locally advanced and unresectable. Patients with a diagnosis of ampullary cancer were not eligible. Patients must not have received previous systemic therapy for metastatic or locally advanced biliary cancer, nor received adjuvant therapy within 6 months of registration on the trial. Patients were required to have a Zubrod performance status of 0 or 1; adequate hematologic, hepatic, and renal function; no history of grade 2 or higher peripheral neuropathy; and no active infection requiring systemic therapy. The full list of inclusion and exclusion criteria is provided in the protocol.

Treatments

GAP was composed of gemcitabine 800 mg/m^2, cisplatin 25 mg/m^2, and nab-paclitaxel 100 mg/m^2 intravenously once per day on days 1 and 8 of a 21-day cycle. GC included standard dosing of gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2 intravenously once per day on days 1 and 8 of a 21-day cycle. Trial participants were treated until disease progression or unacceptable toxicity, and followed until death or 3 years after random assignment, whichever occurred first. The decision to administer WBC growth factor support was left to the discretion of the treating physician and, if used, was required to follow ASCO and National Comprehensive Cancer Network guidelines.

Study End Points and Assessments

The primary end point of the study was OS, defined as the time from random assignment to death due to any cause, with censoring at the time of last contact. Secondary outcomes included PFS, ORR (confirmed and unconfirmed, complete response and partial response), and DCR (ORR + stable disease) among participants with measurable disease, toxicity, and change in cancer antigen (CA) 19-9 from baseline to post-treatment (after three cycles). PFS was defined as the time from random assignment to first documentation of progression or symptomatic deterioration, or death, with censoring at the time of last contact. Adverse events (AEs) were assessed for severity using NCI Common Toxicity Criteria for Adverse Events version 5.0 (Cancer

Therapy Evaluation Program[8]). Participants were evaluated for tumor response every 9 weeks according to RECIST version 1.1.[9] RECIST assessment was performed by the local investigator without central review. Archival tumor tissue was collected, when available, for future exploratory studies.

Statistical Considerations

With a null hypothesis of 11.7 months as median OS for the GC arm, we targeted a hazard ratio (HR) of 0.7 (experimental arm *v* control arm; median OS of 16.7 months for the GAP arm), which required 384 eligible participants assuming 24 months of follow-up, 85% power, and a one-sided α of .025. A total sample size of 441 participants was planned to allow for up to 13% ineligibility.[7]

The primary analysis of OS was undertaken in all eligible study participants according to a modified intention-to-treat principle. That is, randomly assigned, eligible study participants were included in survival analyses even if they did not receive study treatment. The distributions of OS and PFS were estimated using the Kaplan-Meier method, and statistical differences in event rates between treatment arms were assessed via stratified log-rank test (stratification factors: disease site, disease stage, and performance status as described above). HR with 95% CI were estimated via stratified Cox regression models. Exploratory subset analyses evaluated differential effects of treatment on OS and PFS according to disease site and disease stage in models fitted with interaction terms.

The chi-square test was used to compare ORR, DCR, and rates of toxicity events across arms. ORR analysis included all eligible participants with measurable disease; those with inadequate assessment were counted as nonresponders. Participants who received at least one dose of any drug on any arm were included in the assessment of AEs. Only treatment-related AEs thought to be possibly, probably, or definitely related to treatment are described. Associations between changes in CA 19-9 levels from baseline to post-treatment and ORR were estimated via logistic regression models, both within each treatment arm and in the overall cohort. An interaction term of change in CA 19-9 by treatment arm was applied to test whether the associations of treatment response and CA 19-9 change varied according to treatment arm. Meaningful change in CA 19-9 was quantified as a 1,500-point increase versus a <1,500 change.

RESULTS

Patients

The trial met its accrual goal with 452 participants randomly assigned between December 3, 2018, and February 15, 2021 (26.5 months). Ten participants were ineligible, as described

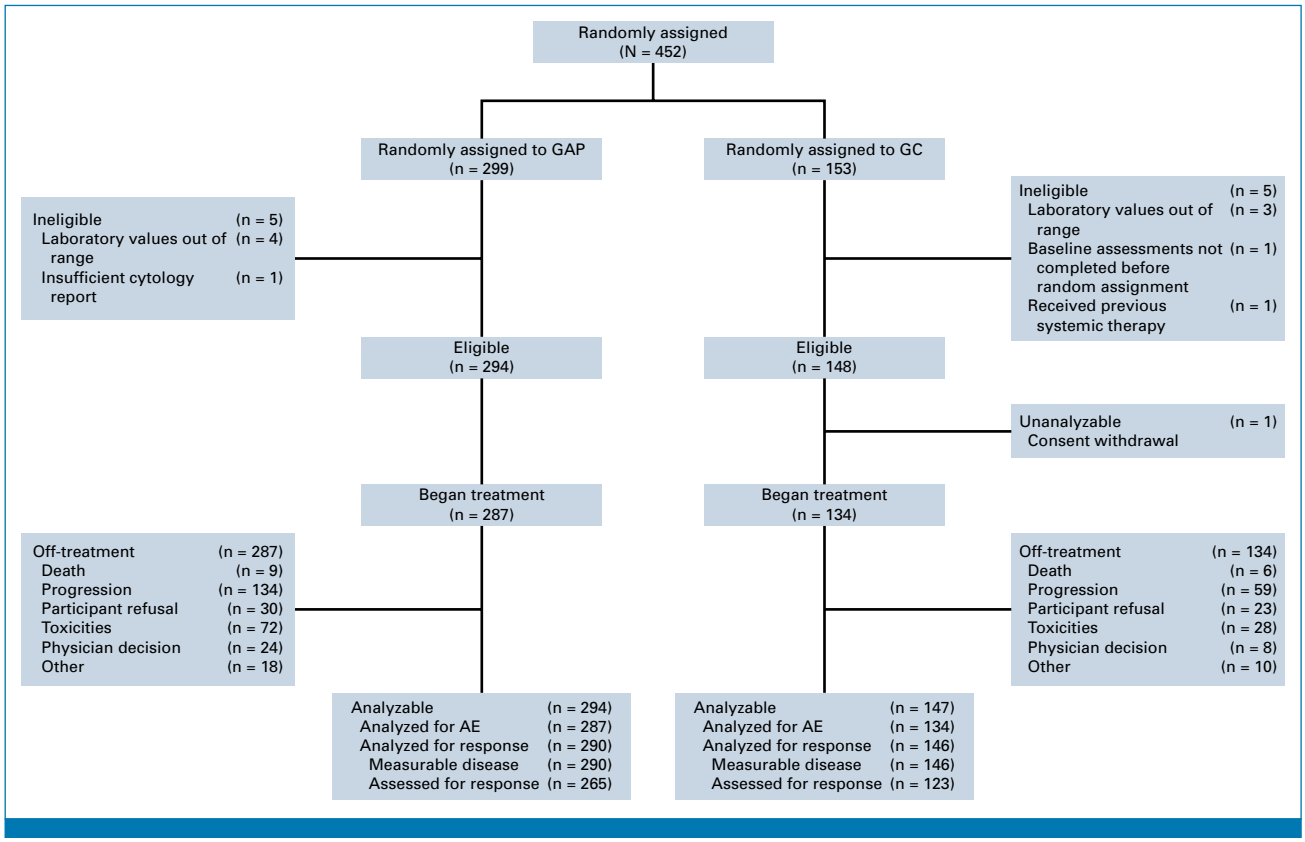

FIG 1. CONSORT diagram. AE, adverse event; GAP, gemcitabine, nab-paclitaxel, and cisplatin; GC, gemcitabine and cisplatin.

TABLE 1. Baseline Demographic and Clinical Characteristics

Characteristic	GAP (n = 294)	GC (n = 147)
Age, years, No.		
Median	63.2	63.9
Minimum	23.2	23.2
Maximum	88.8	83.6
Sex, No. (%)		
Males	132 (45)	66 (45)
Females	162 (55)	81 (55)
Race/ethnicity, No. (%)		
White	244 (83)	119 (81)
Black	18 (6)	7 (5)
Asian	14 (5)	7 (5)
Pacific Islander	1 (0)	0
Native American	2 (1)	1 (1)
Multiracial	0	1 (1)
Unknown	15 (5)	12 (8)
Hispanic, No. (%)		
Yes	30 (10)	15 (10)
No	256 (87)	125 (85)
Unknown	8 (3)	7 (5)
Biliary tract cancer disease site, No. (%)		
GBC	46 (16)	24 (16)
ICC	198 (67)	99 (67)
ECC	50 (17)	24 (16)
Disease stage, No. (%)		
Locally advanced	77 (26)	41 (28)
Metastatic	217 (74)	106 (72)
Performance status, No. (%)		
0	147 (50)	75 (51)
1	147 (50)	72 (49)

Abbreviations: ECC, extrahepatic cholangiocarcinoma; GAP, gemcitabine, nab-paclitaxel, and cisplatin; GBC, gallbladder carcinoma; GC, gemcitabine and cisplatin; ICC, intrahepatic cholangiocarcinoma.

in Figure 1. One participant refused protocol treatment and withdrew consent immediately after random assignment and thus was not included in the analyses. Of 441 eligible and analyzable participants, 55% were female; 67% of participants had ICC, 16% had GBC, and 17% had ECC. Most participants had metastatic disease (73%). Twenty additional participants never started protocol treatment and thus were not evaluable for AEs or response. Another 28 participants were not evaluable for response due to death or withdrawal before first disease assessment or inadequate disease assessments. These 48 participants are counted as nonresponders. Baseline participant characteristics were comparable across arms (Table 1).

Survival Analysis

OS was not statistically significantly different with GAP versus GC treatment (Fig 2A). The median OS with GAP was 14.0 months (95% CI, 12.4 to 16.1) and 13.6 months with GC (95% CI, 9.7 to 16.6); HR, 0.91 (95% CI, 0.72 to 1.14; $P = .41$). OS estimates at 12 and 24 months were 56% and 25%, respectively, in the GAP arm, and 53% and 28%, respectively, in the GC arm. PFS was also similar between the two arms. The median PFS for participants treated with GAP was 7.5 months (95% CI, 6.4 to 8.5) versus 6.3 months for participants treated with GC (95% CI, 4.4 to 8.2); HR, 0.89 (95% CI, 0.71 to 1.12; $P = .32$; Fig 2B).

In subset analyses, treatment with GAP versus GC showed greater improvement in PFS among participants with GBC than those with ICC or ECC (interaction $P = .01$), although the same was not true for OS (interaction $P = .28$; Figs 3A and 3B). There were greater gains in both OS and PFS for participants with locally advanced disease compared with those with metastatic disease, but the differences were not statistically significant (interaction $P = .14$ for OS and $P = .17$ for PFS; Figs 3C and 3D). Additional subgroup analyses are described in Table 2.

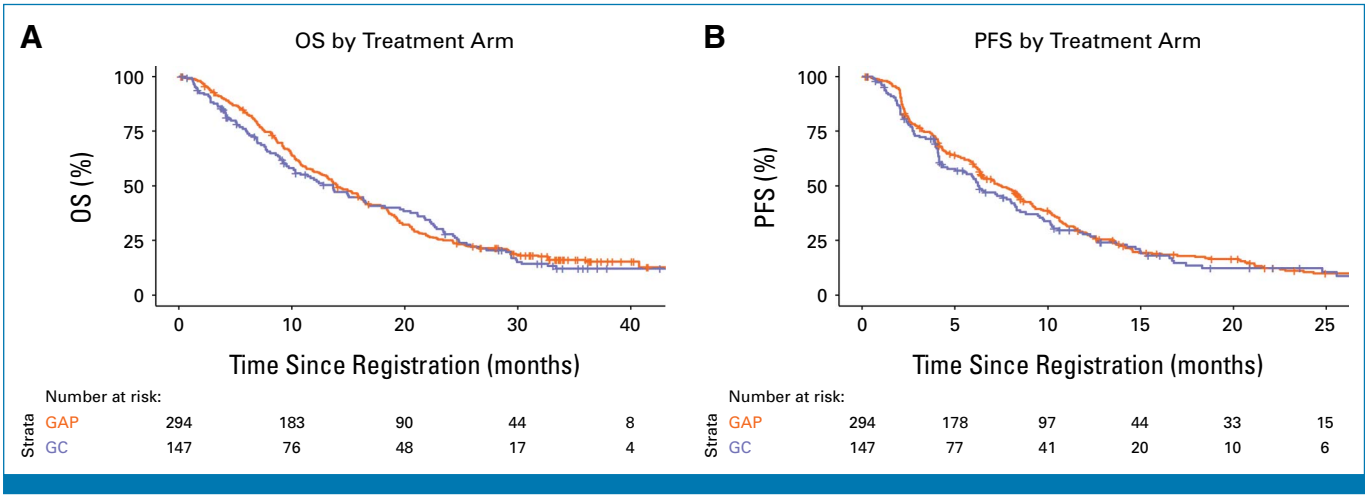

FIG 2. (A) OS by treatment arm. (B) PFS by treatment arm. GAP, gemcitabine, nab-paclitaxel, and cisplatin; GC, gemcitabine and cisplatin; OS, overall survival; PFS, progression-free survival.

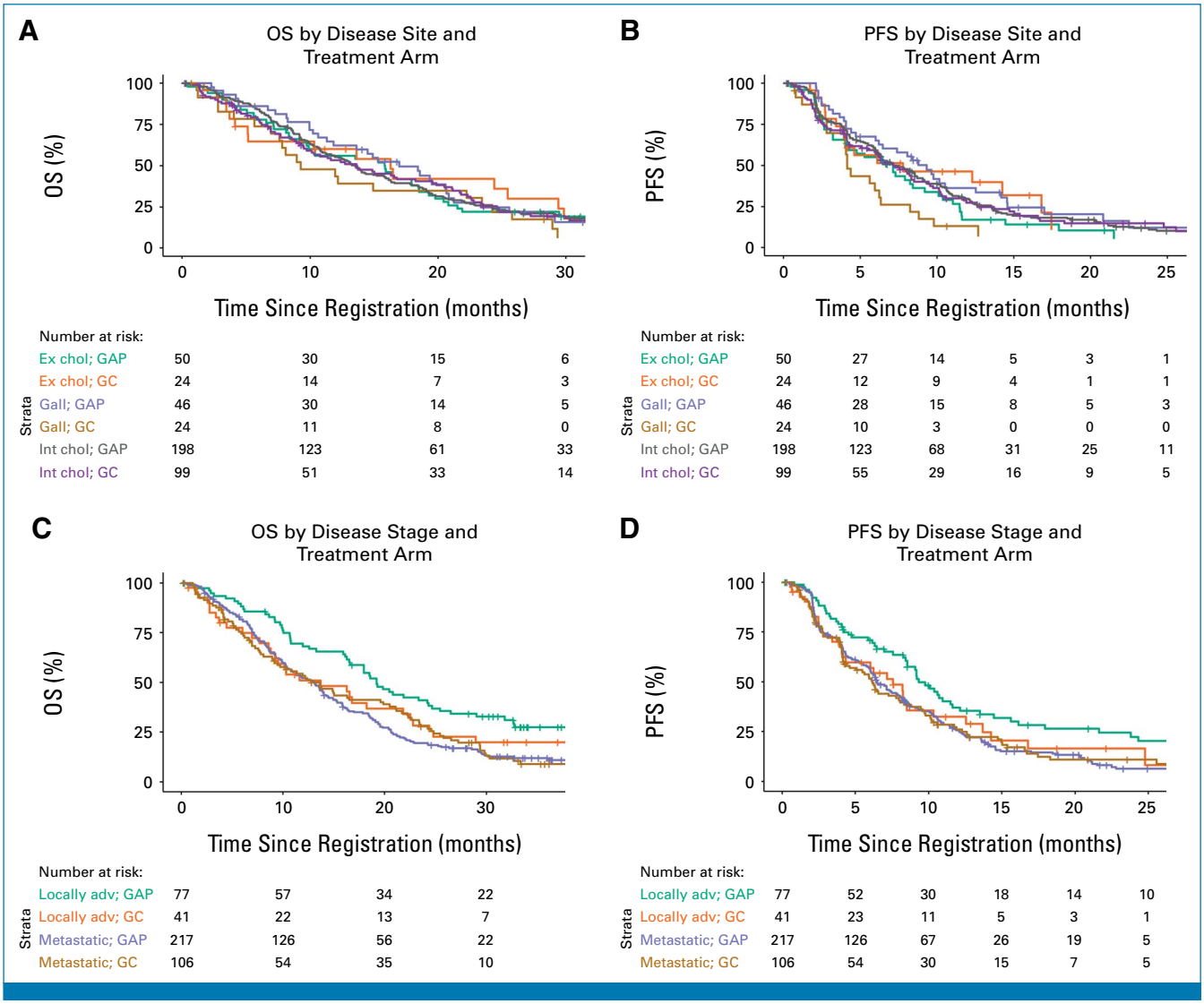

FIG 3. (A) OS by disease site and treatment arm. (B) PFS by disease site and treatment arm. (C) OS by disease stage and treatment arm. (D) PFS by disease stage and treatment arm. Ex chol, extrahepatic cholangiocarcinoma; Gall, gallbladder carcinoma; GAP, gemcitabine, nab-paclitaxel, and cisplatin; GC, gemcitabine and cisplatin; Int chol, intrahepatic cholangiocarcinoma; OS, overall survival; PFS, progression-free survival.

Radiographic Response to Therapy

Six complete and 85 partial responses were observed in the 290 participants with measurable disease in the GAP arm; one complete and 30 partial responses were observed in the 146 participants with measurable disease in the GAP arm (Appendix Table A1, online only). ORR and DCR were significantly higher in participants assigned to GAP compared with participants assigned to GC treatment, with ORR of 31% versus 21% (P = .03) and DCR of 78% versus 67% (P = .03), respectively. ORR by site and stage is described in Appendix Tables A2 and A3.

Treatment Response by CA 19-9 Levels

Baseline and post-cycle 3 CA 19-9 levels were available for 339/441 (77%) of the eligible and analyzable participants with measurable disease: one participant had a missing baseline CA 19-9 and 96 participants had missing post-treatment CA 19-9 level. Change in post-treatment CA 19-9 did not significantly vary between the GAP versus GC arms: median, −12; IQR, 292.31 U/mL, versus −3, 138.38 U/mL; P = .63. An increase in CA 19-9 was not significantly associated with ORR in the overall combined cohort of GAP (n = 237) plus GC (n = 102) participants. However, this association varied across treatment arms: a CA 19-9 increase was associated with a lower odds of response in the GAP arm, but no significant association was observed in the GC arm (interaction P = .09).

AEs and Safety

A total of 421 of the 441 eligible participants (95%) were evaluable for AEs. Grade 3-4 treatment-related AEs that

TABLE 2. Survival by Disease Site, Stage, and Treatment Arm

Disease Site/Stage	PFS, Months, Median (95% CI)	OS, Months, Median (95% CI)
Disease site and arm		
Intrahepatic cholangiocarcinoma		
GAP	7.5 (6.2 to 8.7)	13.5 (11.3 to 15.8)
GC	7.2 (5.0 to 9.5)	13.6 (9.5 to 19.6)
Extrahepatic cholangiocarcinoma		
GAP	7.1 (4.1 to 9.2)	15.9 (9.2 to 18.5)
GC	7.8 (4.0 to 16.8)	16.3 (5.1 to 29.4)
Gallbladder carcinoma		
GAP	9.3 (6.0 to 12.5)	17.0 (11.3 to 20.7)
GC	4.1 (2.8 to 6.2)	9.3 (7.0 to 22.2)
Disease stage and arm		
Locally advanced		
GAP	9.3 (8.3 to 11.5)	19.2 (16.3 to 24.3)
GC	7.6 (4.1 to 10.3)	13.7 (8.8 to 21.8)
Metastatic		
GAP	6.5 (5.9 to 7.9)	13.0 (10.6 to 14.3)
GC	6.1 (4.1 to 8.0)	13.6 (9.3 to 19.6)

Abbreviations: GAP, gemcitabine, nab-paclitaxel, and cisplatin; GC, gemcitabine and cisplatin; OS, overall survival; PFS, progression-free survival.

were seen in at least 10% of trial participants were anemia, neutropenia, and thrombocytopenia (Table 3). A significantly higher number of participants randomly assigned to GAP had grade 3 or higher treatment-related hematologic AEs than in the GC arm (60% *v* 45%; $P = .003$). The grade 3-4 treatment-related nonhematologic AEs, occurring significantly more frequently with GAP versus GC, were ALT increase, anorexia, constipation, diarrhea, edema, fatigue, hypomagnesemia, nausea, sepsis, sensory peripheral neuropathy, and vomiting. Seven deaths (grade 5 events) occurred and were attributable to GAP: cardiac arrest (one), sepsis (three), superior vena cava syndrome (one), thromboembolic event (one), and upper GI hemorrhage (one). Only one participant on the GC arm experienced a grade 5 event, secondary to progressive disease and potentially contributed to by cisplatin. A detailed tabulation of higher-grade AEs and their attribution is provided in Appendix Table A4.

The GAP arm also had significantly higher rates of dose modifications than GC: 88% versus 78%, $P = .008$. Rates of protocol treatment discontinuation because of toxicity were similar across arms: 72 of 294 (24%) versus 28 of 147 (19%, $P = .20$) with GAP versus GC, respectively.

DISCUSSION

To our knowledge, SWOG S1815 was the first randomized, phase III trial conducted entirely in the United States for newly diagnosed advanced BTCs. The study accrued over 450 patients in just over 2 years, demonstrating the large unmet need for novel therapies for this patient population. OS was not significantly improved with GAP triplet versus the standard doublet GC (median, 14.0 *v* 13.6 months). Not surprisingly, grades 3 and 4 hematologic AEs and grade 3 peripheral sensory neuropathy were higher with GAP treatment versus GC alone. Therefore, despite the promising efficacy signal in the phase II study of GAP, this phase III study did not confirm the benefit of triplet cytotoxic therapy in an unselected BTC population.

For more than a decade since the pivotal ABC-02 study in 2010, GC has been the standard first-line systemic treatment for patients with advanced BTCs, with median OS of 11.7 months.[7] Two randomized phase III trials have since established the role of combining ICIs with GC, resulting in improvements in median OS from 11.5 to 12.8 months (HR, 0.80), and from 10.9 to 12.7 months (HR, 0.83) respectively, compared with GC alone.[2,3] The advent of molecular profiling has also led to the identification of targetable alterations and expansion of the treatment armamentarium in subsets of patients with advanced BTC in the second line and beyond.[10] However, precision treatments are not applicable for most BTCs and the magnitude of improvement with the addition of ICIs to GC appears modest, with median OS remaining around 12 months.[2,3] As such, improving therapeutic options for newly diagnosed patients with advanced BTC remains an area of priority.

The observed median OS of approximately 14 months in both arms is among the highest OS reported to date for a phase III randomized trial in BTCs. Although BTCs are heterogeneous, S1815 enrolled similar numbers of participants with ICC, ECC, and GBC compared with other randomized studies, and the proportion of participants with locally advanced disease

TABLE 3. Treatment-Related AEs

	GAP (n = 287), No. (%)		GC (n = 134), No. (%)	
AE	Grade 1 and 2	Grade 3 and 4	Grade 1 and 2	Grade 3 and 4
Alkaline phosphatase increased	58 (20)	3 (1)	20 (15)	1 (1)
ALT increased	72 (25)	6 (2)	24 (18)	1 (1)
Anemia	132 (46)	95 (33)	49 (37)	30 (22)
Anorexia	73 (25)	8 (3)	36 (26)	0
AST increased	58 (20)	5 (2)	20 (15)	0
Constipation	76 (27)	1 (0)	38 (28)	0
Creatinine increased	49 (17)	1 (0)	24 (18)	0
Dehydration	30 (11)	4 (2)	6 (5)	2 (2)
Diarrhea	99 (35)	13 (5)	34 (26)	1 (1)
Dizziness	41 (14)	1 (0)	13 (10)	0
Dyspnea	41 (14)	0	9 (7)	2 (2)
Edema limbs	75 (26)	4 (2)	19 (14)	0
Epistaxis	29 (10)	2 (1)	7 (5)	0
Fatigue	173 (60)	27 (9)	77 (57)	8 (6)
Fever	35 (12)	1 (0)	9 (7)	0
Headache	32 (11)	1 (0)	19 (14)	0
Hyperglycemia	18 (6)	0	13 (10)	1 (1)
Hypoalbuminemia	45 (16)	5 (2)	10 (7)	1 (1)
Hypocalcemia	37 (13)	3 (1)	16 (12)	1 (1)
Hypokalemia	27 (9)	9 (3)	14 (10)	2 (2)
Hypomagnesemia	103 (36)	6 (2)	41 (30)	5 (4)
Hyponatremia	53 (18)	6 (2)	15 (11)	4 (3)
Lymphocyte count decreased	55 (19)	30 (11)	21 (16)	4 (3)
Mucositis oral	31 (10)	2 (1)	15 (11)	0
Nausea	148 (52)	11 (4)	79 (59)	1 (1)
Neutrophil count decreased	61 (21)	105 (37)	38 (28)	37 (28)
Peripheral sensory neuropathy	123 (43)	10 (4)	30 (22)	1 (1)
Platelet count decreased	111 (39)	56 (20)	33 (24)	20 (15)
Vomiting	70 (24)	5 (2)	37 (28)	0
WBC decreased	75 (26)	46 (16)	37 (28)	10 (8)
Maximum grade, all hematologic toxicities	78 (27)	173 (60)	44 (33)	60 (45)
Maximum grade, all nonhematologic toxicities	155 (54)	118 (41)	88 (66)	38 (28)
Maximum grade, any AE	68 (24)	206 (71)	49 (37)	81 (60)

Abbreviations: AE, adverse event; GAP, gemcitabine, nab-paclitaxel, and cisplatin; GC, gemcitabine and cisplatin.

was also similar. Triplet chemotherapy combinations have a role in the treatment of several GI cancers; several regimens demonstrated superior OS with triplet versus doublet chemotherapy in randomized studies.[11-13] In our previous phase II study, GAP demonstrated an ORR of 45% with a conversion rate from unresectable to resectable disease of 20%.[6] Although the current study does not reflect a similarly high ORR, there was a significant difference between the two treatment arms with GAP demonstrating an ORR of 31% versus 21% for GC ($P = .04$). The 31% ORR with GAP from SWOG 1815 is similar to those reported for ICI combinations with GC in TOPAZ-1 (26.7%) and KEYNOTE 966 (29%).[2,3] Despite encouraging trends for ORR, OS benefit for GAP versus GC could not be demonstrated. A similar pattern was shown in the phase III PRODIGE 38 AMEBICA trial, which evaluated modified fluourouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) versus GC in advanced BTC. In the previous phase II study of oxaliplatin and irinotecan and S-1 triplet chemotherapy, ORR was 50%, while the phase III AMEBICA trial demonstrated an ORR of 25% only, without an OS advantage over doublet GC alone. In fact, the mOS was lower for modified FOLFIRINOX at 11.7 months (95% CI, 9.5 to 14.2) versus 13.8 months (95% CI, 10.9 to 16.1) for GC.[14,15] As such, the survival benefit of intensifying cytotoxic chemotherapy to triplet regimens in an unselected population of newly diagnosed advanced BTC remains elusive.

The toxicity of the triplet regimen was also apparent in this SWOG S1815. GAP treatment resulted in a significantly higher

frequency of treatment-related grade 3 or higher AEs and higher rates of dose modifications because of toxicity. Although we do not have specific data on dose intensity and length on treatment, it would have been helpful to have obtained these data to assess its relationship with survival. In addition, although it is difficult to ascertain causality of grade 5 events on the GAP arm, the difference in the frequency of grade 5 events between the two arms is noteworthy (seven grade 5 events for GAP, one for GC). Moreover, the starting doses for GAP chemotherapy on SWOG S1815 were adapted from dose adjustments from the previous phase II study, where a more dose-dense regimen was initially used.[6] Despite the prudence of this adjustment, toxicity remained significant without providing clear survival benefit over standard GC.

Although based on exploratory subset analyses, the greater OS and PFS treatment effects with GAP versus GC in GBC compared with other BTCs are noteworthy in S1815. These results suggest tumor heterogeneity and differences in therapeutic susceptibility among BTCs, as these effects were not observed in TOPAZ-1 with GC plus durvalumab. In addition, greater OS and PFS treatment effects of GAP versus GC were observed in the S1815 locally advanced population compared with metastatic disease. These observations suggest further study of differential chemotherapy regimens in these specific populations. The feasibility of administering GAP in a neoadjuvant setting for patients with high-risk, resectable cholangiocarcinoma was demonstrated in the NEO-GAP study, suggesting that studying this combination in a perioperative approach could be meaningful.[16]

Analysis of radiographic response according to CA 19-9 dynamics is potentially useful to identify early responders. Although not used in this study, circulating tumor DNA is potentially more sensitive and specific than CA 19-9 and can be considered in future studies.[17,18] Ongoing molecular profiling for participants in this study will be important to potentially identify specific genomic subsets that derive benefit from GAP over GC.

In conclusion, triplet cytotoxic therapy with GAP did not improve OS compared with GC in newly diagnosed patients with advanced BTC. Acknowledging the heterogeneous biology of biliary malignancies, there is a need for rational genomic, transcriptomic, and artificial intelligence tools to not only select patients for targeted molecular and immune therapies, but also to guide targeted cytotoxic chemotherapies in future clinical trials.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Valle JW, Kelley RK, Nervi B, et al: Biliary tract cancer. Lancet 397:428-444, 2021
2. Kelley RK, Ueno M, Yoo C, et al: Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 401:1853-1865, 2023
3. Oh D-Y, Ruth He A, Qin S, et al: Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid 1:EVIDoa2200015, 2022
4. Wei D, Cheng X, Du C, et al: Stroma-targeted nanoparticles that remodel stromal alignment to enhance drug delivery and improve the antitumor efficacy of nab-paclitaxel in pancreatic ductal adenocarcinoma models. Nano Today 45:101533, 2022
5. Chang PM, Cheng CT, Wu RC, et al: Nab-paclitaxel is effective against intrahepatic cholangiocarcinoma via disruption of desmoplastic stroma. Oncol Lett 16:566-572, 2018
6. Shroff RT, Javle MM, Xiao L, et al: Gemcitabine, cisplatin, and nab-paclitaxel for the treatment of advanced biliary tract cancers: A phase 2 clinical trial. JAMA Oncol 5:824-830, 2019
7. Valle J, Wasan H, Palmer DH, et al: Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 362:1273-1281, 2010
8. US Department of Health and Human Services: Common Terminology Criteria for Adverse Events (CTCAE) v.5, Cancer. 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50
9. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247, 2009
10. Scott AJ, Sharman R, Shroff RT: Precision medicine in biliary tract cancer. J Clin Oncol 40:2716-2734, 2022
11. Conroy T, Desseigne F, Ychou M, et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817-1825, 2011
12. Cremolini C, Antoniotti C, Rossini D, et al: Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): A multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol 21:497-507, 2020
13. Al-Batran S-E, Homann N, Pauligk C, et al: Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): A randomised, phase 2/3 trial. Lancet 393:1948-1957, 2019
14. Phelip JM, Desrame J, Edeline J, et al: Modified FOLFIRINOX versus CISGEM chemotherapy for patients with advanced biliary tract cancer (PRODIGE 38 AMEBICA): A randomized phase II study. J Clin Oncol 40:262-271, 2022
15. Yoo C, Han B, Kim HS, et al: Multicenter phase II study of oxaliplatin, irinotecan, and S-1 as first-line treatment for patients with recurrent or metastatic biliary tract cancer. Cancer Res Treat 50:1324-1330, 2018
16. Maithel SK, Keilson JM, Cao HST, et al: NEO-GAP: A single-arm, phase II feasibility trial of neoadjuvant gemcitabine, cisplatin, and nab-paclitaxel for resectable, high-risk intrahepatic cholangiocarcinoma. Ann Surg Oncol 30:6558-6566, 2023
17. King G, Cohen SA, Chiorean EG, et al: 114P Prospective longitudinal tumor-informed ctDNA in resectable biliary tract cancers. Ann Oncol 34:S225, 2023
18. Yoo C, Laliotis G, Jeong H, et al: Utility of circulating tumor DNA (ctDNA) as a predictive biomarker for disease monitoring in patients (pts) with cholangiocarcinoma (CCA) before and during adjuvant chemotherapy (ACT): Sub-analysis of the randomized phase 2 STAMP trial. J Clin Oncol 41, 2023 (suppl 16; abstr 4123)

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APPENDIX

TABLE A1. Radiographic Response by Treatment Arm

Characteristic	GAP, No. (%)	GC, No. (%)
Complete response	6 (2)	1 (1)
Partial response	55 (19)	11 (8)
Unconfirmed complete response	0	0
Unconfirmed partial response	30 (10)	19 (13)
Stable/no response	134 (46)	67 (46)
Increasing disease	38 (13)	22 (15)
Symptomatic deterioration	2 (1)	3 (2)
Assessment inadequate	25 (9)	23 (16)
Total	290 (100)	146 (100)

Abbreviations: GAP, gemcitabine, nab-paclitaxel, and cisplatin; GC, gemcitabine and cisplatin.

TABLE A2. Radiographic Response by Disease Site and Treatment Arm

Disease Site, Response	GAP, No. (%)	GC, No. (%)
Intrahepatic cholangiocarcinoma	N = 196	N = 98
Overall response	55 (28)	21 (21)
Disease control	152 (78)	63 (64)
Extrahepatic cholangiocarcinoma	N = 48	N = 24
Overall response	16 (33)	5 (21)
Disease control	37 (77)	19 (79)
Gallbladder carcinoma	N = 46	N = 24
Overall response	20 (43)	5 (21)
Disease control	36 (78)	16 (67)

Abbreviations: GAP, gemcitabine, nab-paclitaxel, and cisplatin; GC, gemcitabine and cisplatin.

TABLE A3. Radiographic Response by Disease Stage and Treatment Arm

Disease Stage, Response	GAP, No. (%)	GC, No. (%)
Locally advanced	N = 74	N = 41
Overall response	21 (28)	8 (20)
Disease control	65 (88)	27 (66)
Metastatic	N = 216	N = 105
Overall response	70 (32)	23 (22)
Disease control	160 (74)	71 (68)

Abbreviations: GAP, gemcitabine, nab-paclitaxel, and cisplatin; GC, gemcitabine and cisplatin.

TABLE A4. Number of Participants With a Given Type and Grade of AE

	Gemcitabine + Cisplatin + Nab-Paclitaxel (n = 287), No.					Gemcitabine + Cisplatin (n = 134), No.				
	Grade					Grade				
AE	1	2	3	4	5	1	2	3	4	5
Abdominal pain	10	7	2	0	0	4	3	0	0	0
Acute kidney injury	0	0	5	0	0	0	0	3	0	0
Alkaline phosphatase increased	46	12	3	0	0	14	6	1	0	0
ALT increased	60	12	6	0	0	21	3	1	0	0
Anemia	33	99	91	4	0	17	32	30	0	0
Anorexia	45	28	8	0	0	20	16	0	0	0
Arthralgia	15	3	1	0	0	8	0	0	0	0
Ascites	0	3	2	0	0	1	2	0	0	0
AST increased	55	3	5	0	0	18	2	0	0	0
Ataxia	3	0	1	0	0	0	0	0	0	0
Atrial fibrillation	0	1	1	0	0	0	0	0	0	0
Back pain	3	1	1	0	0	2	0	0	0	0
Blood bilirubin increased	9	4	3	0	0	7	3	1	0	0
Blood/lymph disorder—other	7	4	1	0	0	0	1	1	0	0
Cardiac arrest	0	0	0	0	1	0	0	0	0	0
Catheter-related infection	0	0	0	0	0	0	0	1	0	0
Cholecystitis	0	0	1	0	0	0	0	0	0	0
Chronic kidney disease	0	6	2	0	0	0	5	0	1	0
Colitis	0	3	2	0	0	0	0	0	0	0
Constipation	59	17	1	0	0	31	7	0	0	0
Creatinine increased	33	16	1	0	0	12	12	0	0	0
Death NOS	0	0	0	0	0	0	0	0	0	1
Dehydration	5	25	4	0	0	0	6	2	0	0
Delirium	0	0	1	0	0	0	0	0	0	0
Diarrhea	75	24	13	0	0	29	5	1	0	0
Dizziness	36	5	1	0	0	11	2	0	0	0
Dysphagia	3	1	1	0	0	1	0	0	0	0
Dyspnea	35	6	0	0	0	7	2	2	0	0
Edema limbs	59	16	4	0	0	16	3	0	0	0
Endocarditis infective	0	0	0	0	0	0	0	0	1	0
Enterocolitis	0	0	0	1	0	0	0	0	0	0
Enterocolitis infectious	0	0	3	0	0	0	0	0	0	0
Epistaxis	27	2	2	0	0	7	0	0	0	0
Esophagitis	0	0	1	0	0	0	0	0	0	0
Fatigue	89	84	27	0	0	47	30	8	0	0
Febrile neutropenia	0	0	7	3	0	0	0	1	1	0
Fever	30	5	1	0	0	5	4	0	0	0
Flu-like symptoms	13	1	2	0	0	2	1	0	0	0
Gallbladder infection	0	0	0	0	0	0	0	1	0	0
Gastric hemorrhage	0	0	0	1	0	0	0	0	0	0
Generalized disorders—other	6	2	1	0	0	3	0	0	0	0
Generalized muscle weakness	15	7	3	0	0	4	5	1	0	0
GGT increased	0	0	2	0	0	0	0	0	0	0
GI disorders—other	7	2	1	0	0	1	0	0	0	0
Headache	28	4	1	0	0	18	1	0	0	0
Hearing impaired	4	3	1	0	0	3	2	0	0	0

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TABLE A4. Number of Participants With a Given Type and Grade of AE (continued)

	Gemcitabine + Cisplatin + Nab-Paclitaxel (n = 287), No.					Gemcitabine + Cisplatin (n = 134), No.				
	Grade					Grade				
AE	1	2	3	4	5	1	2	3	4	5
Heart failure	0	0	0	0	0	0	0	0	1	0
Hematuria	2	0	1	0	0	0	0	0	0	0
Hepatic infection	0	0	1	0	0	0	0	1	0	0
Hepatobiliary disorders—other	0	0	2	0	0	0	0	0	0	0
Hyperglycemia	12	6	0	0	0	12	1	1	0	0
Hyperkalemia	4	0	2	0	0	2	0	0	0	0
Hypertension	3	9	7	0	0	3	5	1	0	0
Hypoalbuminemia	23	22	5	0	0	6	4	1	0	0
Hypocalcemia	24	13	3	0	0	12	4	1	0	0
Hypokalemia	17	10	8	1	0	12	2	2	0	0
Hypomagnesemia	74	29	6	0	0	31	10	4	1	0
Hyponatremia	47	6	5	1	0	13	2	3	1	0
Hypotension	4	6	2	1	0	2	1	1	0	0
Infections/infestations—other	0	0	3	0	0	0	0	2	0	0
Infusion-related reaction	0	9	0	0	0	0	1	1	0	0
Investigations—other	8	3	1	0	0	5	0	0	0	0
Lung infection	0	1	2	0	0	0	0	0	0	0
Lymphocyte count decreased	20	35	24	6	0	9	12	3	1	0
Memory impairment	1	0	1	0	0	0	0	0	0	0
Mucositis oral	24	7	2	0	0	14	1	0	0	0
Multiorgan failure	0	0	1	0	0	0	0	0	0	0
Muscle weakness lower limb	5	2	1	0	0	1	0	0	0	0
Myalgia	15	8	1	0	0	9	2	0	0	0
Nausea	106	42	11	0	0	57	22	1	0	0
Neutrophil count decreased	13	48	75	30	0	7	31	30	7	0
Pain	4	2	1	0	0	3	2	0	0	0
Paresthesia	10	5	1	0	0	11	0	0	0	0
Peripheral motor neuropathy	11	10	1	0	0	3	2	0	0	0
Peripheral sensory neuropathy	52	71	10	0	0	22	8	1	0	0
Peritoneal infection	0	0	0	0	0	0	0	1	0	0
Platelet count decreased	62	49	32	24	0	22	11	11	9	0
Pleural effusion	0	1	1	0	0	0	0	0	0	0
Portal vein thrombosis	0	0	0	0	0	0	0	1	0	0
Rectal hemorrhage	2	0	1	0	0	0	0	0	0	0
Respiratory disease—other	1	0	1	0	0	0	1	0	0	0
Respiratory failure	0	0	0	1	0	0	0	0	0	0
Seizure	0	0	0	0	0	0	0	1	0	0
Sepsis	0	0	9	3	3	0	0	3	0	0
Skin infection	3	5	4	0	0	1	2	1	0	0
Superior vena cava syndrome	0	0	0	0	1	0	0	0	0	0
Supraventricular tachycardia	1	0	1	0	0	0	0	0	0	0
Syncope	0	0	2	0	0	0	0	1	0	0
Thromboembolic event	3	13	7	1	1	0	5	1	0	0
Thrush	8	11	1	0	0	0	1	0	0	0
Typhlitis	0	0	1	0	0	0	0	0	0	0
Upper GI hemorrhage	0	1	0	1	1	0	0	0	0	0

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TABLE A4. Number of Participants With a Given Type and Grade of AE (continued)

	Gemcitabine + Cisplatin + Nab-Paclitaxel (n = 287), No.					Gemcitabine + Cisplatin (n = 134), No.				
	Grade					Grade				
AE	1	2	3	4	5	1	2	3	4	5
Urinary tract infection	0	7	4	0	0	0	3	0	1	0
Vascular access complication	0	0	1	0	0	0	0	0	0	0
Vasovagal reaction	0	0	1	0	0	0	0	0	0	0
Vomiting	46	24	5	0	0	28	9	0	0	0
Wheezing	1	0	0	0	0	0	0	1	0	0
WBC decreased	27	48	31	15	0	15	22	8	2	0
Maximum grade, all hematologic toxicities	11	67	120	53	0	14	30	44	16	0
Maximum grade, all nonhematologic toxicities	31	124	109	9	7	30	58	31	7	1
Maximum grade any AE	12	56	150	56	7	16	33	60	21	1

NOTE. AEs unlikely or not related to treatment excluded. AEs with no entries for grades 3-5 have been suppressed. Data as of October 4, 2023.
Abbreviations: AE, adverse event; GGT, gamma glutamyl transferase; NOS, not otherwise specified.