Ibrutinib in Combination with Nab-Paclitaxel and Gemcitabine for First-Line Treatment of Patients with Metastatic Pancreatic Adenocarcinoma: Phase 3 RESOLVE Study

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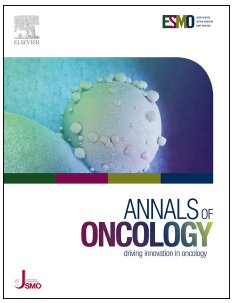

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Ibrutinib in Combination with Nab-Paclitaxel and Gemcitabine for First-Line Treatment of Patients with Metastatic Pancreatic Adenocarcinoma: Phase 3 RESOLVE Study

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SHORT RUNNING TITLE (54 / 80 characters with spaces max): First-line ibrutinib plus Nab-P/GCB in metastatic PDAC

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Abstract

Background

First-line treatment for metastatic pancreatic ductal adenocarcinoma (PDAC) includes nab-paclitaxel/gemcitabine. Ibrutinib, a Bruton's tyrosine kinase inhibitor, exhibits antitumor activity through tumor microenvironment modulation. The safety and efficacy of first-line ibrutinib plus nab-paclitaxel/gemcitabine treatment in patients with PDAC was evaluated.

Patients and methods

RESOLVE (NCT02436668) was a phase 3, randomized, double-blind, placebo-controlled study. Patients (histologically-confirmed PDAC; stage IV diagnosis ≥6 weeks of randomization; Karnofsky performance score ≥70) were randomized to once-daily oral ibrutinib (560 mg) or placebo plus nab-paclitaxel (125 mg/m^2) and gemcitabine (1,000 mg/m^2). Primary endpoints were overall survival (OS) and investigator-assessed progression-free survival (PFS); overall response rate (ORR) and safety were assessed.

Results

In total, 424 patients were randomized (ibrutinib arm, *n*=211; placebo arm, *n*=213). Baseline characteristics were balanced across arms. After median follow-up of 25 months, there was no significant difference in OS between ibrutinib plus nab-paclitaxel/gemcitabine vs placebo plus nab-paclitaxel/gemcitabine (median of 9.7 vs 10.8 months; *P*=0.3225). PFS was shorter for ibrutinib plus nab-paclitaxel/gemcitabine compared with placebo plus nab-paclitaxel/gemcitabine (median 5.3 vs 6.0 months; *P*<0.0001). ORRs were 29% and 42%, respectively (*P*=0.0058). Patients in the ibrutinib arm had less time on treatment and received lower cumulative dose for all agents compared to placebo arm. Most common grade ≥3 adverse events (AEs) for ibrutinib vs placebo arms included neutropenia (24% vs 35%), peripheral sensory neuropathy (17% vs 8%), and anemia (16% vs 17%). Primary reasons for any treatment discontinuation were disease progression and AEs.

Conclusions

Ibrutinib plus nab-paclitaxel/gemcitabine did not improve OS or PFS for patients with PDAC. Safety was consistent with known profiles for these agents.

ClinicalTrials.gov registration: NCT02436668; EudraCT Number: 2015-000905-38

KEY WORDS: phase 3, ibrutinib, metastatic pancreatic adenocarcinoma

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INTRODUCTION

Advanced pancreatic ductal adenocarcinoma (PDAC) is characterized by rapid disease progression and poor prognosis; the 5-year survival rate of 9%[1] marks PDAC as one of the most intractable malignancies. Gemcitabine monotherapy represented the standard of care for first-line treatment of patients with PDAC for several years.[2,3] Modest advances in survival came with combination therapies including FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) and gemcitabine plus nab-paclitaxel (albumin bound paclitaxel particles). FOLFIRINOX treatment of patients with good performance status has resulted in a median overall survival of 11.1 months (versus 6.8 months, gemcitabine alone).[4] The combination of gemcitabine plus nab-paclitaxel demonstrated a median overall survival of 8.5 months,[3] an increase in 1.8 months versus gemcitabine alone.

There remains, however, an ongoing unmet need for novel and innovative approaches for this challenging malignancy, as current regimens are only marginally effective in extending survival and few advances have been made in over 3 decades.[5-7] Several emerging lines of evidence indicate that inhibition of the B-cell and myeloid cell signaling molecule Bruton's tyrosine kinase (BTK) may represent a novel anti-tumor target.[8] Ibrutinib, a first-in-class inhibitor of BTK, is approved for the treatment of various B-cell malignancies and chronic graft-versus-host-disease.[9]

In pre-clinical models of PDAC, ibrutinib plus gemcitabine resulted in significantly reduced late-stage tumor burden and significantly increased survival by $CD8^+$ T cell-dependent mechanisms.[8,10] Additional mechanisms implicated in the anti-tumor activity of ibrutinib plus chemotherapy include: (1) changes in the tumor microenvironment, e.g., inhibition of mast cell function, decreased angiogenesis, decreased desmoplasia[10,11]; and (2) changes in immune profiles, e.g., alteration of Th1/Th2 transcriptional profiles[12] accompanying increased $CD8^+$ T-cell cytotoxicity.[8] Given these findings from PDAC models, the combination of ibrutinib plus nab-

paclitaxel and gemcitabine was evaluated for first-line treatment of patients with PDAC in the phase 3 RESOLVE study.

PATIENTS AND METHODS

Study design

RESOLVE (PCYC-1137; ClinicalTrials.gov ID NCT02436668) was a randomized, multicenter, double-blind, placebo-controlled, phase 3 study comparing ibrutinib plus nab-paclitaxel and gemcitabine versus placebo plus nab-paclitaxel and gemcitabine in the first-line treatment of patients with metastatic PDAC. Prior to the randomization portion of the trial, a safety run-in of 6 patients (ibrutinib plus nab-paclitaxel and gemcitabine) was conducted. The results of this safety run-in were reviewed by the Data Monitoring Committee (DMC) and used to determine the ibrutinib dose for the randomized portion (560 mg). Patients were randomly assigned in a 1:1 fashion to receive either ibrutinib in combination with nab-paclitaxel and gemcitabine or placebo in combination with nab-paclitaxel and gemcitabine. Randomization was stratified according to Karnofsky Performance Status (KPS; 70–80 vs 90–100), liver metastasis (present vs absent), and age (≤65 years vs >65 years). Patients and investigators were blinded to treatment assignment. Treatment in the double-blind randomized phase consisted of oral ibrutinib or placebo (560 mg once daily) given until disease progression or unacceptable toxicity in combination with intravenous nab-paclitaxel (125 mg/m^2) and intravenous gemcitabine (1000 mg/m^2) on day 1, 8, and 15 of each 28-day cycle until disease progression or unacceptable toxicity.

The study was done in accordance with International Conference on Harmonization Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol was

approved by institutional review boards or independent ethics committees of all participating institutions. All patients provided written, informed consent.

Patients

Eligible patients were aged ≥18 years and had a histologically confirmed diagnosis of Stage IV PDAC within 6 weeks of randomization that was also evaluable per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines[13] with at least 1 measurable metastatic lesion. Additional eligibility criteria were adequate hematologic function independent of transfusion and growth factor support, adequate hepatic and renal function, KPS of ≥70, and Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1. Key exclusion criteria included patients with any previous cytotoxic chemotherapy for primary disease of PDAC, radiotherapy in the adjuvant setting within the last 6 months, and non-adenocarcinoma of the pancreas.

Study endpoints and assessments

Efficacy was assessed in the intent-to-treat (ITT) population, defined as all patients randomly assigned to each arm. The primary endpoints were OS and investigator-assessed progression-free survival (PFS). Secondary endpoints included clinical benefit response (CBR) rate, overall response rate (ORR) per investigator assessment, carbohydrate antigen 19-9 (CA19-9) response, and patient-reported outcomes (PRO) via the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30), measured by time until definitive deterioration (TUDD1, defined as time between randomization and first occurrence of a decrease ≥10 points in QLQ-C30 score without further improvement ≥10 points or further data due to discontinuation).[14] Additional secondary endpoints were rate of venous thromboembolic events and evaluation of the safety and tolerability of ibrutinib plus nab-paclitaxel and gemcitabine versus placebo plus nab-paclitaxel and gemcitabine.

Response evaluations were performed every 8 weeks and all radiologic scans were assessed for response or progression using RECIST 1.1 guidelines. Grading for best response was categorized as complete response (CR), partial response (PR), stable disease (SD; ≥8 weeks), or progressive disease (PD). Safety was assessed in the safety population, defined as all patients receiving ≥1 dose of any study drug. Adverse events (AEs) were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. An independent DMC monitored data on an ongoing basis to ensure the continuing safety of the patients enrolled/randomized in this study.

Statistical analysis

The primary endpoints OS and PFS per investigator assessment were summarized for each treatment arm using Kaplan-Meier estimates and compared using a stratified log-rank test. A 2-sided family-wise Type I error rate of 0.05 was used, with 0.043 allocated to the OS primary analysis and 0.007 allocated to the PFS primary analysis. All *P*-values reported are nominal, with the exception of primary endpoints.

RESULTS

Patients and disposition

RESOLVE enrolled a total of 424 eligible patients beginning on 08 May 2015 (**Figure 1**). The ITT population consisted of 211 patients randomly assigned to receive ibrutinib plus nab-paclitaxel and gemcitabine, and 213 patients randomly assigned to receive placebo plus nab-paclitaxel and gemcitabine. In the ibrutinib plus nab-paclitaxel and gemcitabine arm, 208 patients received ≥1 dose of study treatment (safety population); 2 patients (1%) were not treated due to investigator decision and 1 patient (0.5%) was not treated due to an AE. In the placebo plus nab-paclitaxel and gemcitabine arm, 212 patients received ≥1 dose of study treatment (safety population); 1 patient (0.5%) was not treated due to investigator decision.

Patient demographics and disease characteristics were well balanced across study arms and are summarized in Table 1. The median age was 64.0 years (range, 32–85), and 23% of patients were aged >70 years. More men were enrolled than women (55% vs 45%, respectively) and the majority of patients were white (68%). Greater than 2 sites of metastatic disease were observed in 125 patients (30%) and liver metastases were present in 341 patients (80%) (**Table 1**).

The median time from stage IV diagnosis to randomization was 3.0 weeks (range, 0.1–55.0). Fifty-nine patients (14%) received a prior cancer surgery (of these, *n*=19 pancreaticoduodenectomy, *n*=3 distal pancreatectomy with or without splenectomy), 5 patients (1%) received prior chemotherapy, and 11 patients (3%) received prior radiation therapy (**Table 1**). Two patients (0.5%) were enrolled who received prior chemotherapy for pancreatic cancer. The primary reason for discontinuation of any drug, inclusive of placebo, was disease progression followed by AEs not related to disease progression (**Table 2**). The median follow-up was 24.9 months (range: 0.1+–31.1+).

Efficacy

The primary endpoint of OS was not significantly different for ibrutinib plus nab-paclitaxel and gemcitabine versus placebo plus nab-paclitaxel and gemcitabine (HR=1.109; 95% CI: 0.903–1.363; *P*=0.3225) (**Figure 2A**). The median OS was 9.7 months for ibrutinib plus nab-paclitaxel and gemcitabine versus 10.8 months for placebo plus nab-paclitaxel and gemcitabine. Estimated OS rates at 24 months were 9.5% for the ibrutinib plus nab-paclitaxel and gemcitabine arm and 10.5% for placebo plus nab-paclitaxel and gemcitabine. No significant differences were observed in a subgroup analysis (**Supplementary Figure S1**).

PFS per investigator assessment was significantly different for ibrutinib plus nab-paclitaxel and gemcitabine versus placebo plus nab-paclitaxel and gemcitabine (HR=1.564; 95% CI: 1.277–

1.916; *P*<0.0001) (**Figure 2B**). Median PFS times were 5.3 months for ibrutinib plus nab-paclitaxel and gemcitabine, and 6.0 months for placebo plus nab-paclitaxel and gemcitabine. Estimated PFS rates per investigator assessment at 18 months were 3% for ibrutinib plus nab-paclitaxel and gemcitabine versus 6% for placebo plus nab-paclitaxel and gemcitabine.

The secondary endpoint of ORR per investigator assessment was 29% (62/211) for ibrutinib plus nab-paclitaxel and gemcitabine, versus 42% (90/213) for placebo plus nab-paclitaxel and gemcitabine (*P*=0.0058). No patients achieved a complete response (CR) in the ibrutinib plus nab-paclitaxel and gemcitabine arm and 3/213 patients (1%) achieved CR in the placebo plus nab-paclitaxel and gemcitabine arm.

Percentages of patients with ≥60% reduction in CA19-9 were 54% (113/211) for ibrutinib plus nab-paclitaxel and gemcitabine and 63% (134/213) for placebo plus nab-paclitaxel and gemcitabine. With respect to the PRO measure, median times until definitive deterioration (TUDD1) in QLQ-C30 score were 4.2 months (95% CI: 2.86, 5.82) for patients who received ibrutinib plus nab-paclitaxel and gemcitabine and 6.1 months (95% CI: 4.86, 8.21) for patients who received placebo plus nab-paclitaxel and gemcitabine. Venous thromboembolic events were reported in 8% of patients who received ibrutinib plus nab-paclitaxel and gemcitabine and in 11% of patients who received placebo plus nab-paclitaxel and gemcitabine.

Treatment exposure

The median duration of ibrutinib exposure was 3.7 months (range, 0.1–24.4) in the ibrutinib plus nab-paclitaxel and gemcitabine arm (**Table 3**). In the placebo plus nab-paclitaxel and gemcitabine arm, median duration of placebo exposure was 5.5 months (range, 0.1–26.1). Median treatment duration for nab-paclitaxel was shorter in the ibrutinib versus the placebo arm (3.0 months vs 4.5 months). The median number of nab-paclitaxel cycles was 4.0 versus 5.0 for the ibrutinib and placebo arms, and the median cumulative dose was lower for nab-paclitaxel in

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the ibrutinib versus the placebo arm (989.4 mg/m^2 vs 1551.2 mg/m^2, respectively) (**Table 3**). For gemcitabine, the median treatment duration was also shorter in the ibrutinib versus the placebo arm (3.5 months vs 5.1 months). Patients in the ibrutinib versus the placebo arm had fewer median number of cycles (4.0 vs 6.0) and a lower median cumulative dose (9874.5 mg/m^2 vs 13822.4 mg/m^2, respectively) (**Table 3**).

Safety

Grade ≥3 AEs occurred in a similar proportion of patients in the ibrutinib plus nab-paclitaxel and gemcitabine arm compared with those in the placebo plus nab-paclitaxel and gemcitabine arm (86% vs 87%, respectively) (**Table 4**). The most common grade ≥3 AEs (≥5% of patients) were neutropenia (24%), peripheral sensory neuropathy (17%), anemia (16%), asthenia (16%), and diarrhea (14%) in the ibrutinib plus nab-paclitaxel and gemcitabine arm, and neutropenia (35%), anemia (17%), and asthenia (12%) in the placebo plus nab-paclitaxel and gemcitabine arm (**Table 4**). Major hemorrhage of any grade was observed in 6% of patients in each arm; grade ≥3 atrial fibrillation was observed in 1% of ibrutinib plus nab-paclitaxel and gemcitabine-treated patients and 2% of placebo plus nab-paclitaxel and gemcitabine-treated patients.

AEs leading to discontinuation were the same in each arm (18% each). In both arms, asthenia was the most common AE leading to ibrutinib/placebo or gemcitabine discontinuation. The most common AE leading to nab-paclitaxel discontinuation was peripheral sensory neuropathy (**Table 4**).

DISCUSSION

In the phase 3 RESOLVE study, the combination of ibrutinib plus nab-paclitaxel and gemcitabine did not meet the primary endpoint of an OS or investigator-assessed PFS benefit

compared to placebo plus nab-paclitaxel and gemcitabine. The rationale for investigating the combination of ibrutinib plus nab-paclitaxel and gemcitabine was based on fixed-term studies of ibrutinib plus gemcitabine in pre-clinical models of PDAC, wherein the combination demonstrated powerful anti-tumor responses by modulating the tumor microenvironment, resulting in an increase in effector $CD8^+$ T cells and subsequent reduced tumor size.[8,10] Ibrutinib combined with gemcitabine also led to mast cell inhibition, decreased angiogenesis, and reduced desmoplasia in multiple mouse models of PDAC, resulting in a significant increase in survival.[8,10,11] Ibrutinib has demonstrated additional immunomodulatory capabilities; for example, in a mouse model of leukemia and in T cells isolated from patients with chronic lymphocytic leukemia, ibrutinib inhibited activation of Th2 cells, thus altering potential for activation of Th1 and $CD8^+$ T cells.[12] Furthermore, in a phase 1b study, patients with PDAC received a 7-day run-in treatment of ibrutinib 560 mg/day, followed by a standard regimen of gemcitabine and nab-paclitaxel plus ibrutinib.[15] Blood samples and tumor tissue biopsies collected ≥5 days after the run-in period showed that treatment with ibrutinib alone led to systemic and intra-tumoral immunomodulatory changes in circulating lymphocytes, specifically in T and B cells and monocytes, suggesting ibrutinib's potential for an anti-tumor response in patients with PDAC.[15]

The investigational combination of ibrutinib plus nab-paclitaxel and gemcitabine in patients with PDAC did not yield a significant difference in OS between the two arms, with a HR of 1.109 (*P*=0.3225), which did not meet the targeted HR of 0.735. The median OS reported in the phase 3 MPACT trial for the combination of gemcitabine and nab-paclitaxel was 8.5 months[3]; this was the historical control used to determine sample size in the current study. In RESOLVE, the median OS in the placebo plus nab-paclitaxel and gemcitabine arm (10.8 months) was higher than observed in MPACT, but in line with the median OS observed in the western European cohort of the MPACT trial (10.7 months).[16] The median OS of 9.7 months in the ibrutinib plus nab-paclitaxel and gemcitabine arm of RESOLVE was also higher than that reported in the

phase 3 MPACT trial,[16] but lower than that in the placebo arm of RESOLVE. There were no significant differences in OS observed in the subgroup analysis. The median PFS for ibrutinib plus nab-paclitaxel and gemcitabine was 5.3 months, lower than 6.0 months as observed for placebo plus nab-paclitaxel and gemcitabine, although both values were similar to the reported 5.5 months for nab-paclitaxel and gemcitabine in the MPACT trial[3] and the reported 6.4 months for FOLFIRINOX.[4]

The addition of ibrutinib to nab-paclitaxel and gemcitabine may have mitigated the ability to deliver the complete chemotherapy regimen, as patients in the ibrutinib arm had less time on treatment and received a lower cumulative dose for all agents compared to patients in the placebo arm. The differences in treatment duration and dosing of nab-paclitaxel or gemcitabine may confound our ability to interpret any potential benefit of adding ibrutinib to this chemotherapy regimen. However, in previous studies, ibrutinib has successfully been combined with other chemotherapeutic agents, in particular alkylating agents, for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma.[17-19] In the current study, there were no other notable safety findings, and safety observations were consistent with the known profiles of the individual agents.

Overall, the investigational combination of ibrutinib with nab-paclitaxel and gemcitabine in the first-line setting did not improve overall survival or progression-free survival in patients with metastatic PDAC.

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GC: employment with Pharmacyclics LLC, an AbbVie Company; stock ownership in AbbVie

DJ: employment with Pharmacyclics LLC, an AbbVie Company; leadership role with Pharmacyclics LLC, an AbbVie Company; stock ownership in AbbVie; patents, royalties, or other intellectual property with Pharmacyclics LLC, an AbbVie Company

TM: consultancy/advisory role with Advance Medical HCMS, Baxter, BioLineRX Ltd, Celgene SLU, Eisai, Genzyme, Incyte, IPSEN Pharma Lab. Menarini, Lab. Servier, Lilly, QED Therapeutics, Merck, Sharp and Dohme, Prime Oncology EU, QED Therapeutics Inc, Sanofi-Aventis; research funding from Agios, ASLAN, AstraZeneca, Bayer, Celgene, Genentech, Hallozyme, Immunomedics, Lilly, Merimarck, Millenium, Novartis, Pfizer, Pharmacyclics LLC, an AbbVie Company, and Roche; travel expenses from Servier and Incyte

LCT: no relevant disclosures

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AUTHOR CONTRIBUTIONS

MT, GC, and DJ designed the analysis; MT, D-YO, JT, MR, EVC, AH, D-TW, NS, J-BB, H-MC, JM, RG-C, SL, LMC, LF, and TM collected data; LCT, GC, and DJ confirmed the accuracy of the data and compiled it for analysis; LCT performed statistical analysis; all authors had access to the data and were involved in the interpretation of data. All authors contributed to the manuscript preparation and approved the final version of the manuscript for submission.

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HIGHLIGHTS (each 125 characters max including spaces)

- Addition of ibrutinib to nab-paclitaxel/gemcitabine did not improve efficacy outcomes for pancreatic ductal adenocarcinoma (124 characters)
- Primary endpoints—overall survival and investigator-assessed progression-free survival—were not met in this phase 3 study (123 characters)
- Ibrutinib treatment led to less time on treatment and lower cumulative dose for all agents compared to placebo treatment (123 characters)
- Reported safety was consistent with the known profiles for ibrutinib and nab-paclitaxel/gemcitabine (101 characters)

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Table 1. Baseline demographic and disease characteristics (ITT Population)

	Ibrutinib+nab-paclitaxel/gemcitabine (*n*=211)	Placebo+nab-paclitaxel/gemcitabine (*n*=213)	Total (*N*=424)
Median age, years (range)	64 (32–82)	64 (32–85)	64 (32–85)
>70 years, *n* (%)	47 (22)	49 (23)	96 (23)
Gender, *n* (%)			
Male	114 (54)	121 (57)	235 (55)
Female	97 (46)	92 (43)	189 (45)
Ethnicity, *n* (%)			
Hispanic or Latino	7 (3)	11 (5)	18 (4)
Not Hispanic or Latino	198 (94)	197 (92)	395 (93)
Missing	6 (3)	5 (2)	11 (3)
Race, *n* (%)			
Asian	53 (25)	59 (28)	112 (26)
Black or African American	5 (2)	7 (3)	12 (3)
White	146 (69)	142 (67)	288 (68)
Median time from initial diagnosis to randomization, weeks (range)	3.7 (0.7–101.3)	3.7 (0.6–71.4)	3.7 (0.6–101.3)
Median time from stage IV diagnosis to randomization, weeks (range)	3.0 (0.1–55.0)	3.0 (0.4–8.1)	3.0 (0.1–55.0)
Metastatic sites of disease, *n* (%)			
1	79 (37)	73 (34)	152 (36)
2	85 (40)	62 (29)	147 (35)
>2	47 (22)	78 (37)	125 (29)
Liver metastases per EDC, *n* (%)			
Present	169 (80)	172 (81)	341 (80)
Absent	42 (20)	41 (19)	83 (20)
Baseline Karnofsky Performance Status			

per EDC, *n* (%)			
100	39 (18)	46 (22)	85 (20)
90	108 (51)	101 (47)	209 (49)
80	54 (26)	53 (25)	107 (25)
70	10 (5)	13 (6)	23 (5)
<70	0	0	0
Creatinine clearance (mL/min), *n* (%)			
<30	1 (0.5)	0	1 (0.2)
30–<60	20 (9)	16 (8)	36 (8)
≥60	190 (90)	195 (92)	385 (91)
Missing	0	2 (1)	2 (0.5)
Hepatic function per NCI-ODWG classification, *n* (%)			
Normal	153 (73)	155 (73)	308 (73)
Mild	57 (27)	54 (25)	111 (26)
Moderate	0	2 (1)	2 (0.5)
Severe	1 (0.5)	0	1 (0.2)
Missing	0	2 (1)	2 (0.5)
Prior cancer treatment, *n* (%)			
Surgery	30 (14)	29 (14)	59 (14)
Chemotherapy	1 (0.5)	4 (2)	5 (1)
Radiation therapy	6 (3)	5 (2)	11 (3)

EDC, electronic data capture; NCI-ODWG: National Cancer Institute Organ Dysfunction Working Group.

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Table 2. Patient Disposition (Safety Population)

	Ibrutinib+nab-paclitaxel/gemcitabine (*n*=208)	Placebo+nab-paclitaxel/gemcitabine (*n*=212)
Median time on study treatment, months (range)[a,c]	3.91 (0.10–24.41)	5.52 (0.07–26.32)
Median time on study, months (range)[b,c]	24.28 (0.30–29.70)	25.26 (0.10+–31.08+)
Primary reasons for ibrutinib/placebo discontinuation, *n* (%)		
Disease progression	154 (74)	150 (71)
Adverse events[d]	25 (12)	26 (12)
Primary reasons for nab-paclitaxel discontinuation, *n* (%)		
Disease progression	117 (56)	125 (59)
Adverse events[d]	65 (31)	48 (23)
Primary reasons for gemcitabine discontinuation, *n* (%)		
Disease progression	147 (71)	145 (68)
Adverse events[d]	30 (14)	25 (12)

[a]Time from the earliest study treatment start date to the last dose date of study treatment. Study treatment includes ibr/placebo, nab-paclitaxel, or gemcitabine.
[b]Ibrutinib+nab-paclitaxel/gemcitabine, *n*=211; Placebo+nab-paclitaxel/gemcitabine, *n*=213 (ITT population).
[c]Time on study is based on the follow-up time of overall survival using reverse Kaplan-Meier estimates. + indicates censored observation for patient who died.
[d]Not related to disease progression.

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Table 3. Treatment Exposure (Safety Population)

	Ibrutinib+nab-paclitaxel/gemcitabine (*n*=208)	Placebo+nab-paclitaxel/gemcitabine (*n*=212)
Median treatment duration, months (range)		
Ibrutinib/placebo	3.7 (0.1–24.4)	5.5 (0.1–26.1)
Nab-paclitaxel	3.0 (0.0–24.0)	4.5 (0.0–21.2)
Gemcitabine	3.5 (0.0–24.4)	5.1 (0.0–26.3)
Median total cumulative dose		
Ibrutinib/placebo, grams (range)	57.3 (1.1–397.0)	78.1 (1.1–426.4)
Nab-paclitaxel, mg/m^2 (range)	989.4 (122.1–7813.3)	1551.2 (116.3–4672.6)
Gemcitabine, mg/m^2 (range)	9874.5 (977.1–73061.3)	13822.4 (930.3–79593.6)
Median dose intensity, mg/week (range)		3760.9 (751.2–3973.7)
Ibrutinib/placebo	3742.2 (833.0–4051.9)	
Median relative dose intensity, % (range)		
Ibrutinib/placebo	96 (21–103)	96 (19–101)
Number of cycles received, median (range)		
Nab-paclitaxel	4 (1–24)	5 (1–22)
Gemcitabine	4 (1–27)	6 (1–29)

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Table 4. Safety Summary (Safety Population)

	Ibrutinib+nab-paclitaxel/gemcitabine (*n*=208)		Placebo+nab-paclitaxel/gemcitabine (*n*=212)	
	Any grade n (%)	**Grade ≥3 n (%)**	**Any grade n (%)**	**Grade ≥3 n (%)**
Patients with any AE, n (%)	208 (100)	178 (86)	212 (100)	184 (87)
Most Common[a] AEs				
Diarrhea	148 (71)	30 (14)	111 (52)	19 (9)
Nausea	117 (56)	6 (3)	111 (52)	8 (4)
Asthenia	101 (49)	33 (16)	98 (45)	25 (12)
Pyrexia	91 (44)	6 (3)	86 (41)	8 (4)
Anemia	92 (44)	34 (16)	95 (45)	36 (17)
Alopecia	90 (43)	2 (1)	87 (41)	4 (2)
Vomiting	87 (42)	11 (5)	89 (42)	6 (3)
Decreased appetite	85 (41)	7 (3)	76 (36)	5 (2)
Fatigue	79 (38)	17 (8)	65 (31)	11 (5)
Thrombocytopenia	76 (37)	20 (10)	56 (26)	21 (10)
Neutropenia	72 (35)	50 (24)	85 (40)	74 (35)
Constipation	69 (33)	3 (1)	79 (37)	2 (1)
Peripheral sensory neuropathy	69 (33)	35 (17)	63 (30)	16 (8)
Abdominal pain	66 (32)	14 (7)	73 (34)	14 (7)
Peripheral edema	60 (29)	4 (2)	77 (36)	6 (3)
Dyspnea	26 (13)	3 (1)	43 (20)	4 (2)
Pneumonia	15 (7)	12 (6)	13 (6)	5 (2)
Most common AE leading to discontinuation of ibrutinib/placebo, *n* (%)				
Asthenia	5 (2)		5 (2)	
Most common AE leading to discontinuation of Nab-paclitaxel, *n* (%)				
Peripheral sensory	20 (10)		8 (4)	

neuropathy		
Most common AE leading to discontinuation of gemcitabine, *n* (%)		
Asthenia	6 (3)	4 (2)

[a]Any grade incidence ≥20% and/or grade ≥3 incidence ≥5%.

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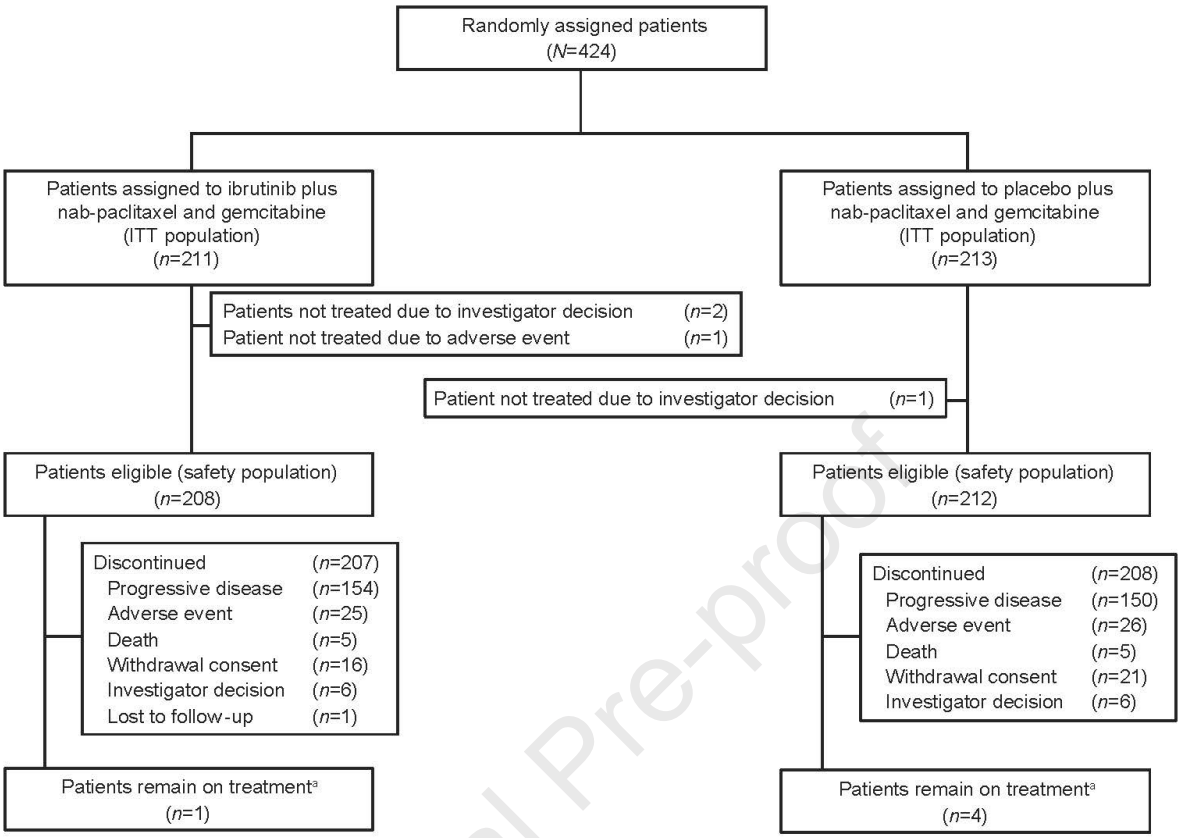

[a]As of October 22, 2018.

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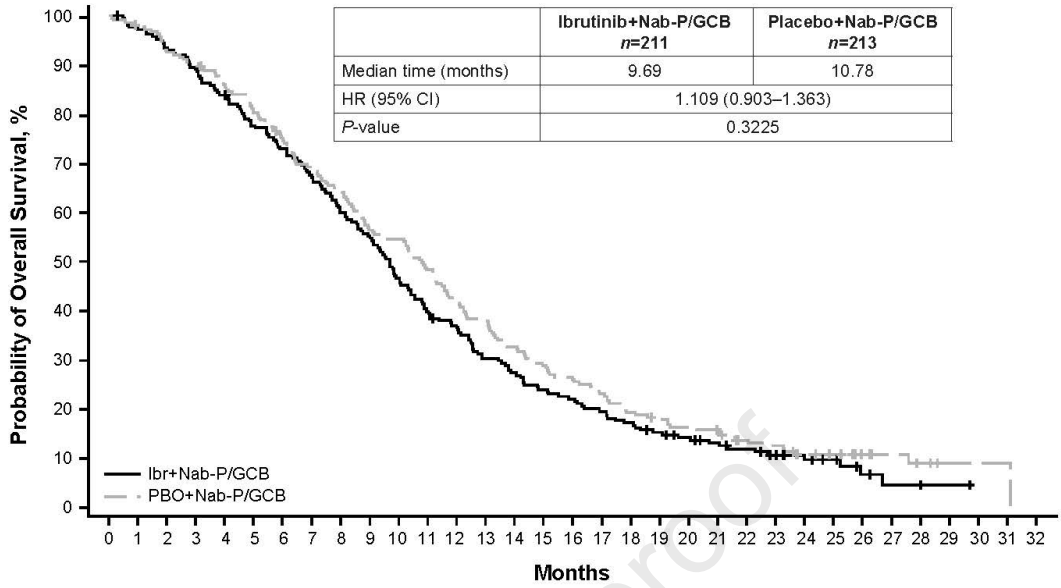
A

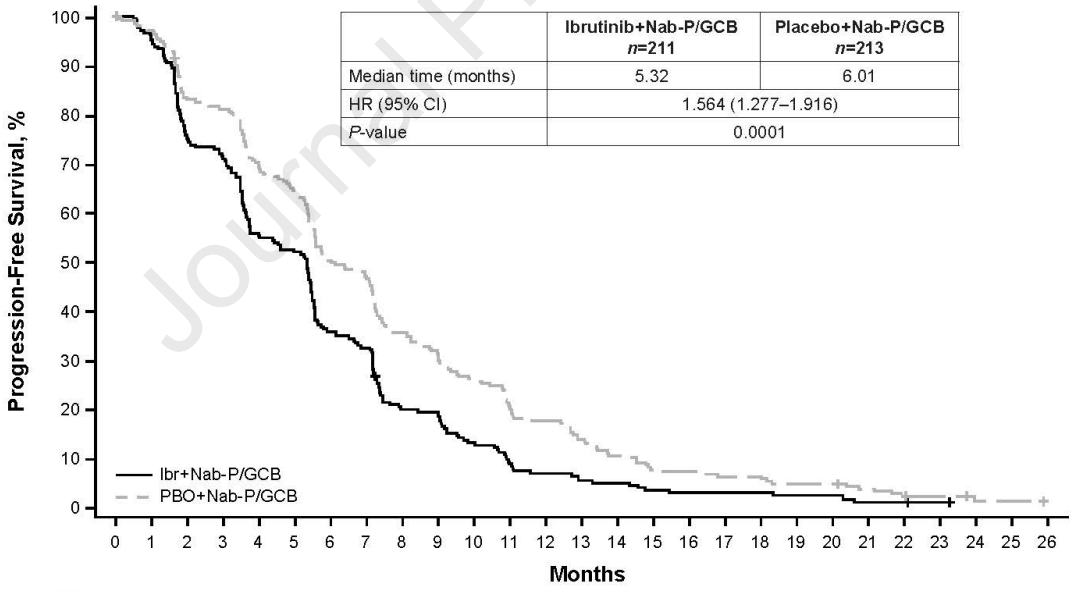


	Ibrutinib+Nab-P/GCB *n*=211	Placebo+Nab-P/GCB *n*=213
Median time (months)	9.69	10.78
HR (95% CI)	1.109 (0.903–1.363)	
P-value	0.3225	

Number of patients at risk:

Ibr+Nab-P/GCB:	211	204	196	187	176	162	152	140	125	115	97	83	75	62	56	49	45	40	35	30	26	22	19	15	10	8	4	2	2	1	0
PBO+Nab-P/GCB:	213	208	197	191	181	169	157	144	135	118	114	101	88	79	68	60	55	48	40	35	32	30	23	21	15	12	8	6	4	1	1	1	0

B



	Ibrutinib+Nab-P/GCB *n*=211	Placebo+Nab-P/GCB *n*=213
Median time (months)	5.32	6.01
HR (95% CI)	1.564 (1.277–1.916)	
P-value	0.0001	

Number of patients at risk:

Ibr+Nab-P/GCB:	211	200	158	149	116	109	75	68	41	40	27	18	14	11	10	7	6	6	6	5	5	2	2	1	0
PBO+Nab-P/GCB:	213	206	175	171	146	135	106	98	75	66	54	43	37	29	22	16	15	13	13	10	10	7	4	3	1	1	0

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