JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized, Double-Blind, Phase II Study of Ruxolitinib or Placebo in Combination With Capecitabine in Patients With Metastatic Pancreatic Cancer for Whom Therapy With Gemcitabine Has Failed

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Published online ahead of print at www.jco.org on September 8, 2015.

Written on behalf of the RECAP (Study of Ruxolitinib in Pancreatic Cancer Patients) study investigators.

Supported by Incyte Corporation, Wilmington, DE.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT01423604.

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0732-183X/15/3399-1/$20.00

DOI: 10.1200/JCO.2015.61.4578

ABSTRACT

Purpose
Patients with advanced pancreatic adenocarcinoma have a poor prognosis and limited second-line treatment options. Evidence suggests a role for the Janus kinase (JAK)/signal transducer and activator of transcription pathway in the pathogenesis and clinical course of pancreatic cancer.

Patients and Methods
In this double-blind, phase II study, patients with metastatic pancreatic cancer who had experienced treatment failure with gemcitabine were randomly assigned 1:1 to the JAK1/JAK2 inhibitor ruxolitinib (15 mg twice daily) plus capecitabine (1,000 mg/m^2 twice daily) or placebo plus capecitabine. The primary end point was overall survival (OS); secondary end points included progression-free survival, clinical benefit response, objective response rate, and safety. Prespecified subgroup analyses evaluated treatment heterogeneity and efficacy in patients with evidence of inflammation.

Results
In the intent-to-treat population (ruxolitinib, n = 64; placebo, n = 63), the hazard ratio was 0.79 (95% CI, 0.53 to 1.18; P = .25) for OS and was 0.75 (95% CI, 0.52 to 1.10; P = .14) for progression-free survival. In a prespecified subgroup analysis of patients with inflammation, defined by serum C-reactive protein levels greater than the study population median (ie, 13 mg/L), OS was significantly greater with ruxolitinib than with placebo (hazard ratio, 0.47; 95% CI, 0.26 to 0.85; P = .011). Prolonged survival in this subgroup was supported by post hoc analyses of OS that categorized patients by the modified Glasgow Prognostic Score, a systemic inflammation–based prognostic system. Grade 3 or greater adverse events were observed with similar frequency in the ruxolitinib (74.6%) and placebo (81.7%) groups. Grade 3 or greater anemia was more frequent with ruxolitinib (15.3%; placebo, 1.7%).

Conclusion
Ruxolitinib plus capecitabine was generally well tolerated and may improve survival in patients with metastatic pancreatic cancer and evidence of systemic inflammation.

J Clin Oncol 33. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Pancreatic cancer is a leading cancer-related cause of death in the United States and worldwide.[1,2] Most patients with pancreatic adenocarcinoma present with advanced disease and have a poor prognosis[2]; expected survival with unresectable stage III or IV disease is less than 1 year.[3] FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin) or gemcitabine plus albumin-bound paclitaxel is the current standard of care in the first-line setting for patients with metastatic disease.[4-6] Essentially all patients will experience disease progression on or be intolerant of first-line therapy, and salvage therapy options for these patients are limited. Although there is no standard of care beyond first-line therapy, evidence suggests that patients may benefit from second-line therapy over best supportive care alone.[7,8]

Inflammatory responses in the tumor microenvironment have many tumor-promoting effects, including support of proliferative signaling, resistance to apoptosis, enhancement of angiogenesis,[9,10] and modulation of antitumoral immunity to

support immune evasion.[11] Local inflammation may also be associated with a generalized systemic inflammatory response in the host,[12] which is believed to underlie malignancy-associated cachexia,[13,14] muscle loss,[13] poor performance status,[15] fatigue,[15] cognitive dysfunction,[13,15] and reduced quality of life.[15,16]

In the clinical setting, multiple large studies have demonstrated a negative prognostic value for elevated markers of systemic inflammation in a wide variety of cancers.[17-19] This effect is particularly strong in patients with pancreatic cancer, including in the locally advanced,[19] first-line,[17] and refractory settings.[18] Among the many inflammatory markers studied to date, serum C-reactive protein (CRP) is the most well-characterized systemic inflammation marker in numerous cancer[19-21] and noncancer settings.[22] CRP and hypoalbuminemia are the defining measures used by the modified Glasgow Prognostic Score (mGPS),[23,24] a validated systemic inflammation–based prognostic score that has been examined in more than 60 studies and more than 30,000 patients across multiple tumor types and clinical settings.[19]

Emerging evidence supports a role for Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling in cancer development and progression.[25-38] The JAK/STAT pathway facilitates signal transduction from multiple receptor tyrosine kinases[39] and is a mediator of multiple inflammatory responses in both tumor[40-42] and host tissue.[43,44] In preclinical models, including pancreatic cancer, the JAK/STAT and related inflammatory pathways drive cancer progression.[25,45-53] In particular, proinflammatory cytokines and STAT3 were important for disease initiation and progression in a preclinical pancreatic cancer model.[48,53] STAT3 is required for pancreatic ductal adenocarcinoma progression in mice that harbor activated *KRAS*, which is the oncogenic driver of human pancreatic ductal adenocarcinoma.[25,47]

Ruxolitinib is a potent JAK1/JAK2 inhibitor that has shown clinical benefit in patients with myelofibrosis, a myeloproliferative neoplasm characterized by cachexia, weight loss, elevated proinflammatory cytokines, and dysregulated JAK/STAT signaling.[54-56] In these clinical studies, ruxolitinib treatment resulted in reduced levels of proinflammatory cytokines, improved myelofibrosis-related symptoms, weight gain, and improved overall survival (OS) relative to placebo or standard therapy.[54-56] Given the role of the JAK/STAT pathway in the pathogenesis and clinical course of pancreatic cancer, we investigated ruxolitinib in combination with capecitabine in a randomized, double-blind, placebo-controlled, phase II study in patients with metastatic pancreatic cancer who had experienced failure of gemcitabine therapy.

PATIENTS AND METHODS

Patients

Eligible adult patients had a histologic diagnosis of metastatic pancreatic adenocarcinoma with measurable/evaluable disease; a Karnofsky performance status of 60% or greater; and adequate renal, hepatic, and bone marrow function. In addition, eligible patients must have experienced treatment failure with gemcitabine monotherapy, gemcitabine combination therapy, or an alternate therapy if intolerant to gemcitabine (Data Supplement).

Study Design, Treatment, and End Points

Part one of this two-part study was an open-label run-in to confirm the safety of the capecitabine-ruxolitinib combination regimen. Eligible patients (n = 9) received oral ruxolitinib 15 mg twice daily on days 1 to 21 and oral capecitabine 1,000 mg/m^2 twice daily on days 1 to 14 of a 21-day cycle. The combination was well tolerated and was selected for evaluation in part two; eligible patients were randomly assigned 1:1 to receive capecitabine with ruxolitinib or with matching placebo. Patients, investigators, and the sponsor were blinded to treatment assignment. Treatment continued in repeating 21-day cycles as long as the regimen was tolerated and the patient did not require another therapeutic regimen. In the event of disease progression, patients stopped capecitabine but were allowed to continue ruxolitinib or the matching placebo.

The primary end point was OS. Secondary end points included clinical benefit response (a composite end point of pain intensity, analgesic use, performance status, and body weight; Data Supplement), objective response rate (ORR), confirmed response, progression-free survival (PFS), patient-reported quality of life, and safety. The study was approved by the review boards of participating institutions and was conducted in accordance with the Declaration of Helsinki, as outlined in the International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable regulatory requirements. All patients provided written informed consent.

Assessments

Tumor assessments were performed at screening and every 6 weeks; response was assessed by investigators per Response Evaluation Criteria in Solid Tumors, version 1.1.[57] Adverse events, regardless of causality, were investigator evaluated per National Cancer Institute Common Terminology Criteria for

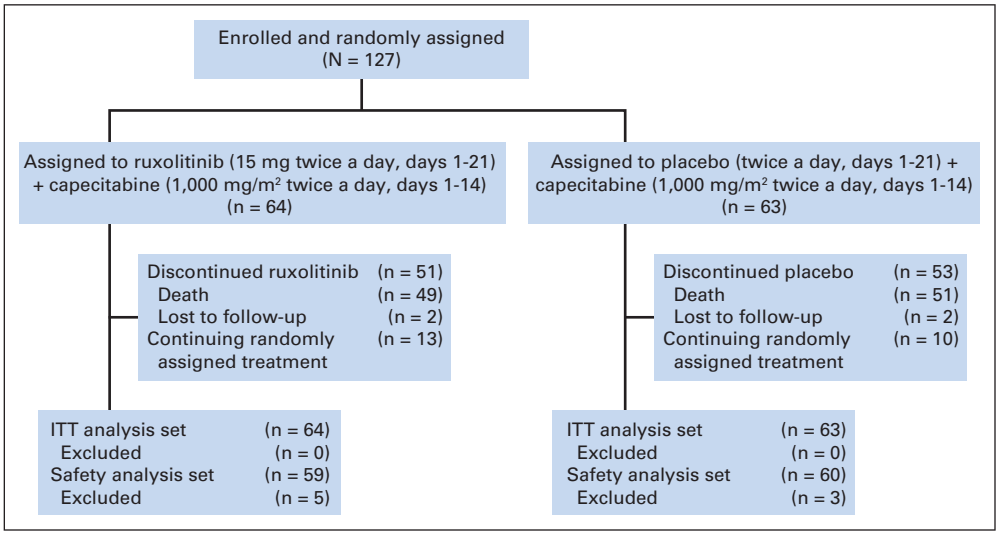

Fig 1. CONSORT diagram. Enrollment onto the safety run-in began July 2011; enrollment onto the randomized phase occurred between November 2011 and January 2013. ITT, intent to treat.

Adverse Events, version 4.03.[58] Patients completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)[59] and the Functional Assessment of Anorexia/Cachexia Therapy (FAACT-A)[60] questionnaire at screening, on day 1 of cycle 1, and then on day 1 of every even-numbered cycle until the end of treatment.

Statistical Analyses

The planned sample size was approximately 60 patients per treatment group. The primary analysis was event driven and was planned to occur after the 97th death was reported, which would permit detection of a 40% reduction in the risk of death with ruxolitinib relative to placebo (hazard ratio [HR], 0.6; power, > 80%; two-sided $\alpha = .2$). A formal interim analysis for futility and efficacy occurred after approximately 48 deaths.

Table 1. Patient Demographics and Disease Characteristics at Baseline (ITT population)

Characteristic	No. (%) of Patients: Ruxolitinib + Capecitabine (n = 64)	Placebo + Capecitabine (n = 63)
Age, years		
Mean (SD)	65.7 (9.3)	66.3 (9.8)
Median (range)	66.0 (48-86)	68.0 (37-84)
Karnofsky performance status, %		
100	7 (10.9)	8 (12.7)
90	23 (35.9)	19 (30.2)
80	18 (28.1)	30 (47.6)
70	14 (21.9)	5 (7.9)
60	2 (3.1)	1 (1.6)
BMI, kg/m^2*		
Mean (SD)	25.4 (6.3)	24.3 (4.2)
Median (range)	23.9 (13.4-52.1)	24.3 (16.3-35.7)
Site of metastases		
Liver	44 (68.8)	41 (65.1)
Lung	29 (45.3)	28 (44.4)
Prior radiation treatment†	16 (25.0)	9 (14.3)
Prior surgery‡	19 (29.7)	11 (17.5)
Prior gemcitabine treatment		
Gemcitabine monotherapy§	40 (62.5)	45 (71.4)
Gemcitabine combination therapy	24 (37.5)	17 (27.0)
Time since initial diagnosis, months		
Mean (SD)	13.3 (15.1)	8.5 (4.7)
Median (range)	7.5 (3-83)	8.0 (3-27)
Albumin‖		
Normal/high	37 (57.8)	46 (73.0)
Low	27 (42.2)	16 (25.4)
Lactate dehydrogenase‖		
Normal/low	46 (71.9)	40 (63.5)
High	17 (26.6)	21 (33.3)
Modified Glasgow Prognostic Score		
0	23 (35.9)	28 (44.4)
1	14 (21.9)	20 (31.7)
2	22 (34.4)	14 (22.2)
Missing	5 (7.8)	1 (1.6)

Abbreviations: BMI, body mass index; ITT, intent to treat; SD, standard deviation.
*For BMI data, n = 60 in each treatment group.
†Prior radiation treatment was defined as radiation therapy received subsequent to the diagnosis of pancreatic cancer but before study entry.
‡Prior surgery for pancreatic cancer was defined as any prior cancer surgery that indicated a Whipple procedure, pancreatectomy, or pancreaticoduodenectomy, but excluded palliative surgeries.
§Patients who received gemcitabine monotherapy but did not receive gemcitabine combination therapy.
‖Criteria for normal, high, and low albumin and lactate dehydrogenase levels were determined by the local institution's laboratory.

All efficacy analyses were performed on the intent-to-treat (ITT) population. OS was defined as the number of days from random assignment to death, and the nonparametric Kaplan-Meier method was used to estimate the survival time distribution and the median survival of each treatment group. The treatment difference between ruxolitinib and placebo was assessed by a log-rank test. HRs and 95% CIs were determined by using a Cox proportional hazards model. All *P* values were reported as two sided. Prospectively defined subgroup analyses of OS were conducted to explore the hypothesis that inflammation—as demonstrated by elevated CRP, hypoalbuminemia, or low Karnofsky performance status—predicts a disproportionate benefit from ruxolitinib therapy. Additional subgroups that were based on patient demographics or disease characteristics at baseline and standard prognostic criteria in pancreatic cancer were performed to test for treatment heterogeneity (Data Supplement). In addition to the prespecified subgroup analysis of OS by CRP status, a post hoc analysis of OS was conducted that categorized patients by their mGPS status (mGPS 0: CRP ≤ 10 mg/L and any albumin level; mGPS 1: CRP > 10 mg/L and albumin ≥ 35 g/L; mGPS 2: CRP > 10 mg/L and albumin < 35 g/L).[61] Detailed descriptions of secondary end points (clinical benefit, ORR, confirmed response, PFS, and quality of life) and a post hoc analysis of weight gain are provided in the Data Supplement. Adverse event rates were assessed in patients who received at least one dose of study medication and were summarized descriptively.

RESULTS

Patients

Overall, 127 patients in 41 centers in the United States were randomly assigned onto the study between November 2011 and January 2013 (ruxolitinib + capecitabine, n = 64; placebo + capecitabine, n = 63; Fig 1). Baseline characteristics were generally balanced except that slightly more patients who were randomly assigned to ruxolitinib had a Karnofsky performance status of 70% or lower, prior surgery, and prior radiation (Table 1).

OS

In the ITT population, after a median follow-up time of 4.4 months, there were 50 deaths in patients randomly assigned to ruxolitinib + capecitabine and 51 deaths in patients randomly assigned to placebo + capecitabine. The HR was 0.79 (95% CI, 0.53 to

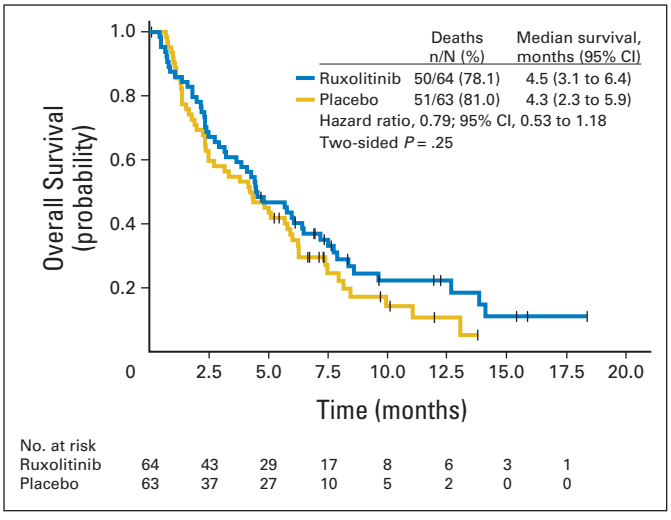

Fig 2. Kaplan-Meier analysis of overall survival in the intent-to-treat population.

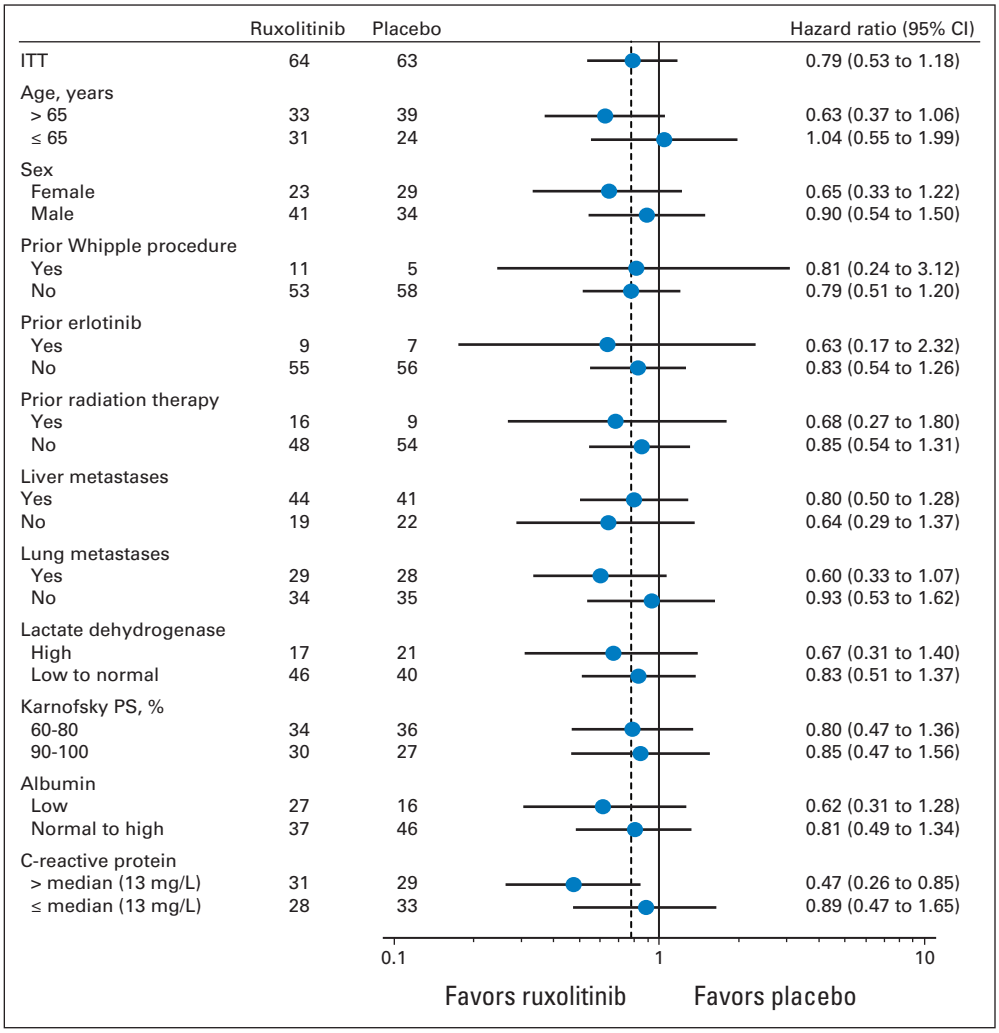

Fig 3. Forest plot of overall survival by subgroups defined by baseline patient disease characteristics and demographics. ITT, intent to treat; PS, performance status.

1.18; $P = .25$; Fig 2). The median OS was 4.5 months (137 days) in the ruxolitinib + capecitabine group and was 4.3 months (130 days) in the placebo + capecitabine group (Data Supplement). The probability of survival at 3, 6, and 12 months was 64%, 42%, and 22%, respectively, in the ruxolitinib + capecitabine group and was 58%, 35%, and 11%, respectively, in the placebo + capecitabine group (Data Supplement).

Prespecified subgroup analyses showed that patients with a CRP level greater than the overall study population median (ie, CRP > 13 mg/L) had the greatest reduction in risk of death with ruxolitinib treatment (ie, lowest HR) among all the subgroups examined (Fig 3). Among the 60 patients in this subgroup, there were 52 deaths. The HR for OS in patients who received ruxolitinib versus placebo in this subgroup was 0.47 (95% CI, 0.26 to 0.85; $P = .011$; Fig 4). The median OS was 2.7 months (83 days) in the ruxolitinib + capecitabine group and 1.8 months (55 days) in the placebo group (Data Supplement). The OS rate at 3, 6, and 12 months was 48%, 42%, and 11%, respectively, in the ruxolitinib + capecitabine group and was 29%, 11%, and 0%, respectively, in the placebo + capecitabine group (Data Supplement). The HR in patients with CRP levels of 13 mg/L or less was 0.89 (95% CI, 0.47 to 1.65; $P = .70$; Data Supplement).

Patient demographics and disease characteristics at baseline were compared between treatment groups to additionally evaluate the effect of ruxolitinib in patients with a CRP level greater than the median for the study population (ie, CRP > 13 mg/L); these were generally balanced between the treatment groups (Data Supplement). A Cox regression analysis was performed which adjusted treatment effects on OS for prognostic variables in the subgroup of patients with a CRP level greater than the median for the study population. The model included several baseline covariates that were prognostic for patient survival, and the adjusted HR remained significant (HR, 0.50; 95% CI, 0.26 to 0.96; $P = .037$; Data Supplement).

In addition to the prespecified subgroup analysis of OS by baseline CRP, post hoc Kaplan-Meier analyses that categorized patients by their mGPS status[62] showed that there was a meaningful separation between the ruxolitinib + capecitabine and placebo + capecitabine groups in OS with increasing mGPS (Fig 5). For patients with an mGPS of 1 or 2 (CRP > 10 mg/L), the HR was 0.60 (95% CI, 0.35 to 1.03; $P = .063$); for patients with an mGPS of 0 (CRP ≤ 10 mg/L), the HR was 0.91 (95% CI, 0.46 to 1.74; $P = .77$).

PFS

In the ITT population, the HR for PFS was 0.75 (95% Cl, 0.52 to 1.10; $P = .14$; Data Supplement). In the subgroup of patients with a CRP level greater than the median for the study population (ie,

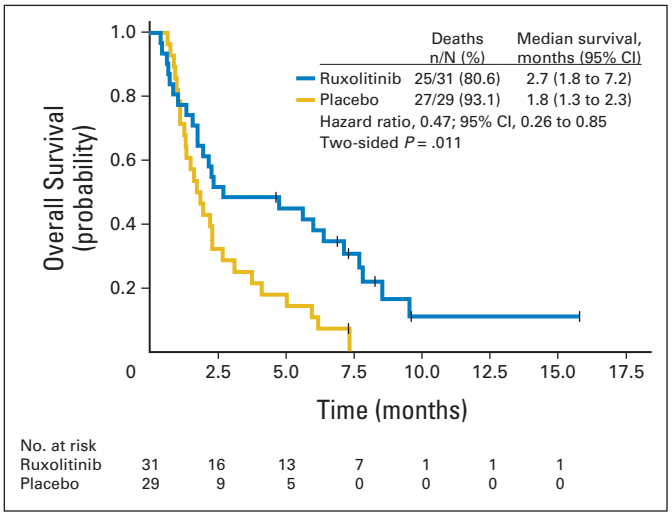

Fig 4. Kaplan-Meier analysis of overall survival in the patients with a C-reactive protein (CRP) level above the median of the study population (ie, CRP > 13 mg/L).

CRP >13 mg/L), the HR for PFS was 0.62 (95% CI, 0.35 to 1.10; P = .10; Data Supplement). The PFS rates of the ruxolitinib + capecitabine versus placebo + capecitabine groups, respectively, were 35% versus 13% at 3 months and 21% versus 5% at 6 months (Data Supplement).

In patients with CRP levels of 13 mg/L or less, the HR for PFS was 0.82 (95% CI, 0.47 to 1.41; P = .47; Data Supplement). Kaplan-Meier analyses of PFS that categorized patients by mGPS status are shown in the Data Supplement.

Change in Target Lesion Tumor Burden and ORR

In the ITT population and CRP subgroups, more patients treated with ruxolitinib + capecitabine experienced reductions in the sum of their target lesion tumor burden (Data Supplement). The ORR was 7.8% for patients who received ruxolitinib + capecitabine compared with 1.6% for patients who received placebo + capecitabine (Data Supplement). Confirmed response rates were 7.8% for ruxolitinib + capecitabine and 0% for placebo + capecitabine. Disease control (stable disease or better) was achieved by 26 patients (40.6%) in the ruxolitinib + capecitabine group and by 23 patients (36.5%) in the placebo group.

In patients with a CRP level greater than the median for the study population (ie, CRP > 13 mg/L), the ORR was 6.5% for patients who received ruxolitinib + capecitabine and 3.4% for patients who received placebo + capecitabine. Disease control was achieved by 35.5% of patients in the ruxolitinib + capecitabine group and by 20.7% in the placebo + capecitabine group. The confirmed response rates were 6.5% for ruxolitinib + capecitabine and 0% for placebo + capecitabine. In patients with a CRP level of 13 mg/L or less, the ORRs were

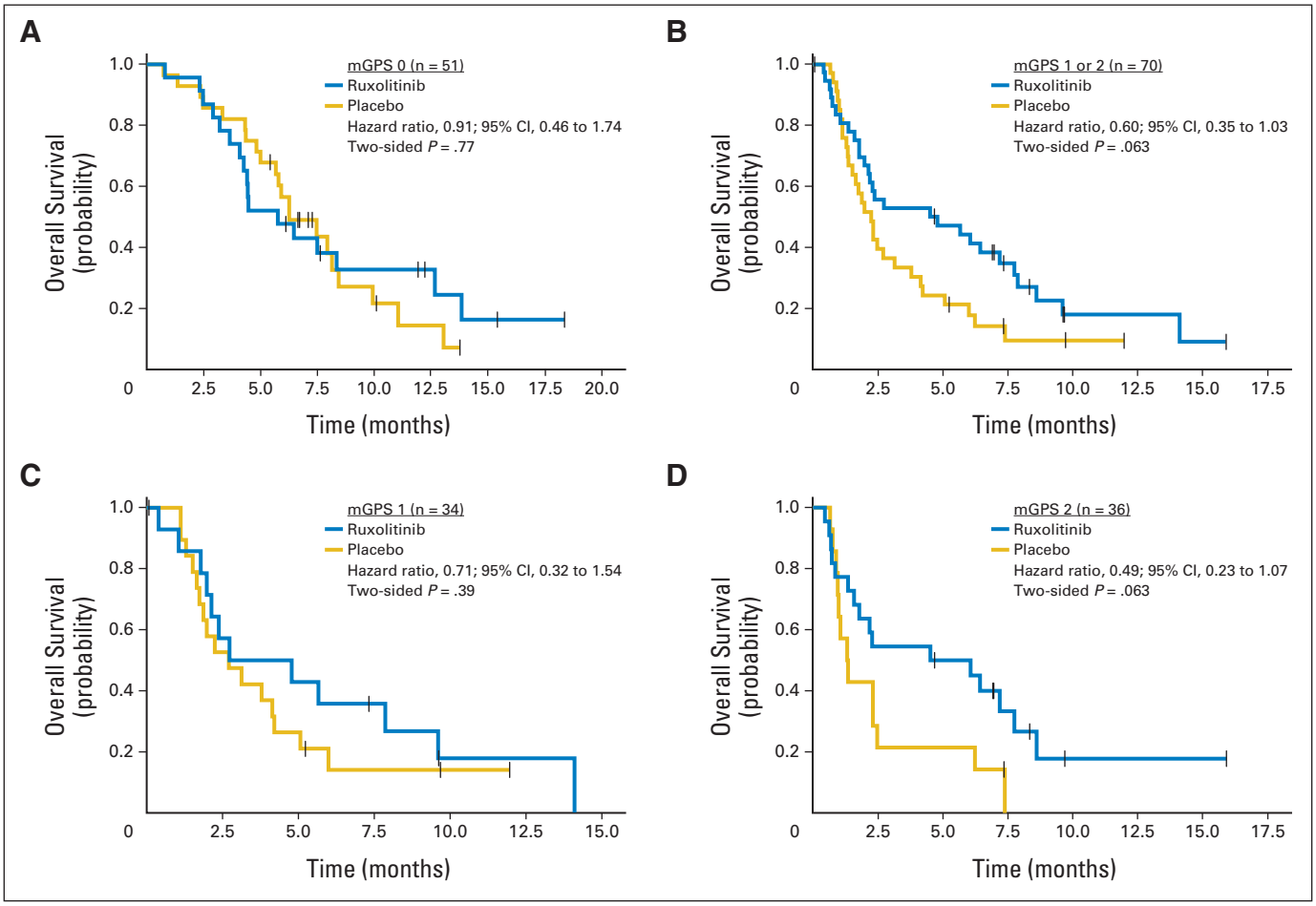

Fig 5. Kaplan-Meier analysis of overall survival by modified Glasgow Prognostic Score (mGPS): (A) 0, (B) 1 or 2, (C) 1, or (D) 2.

10.7% for patients who received ruxolitinib + capecitabine versus 0% for patients who received placebo + capecitabine.

Clinical Benefit Response, Weight, and Quality of Life

A total of eight patients (12.5%) in the ruxolitinib + capecitabine group achieved clinical benefit response compared with one patient (1.6%) in the placebo + capecitabine group ($P = .017$). Similarly, in patients with a CRP level greater than the median for the study population (ie, CRP > 13 mg/L), more patients treated with ruxolitinib + capecitabine achieved a clinical benefit response than did those treated with placebo + capecitabine (19.4% *v* 3.4%). The response for this composite measure was largely driven by a reduction in pain intensity in both the ITT population and the subgroup of patients with an elevated CRP (Data Supplement).

A greater proportion of patients treated with ruxolitinib + capecitabine experienced an increase in body weight compared with patients who received placebo + capecitabine (Data Supplement). Because of inherent variability and the limited number of patients with postbaseline data, which was a result of the large number of patients who were discontinued from the study because of death or disease progression within the first 3 months, the EORTC QLQ-C30 and FAACT-A questionnaire data could not be reliably analyzed beyond the first two cycles of treatment (Data Supplement).

Safety

A total of 59 patients in the ruxolitinib + capecitabine group and 60 in the placebo + capecitabine group received at least one dose of study medication. The mean exposure to study medication was 3.3 months for patients who received ruxolitinib + capecitabine and 2.2 months for patients who received placebo + capecitabine. Thirteen patients who received ruxolitinib + capecitabine had their ruxolitinib dose escalated to 20 mg or greater twice per day. These higher ruxolitinib doses were generally well tolerated by the majority of these patients, as assessed by the lack of dose de-escalations and the lack of new or worsening adverse events.

Seven patients (11.9%) who received ruxolitinib + capecitabine and 12 patients (20.0%) who received placebo + capecitabine experienced an adverse event of any grade that led to discontinuation of study drug. Grade 3 or greater events occurred with similar frequency between treatment groups (ruxolitinib + capecitabine, 74.6%; placebo + capecitabine, 81.7%; Table 2). Nonhematologic grade 3 or greater adverse events of interest that occurred more frequently in the ruxolitinib + capecitabine group included stomatitis, pneumonia, and pulmonary embolism. Time-to-event analyses with these and related terms that were based on the Medical Dictionary for Regulatory Activities preferred terms suggested that differences between the treatment groups seemed to be related to differences in duration of exposure (Data Supplement).

Anemia (all grades and grade ≥ 3) was the most common hematologic adverse event in ruxolitinib-treated patients (Table 2). Grade 3 anemia occurred more frequently with ruxolitinib + capecitabine (15.3%) than with placebo + capecitabine (1.7%). Grade 3 or greater thrombocytopenia and neutropenia were uncommon in patients treated with ruxolitinib + capecitabine (1.7% and 0%, respectively) and occurred at a similar frequency in patients who received placebo + capecitabine (Table 2).

Table 2. Summary of Adverse Events

	No. (%) of Adverse Events Overall and by Grade			
	Ruxolitinib + Capecitabine (n = 59)		Placebo + Capecitabine (n = 60)	
Adverse Event	All	Grade 3 or 4	All	Grade 3 or 4
Nonhematologic*				
Fatigue	29 (49.2)	6 (10.2)	26 (43.3)	7 (11.7)
Abdominal pain	22 (37.3)	6 (10.2)	23 (38.3)	8 (13.3)
Diarrhea	22 (37.3)	3 (5.1)	17 (28.3)	4 (6.7)
Nausea	21 (35.6)	3 (5.1)	27 (45.0)	7 (11.7)
PPE syndrome	19 (32.2)	4 (6.8)	19 (31.7)	6 (10.0)
Stomatitis	16 (27.1)	4 (6.8)	8 (13.3)	0 (0.0)
Vomiting	14 (23.7)	3 (5.1)	21 (35.0)	7 (11.7)
Decreased appetite	12 (20.3)	1 (1.7)	20 (33.3)	1 (1.7)
Dehydration	12 (20.3)	5 (8.5)	10 (16.7)	4 (6.7)
Constipation	10 (16.9)	1 (1.7)	19 (31.7)	3 (5.0)
Pyrexia	9 (15.3)	0 (0.0)	5 (8.3)	1 (1.7)
Asthenia	7 (11.9)	0 (0.0)	8 (13.3)	3 (5.0)
Back pain	7 (11.9)	3 (5.1)	12 (20.0)	0 (0.0)
Dizziness	7 (11.9)	0 (0.0)	5 (8.3)	1 (1.7)
Flatulence	7 (11.9)	0 (0.0)	3 (5.0)	0 (0.0)
Pulmonary embolism	7 (11.9)	7 (11.9)	3 (5.0)	3 (5.0)
Ascites	6 (10.2)	5 (8.5)	10 (16.7)	6 (10.0)
Abdominal pain upper	6 (10.2)	0 (0.0)	7 (11.7)	2 (3.3)
Edema peripheral	6 (10.2)	1 (1.7)	6 (10.0)	0 (0.0)
Peripheral sensory neuropathy	6 (10.2)	1 (1.7)	3 (5.0)	1 (1.7)
Pneumonia	6 (10.2)	5 (8.5)	3 (5.0)	1 (1.7)
Hyponatremia	6 (10.2)	2 (3.4)	2 (3.3)	2 (3.3)
Hypotension	6 (10.2)	3 (5.1)	2 (3.3)	2 (3.3)
Hematologic†				
Anemia	38 (64.4)	9 (15.3)	19 (31.7)	1 (1.7)
Thrombocytopenia	22 (37.3)	1 (1.7)	23 (38.3)	2 (3.3)
Neutropenia	13 (22.0)	0 (0.0)	8 (13.3)	1 (1.7)

Abbreviation: PPE, palmar-plantar erythrodysesthesia.
*Cutoff for nonhematologic events is all-grade adverse events that occurred in ≥10% of patients in the ruxolitinib + capecitabine group.
†Hematologic adverse events were based on laboratory values defined in the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.[58]

DISCUSSION

Patients with refractory pancreatic cancer have few treatment options,[7,8] have poor OS,[3] and often have significant disease-related symptoms.[63] JAK/STAT pathway inhibition represents a novel treatment approach that has the potential to affect intrinsic and extrinsic factors that drive the survival and proliferation of cancer cells[25-28] and the catabolic response to malignancy.[64] Results from this study support the potential clinical benefit of targeting JAK/STAT signaling with the JAK1/JAK2 inhibitor ruxolitinib. Patients randomly assigned to ruxolitinib + capecitabine had a modest but statistically nonsignificant improvement in OS, the primary end point of the study. However, for a prespecified subgroup with biochemical evidence of systemic inflammation (elevated CRP levels), treatment with ruxolitinib + capecitabine was associated with a meaningful and statistically significant improvement in OS relative to treatment with placebo + capecitabine; this improvement was preserved after adjustment for other clinical covariates. Furthermore, benefit across multiple end points, including PFS, reduction in tumor burden, and clinical

benefit response (a composite end point of pain intensity, analgesic use, performance status, and body weight) was observed with ruxolitinib treatment. These results suggest that ruxolitinib may affect the tumor directly and also may potentially modify the host response to the tumor, especially in patients with evidence of systemic inflammation.

The role of inflammatory cytokine signaling in mediation of the pathogenesis of and host response to cancer[65] and the association between systemic inflammation and poor survival in patients with pancreatic cancer and other advanced malignancies is well established. CALGB80303, a phase III study of gemcitabine + bevacizumab in patients with metastatic pancreatic cancer, evaluated more than 30 factors related to inflammation, angiogenesis, and tumor growth and found that multiple inflammatory markers, including CRP and interleukin-6, were highly prognostic for survival.[17] The mGPS has shown that CRP and albumin levels are highly prognostic in other solid tumors, including breast, colorectal, and non–small-cell lung cancers, in addition to pancreatic cancer.[66] Collectively, this suggests that JAK/STAT pathway inhibition is of potential clinical benefit in multiple cancer settings.

Several mechanisms may underlie the ruxolitinib-derived clinical benefit observed in this study. JAK/STAT signaling controls broad aspects of cytokine signaling in cancer[40-42,44] and has important cross-talk with signaling pathways critical for cancer growth, proliferation, and survival, including the epidermal growth factor receptor,[30,32,33] Ras-Raf-mitogen–activated protein kinase kinase,[30,33] Src,[31] Wnt,[29] hepatocyte growth factor receptor c-MET,[67] and transforming growth factor-β pathways.[35,36] Furthermore, JAK/STAT signaling is a key modulator of host immune responses, including programmed cell death protein 1/programmed cell death ligand 1 expression,[42,68] and of the activity of tumor-associated dendritic cells, macrophages, and B cells.[69] As a result, JAK/STAT signaling has been described as a key switch that regulates tumor-promoting inflammation and antitumor immunity.

The results of this study are promising; however, the study had limitations. First, the benefits of ruxolitinib were primarily seen in the prespecified subgroup of patients with elevated CRP levels, and only modest activity was observed in the ITT population. Second, this was a proof-of-concept study with a limited sample size. Phase III studies in larger study populations are being conducted to confirm the activity of ruxolitinib + capecitabine in patients with metastatic pancreatic cancer and an mGPS status of 1 or 2 who are refractory to first-line treatment that could include fluorouracil- and gemcitabine-based regimens (ClinicalTrials.gov identifiers NCT02119663 and NCT02117479).

In summary, in patients with refractory metastatic pancreatic cancer, ruxolitinib demonstrated signs of clinical activity, particularly in patients with elevated CRP levels. In this subgroup, the OS benefit was statistically significant, and clinical activity across other end points was also observed. These results additionally support the importance of cytokine signaling and JAK/STAT signaling in pancreatic cancer and highlight the potential role of JAK inhibition as a novel therapeutic strategy for these patients. Additional clinical trials will evaluate the importance of the modulation of inflammatory cytokine signaling in other tumor histologies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERM

JAK/STAT pathway: the pathway usually (not always) activated by cytokine receptors, where binding of a ligand to the cytokine receptor leads to recruitment and subsequent autophosphorylation of JAK proteins (activated state) at the cellular membrane level. Activated JAKs phosphorylate the receptor, creating docking sites for specific signaling proteins, including STAT proteins. When coupled to the activated receptor, STAT proteins are phosphorylated (activated) by JAK proteins. In contrast to cytokine receptor signaling, receptors with intrinsic tyrosine kinase activity (eg, epidermal growth factor receptor, platelet-derived growth factor) may bypass JAK activation and directly phosphorylate STAT proteins. See JAK (Janus kinase) and STAT.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized, Double-Blind, Phase II Study of Ruxolitinib or Placebo in Combination With Capecitabine in Patients With Metastatic Pancreatic Cancer for Whom Therapy With Gemcitabine Has Failed

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

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Research Funding: Genentech (Inst), GlaxoSmithKline (Inst), Novartis (Inst), TRACON Pharmaceuticals (Inst), Incyte Corporation (Inst)

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Acknowledgment

Presented at the 50th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 30-June3, 2014, and at the European World Congress on Gastrointestinal Cancer, Barcelona, Spain, June 25-28, 2014. Medical writing assistance was provided by Cory Pfeiffenberger, PhD, whose work (via Complete Healthcare Communications) was funded by Incyte Corporation, Wilmington, DE.

Supplementary Appendix

Supplement to: Hurwitz HI, Uppal N, Wagner SA, et al. A Randomized, Double-Blind, Phase II Study of Ruxolitinib or Placebo in Combination With Capecitabine in Patients With Metastatic Pancreatic Cancer for Whom Therapy With Gemcitabine Had Failed

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Study Methods

Patients

Patients were eligible for enrollment if they required second-line treatment for pancreatic adenocarcinoma and were not eligible to receive gemcitabine. Reasons for ineligibility for gemcitabine included prior treatment failure, disease progression, gemcitabine-associated toxicity, and disease recurrence after completion of a gemcitabine-based regimen. Gemcitabine failure and disease progression were per investigator judgment and were not distinguished by the study investigators. Patients were excluded if they had received more than 1 prior chemotherapy regimen (not including adjuvant therapy) for metastatic disease; had received ongoing or prior radiation therapy administered as a second-line treatment; had evidence of central nervous system metastases (unless stable for >3 months) or history of uncontrolled seizures; and had prior severe reaction to fluoropyrimidines, known as dihydropyrimidine dehydrogenase deficiency, or other known sensitivity to 5-fluorouracil. Patients with inadequate renal, hepatic, and bone marrow function characterized by absolute neutrophil count <1500/mm^3, platelet count <75,000/mm^3, aspartate aminotransferase, or alanine aminotransferase >2.5 times the upper limit of normal (ULN) or >5 times the ULN in the presence of liver metastases, total bilirubin >1.5 times the ULN, or creatinine clearance <50 mL/min were also excluded.

Treatment

Ruxolitinib was dispensed in 5-mg tablets. Capecitabine was dispensed in 150- and/or 500-mg tablets.

Statistical Analyses

Patient Subgroup Analyses

Prospectively defined patient subgroups were based on the following patient demographics or disease characteristics at baseline: age, >65 versus ≤65 years; sex, female/male; prior Whipple procedure, yes/no; prior erlotinib, yes/no; prior radiation therapy, yes/no; liver metastases, yes/no; lung metastases, yes/no; lactate dehydrogenase at baseline, high versus low to normal; Karnofsky performance status at baseline, 60% to 80% versus 90% to 100%; albumin at baseline, low versus normal to high; and CRP at baseline, > median versus ≤ median. HRs and 95% CIs were estimated using the Cox proportional hazards model.

Clinical Benefit Endpoint

Clinical benefit response was a composite endpoint of pain intensity, analgesic use, performance status, and body weight and was defined as meeting at least 1 of criteria (a) or (b).

a) Patient showed the indicated improvement in 1 of the following parameters at 2 successive scheduled observations without a worsening in the others:

- 50% improvement in pain intensity (assessed via Memorial Pain questionnaire)
- 50% decrease in opioid analgesic use
- 20-point or greater improvement in performance status (Karnofsky)

Worsening was considered to occur if during the reporting period there was either an increase in pain intensity or analgesic consumption or a 20-point decrease in performance status.

b) Patient was stable on all of the aforementioned parameters and experienced a ≥7% increase in body weight that was maintained for 2 successive reporting periods and was not the result of fluid accumulation.

The proportion of patients who achieved clinical benefit response was compared between treatment groups using Pearson chi-square test. This was an alpha-controlled secondary endpoint and was tested only if the OS difference was significant.

Objective Response Rate Endpoint

For the ORR analysis, each patient was considered a responder if their best overall response was a partial response (PR) or better according to RECIST 1.1[1] criteria at any postbaseline visit. Confirmed response was defined as patients with a response of PR or better at 2 subsequent measurements that were ≥4 weeks apart. Both ORR and confirmed response were summarized descriptively.

Progression-Free Survival Endpoint

Progression-free survival was defined as the length of time between the date of randomization and whichever came earlier, death or progressive disease, as assessed by RECIST 1.1.[1] The nonparametric Kaplan-Meier method was used to estimate the PFS time distribution and median PFS of each treatment group. The treatment difference, HR, and 95% CI were assessed using a Cox proportional hazards model.

Quality-of-Life Endpoints

Quality-of-life assessments (EORTC QLQ-C30[2] and FAACT-A[3]) were analyzed according to their respective manuals and summarized descriptively.

Weight Gain: Post Hoc Analysis

A post hoc analysis of weight gain (2 consecutive weight assessments with a ≥0% or ≥5% increase in weight from baseline without worsening of edema or ascites) was summarized descriptively.

Results Not Included in Main Paper

Patient demographics and disease characteristics at baseline were compared to further evaluate the effect of ruxolitinib in patients with a CRP >13 mg/L; these were generally well balanced between the treatment groups **(Supplementary Table 2)**.

Cox regression analyses were conducted in the subgroup of patients with a CRP above the median of the study population (ie, CRP >13 mg/L) to (1) explore the potential that baseline imbalances may be driving the observed effect and (2) explore the potential interaction with treatment between 3 subgroups identified as groups that, based on the mechanism of action, were most likely to disproportionally benefit from ruxolitinib treatment: elevated CRP (CRP > median of the study population of 13 mg/L); poor performance status (Karnofsky 60%–80%); and low albumin (albumin < lower limit of normal). Accounting for the baseline characteristics in the model, the observed HR in favor of ruxolitinib remained largely preserved **(Supplementary Table 3)**.

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Supplementary Tables

Supplementary Table 1. Summary of Survival and Objective Response Rates in the ITT Population and CRP Subgroups

	Ruxolitinib + Capecitabine (n=64)	Placebo + Capecitabine (n=63)
ITT population, n	**64**	**63**
Median overall survival, mo (95% CI)	4.5 (3.1–6.4)	4.3 (2.3–5.9)
Overall survival rate, % (95% CI) mo		
3	64.1 (51.0–74.5)	58.1 (44.8–69.2)
6	42.0 (29.8–53.7)	34.9 (23.3–46.8)
9	24.6 (14.2–36.5)	17.3 (8.3–29.1)
12	22.3 (12.3–34.2)	10.8 (3.5–22.9)
Median progression-free survival, mo (95% CI)	1.7 (1.4–2.8)	1.5 (1.3–2.3)
Progression-free survival rate, % (95% CI) mo		
3	33.9 (22.5–45.6)	26.0 (15.6–37.8)
6	20.7 (11.6–31.6)	9.3 (3.5–18.7)
9	9.5 (3.3–19.5)	1.9 (0.2–8.6)
12	6.3 (1.5–16.5)	–
Objective response rate, n (%)		
Overall response	5 (7.8)	1 (1.6)
Complete response	1 (1.6)	0 (0.0)
Partial response	4 (6.3)	1 (1.6)
Stable disease	21 (32.8)	22 (34.9)
Progressive disease	24 (37.5)	21 (33.3)
Unable to evaluate	14 (21.9)	19 (30.2)
Confirmed response, n (%)	5 (7.8)	0 (0.0)
Clinical benefit response, n (%)		
Overall	8 (12.5)	1 (1.6)
Pain intensity	7 (10.9)	1 (1.6)
Analgesic use	3 (4.7)	0 (0.0)
Karnofsky PS	2 (3.1)	0 (0.0)
Body weight	2 (3.1)	0 (0.0)
CRP >13 mg/L, n	**31**	**29**
Median overall survival, mo (95% CI)	2.7 (1.8–7.2)	1.8 (1.3–2.3)
Overall survival rate, % (95% CI) mo		
3	48.4 (30.2–64.4)	28.6 (13.5–45.6)
6	41.5 (24.1–58.0)	10.7 (2.7–25.1)
9	16.5 (5.0–33.7)	0.0
12	11.0 (2.2–27.9)	0.0
Median progression-free survival, mo (95% CI)	1.6 (1.1–3.0)	1.4 (1.1–1.9)
Progression-free survival rate, % (95% CI) mo		
3	34.5 (18.2–51.4)	13.4 (3.8–29.0)

6	20.7 (8.4–36.7)	4.5 (0.3–18.2)
9	11.0 (2.4–27.2)	0.0
12	0.0	0.0
Objective response rate, n (%)		
Overall response	2 (6.5)	1 (3.4)
Complete response	0 (0.0)	0 (0.0)
Partial response	2 (6.5)	1 (3.4)
Stable disease	9 (29.0)	5 (17.2)
Progressive disease	9 (29.0)	8 (27.6)
Unable to evaluate	11 (35.5)	15 (51.7)
Confirmed response, n (%)	2 (6.5)	0 (0.0)
Clinical benefit response, n (%)		
Overall	6 (19.4)	1 (3.4)
Pain intensity	6 (19.4)	1 (3.4)
Analgesic use	2 (6.5)	0 (0.0)
Karnofsky PS	2 (6.5)	0 (0.0)
Body weight	2 (6.5)	0 (0.0)
CRP ≤13 mg/L, n	**28**	**33**
Median overall survival, mo (95% CI)	6.1 (4.2–12.7)	6.9 (5.0–8.4)
Overall survival rate, % (95% CI) mo		
3	82.1 (62.3–92.1)	84.8 (67.4–93.4)
6	50.0 (30.6–66.6)	56.7 (37.9–71.7)
9	37.3 (19.4–55.2)	31.8 (15.3–49.8)
12	37.3 (19.4–55.2)	19.9 (6.2–39.1)
Median progression-free survival, mo (95% CI)	2.6 (1.4–4.0)	2.5 (1.4–4.0)
Progression-free survival rate, % (95% CI) mo		
3	39.3 (21.7–56.5)	38.3 (21.4–55.0)
6	25.0 (11.1–41.8)	13.9 (4.4–28.8)
9	10.0 (1.9–26.2)	3.5 (0.3–15.1)
12	–	–
Objective response rate, n (%)		
Overall response	3 (10.7)	0 (0.0)
Complete response	1 (3.6)	0 (0.0)
Partial response	2 (7.1)	0 (0.0)
Stable disease	11 (39.3)	17 (51.5)
Progressive disease	12 (42.9)	13 (39.4)
Unable to evaluate	2 (7.1)	3 (9.1)
Confirmed response, n (%)	3 (10.7)	0 (0.0)
Clinical benefit response, n (%)		
Overall	2 (7.1)	0 (0.0)
Pain intensity	1 (3.6)	0 (0.0)
Analgesic use	1 (3.6)	0 (0.0)
Karnofsky PS	0 (0.0)	0 (0.0)
Body weight	0 (0.0)	0 (0.0)

CRP=C-reactive protein; ITT=intent-to-treat; PS=performance status.

Supplementary Table 2. Patient Demographics and Disease Characteristics in Patients With CRP >13 mg/L at Baseline

	Ruxolitinib + Capecitabine (n=31)	Placebo + Capecitabine (n=29)
Age, y		
Mean (SD)	67.6 (7.5)	66.7 (10.3)
Median (range)	67.0 (48–81)	70.0 (37–80)
Karnofsky PS, n (%)		
100%	2 (6.5)	6 (20.7)
90%	7 (22.6)	3 (10.3)
80%	13 (41.9)	18 (62.1)
70%	7 (22.6)	1 (3.4)
60%	2 (6.5)	1 (3.4)
BMI, kg/m^2*		
Mean (SD)	24.4 (5.4)	25.0 (4.1)
Median (range)	23.6 (13.4–37.0)	25.5 (18.3–33.4)
Sites of metastases, n (%)		
Liver	23 (74.2)	24 (82.8)
Lung	13 (41.9)	18 (62.1)
Prior radiation treatment, n (%)	9 (29.0)	3 (10.3)
Prior surgery, n (%)†	8 (25.8)	5 (17.2)
Months from initial diagnosis		
Mean (SD)	11.9 (13.0)	8.0 (3.3)
Median (range)	9.0 (3–71)	8.0 (3–16)
Albumin, n (%)		
Normal/high	12 (38.7)	17 (58.6)
Low	19 (61.3)	12 (41.4)
Lactate dehydrogenase, n (%)		
Low/normal	19 (61.3)	13 (44.8)
High	11 (35.5)	16 (55.2)
Modified Glasgow Prognostic Score, n (%)		
0	0 (0.0)	0 (0.0)
1	11 (35.5)	16 (55.2)
2	20 (64.5)	13 (44.8)

BMI=body mass index; CRP=C-reactive protein; PS=performance status.
*For BMI data, n=28 for ruxolitinib plus capecitabine group; n=27 for placebo plus capecitabine group.
†Prior surgery for pancreatic cancer was defined as any prior cancer surgery indicating a Whipple procedure pancreatectomy, or pancreaticoduodenectomy.

Supplementary Table 3. Cox Regression Analysis of OS in Patients With a CRP Level Above the Median of the Study Population (CRP >13 mg/L) Using Baseline Predictors

Predictor	HR (95% CI)	*P* value
Treatment (ruxolitinib vs placebo)	0.50 (0.26–0.96)	0.037
Age (>65 vs ≤65 years)	1.67 (0.83–3.44)	0.16
Lactate dehydrogenase (elevated vs low/normal)	2.91 (1.38–6.33)	0.01
Albumin (low vs normal/high)	0.95 (0.50–1.79)	0.88
Liver metastases (yes vs no)	0.73 (0.30–1.88)	0.50
Lung metastases (yes vs no)	0.67 (0.31–1.43)	0.30
Karnofsky performance status (60%–80% vs 90%–100%)	1.58 (0.83–3.16)	0.17
Prior erlotinib (yes vs no)	0.18 (0.05–0.55)	0.01
Prior radiation (yes vs no)	1.17 (0.24–4.66)	0.84
Prior Whipple (yes vs no)	0.83 (0.18–4.04)	0.82
Sex (male vs female)	1.55 (0.73–3.43)	0.27

CRP=C-reactive protein; HR=hazard ratio; OS=overall survival.

Supplementary Figures

Supplementary Figure 1. Kaplan-Meier curves of overall survival in patients with CRP below the median of the study population (CRP ≤13 mg/L) at baseline. CRP=C-reactive protein.

Supplementary Figure 2. Kaplan-Meier curves of progression-free survival in the ITT population (A), patients with CRP above the median of the study population (CRP >13 mg/L) at baseline (B), and patients with CRP ≤13 mg/L at baseline (C). CRP=C-reactive protein; ITT=intent-to-treat.

Supplementary Figure 3. Kaplan-Meier curves of progression-free survival by mGPS. mGPS=modified Glasgow Prognostic Score.

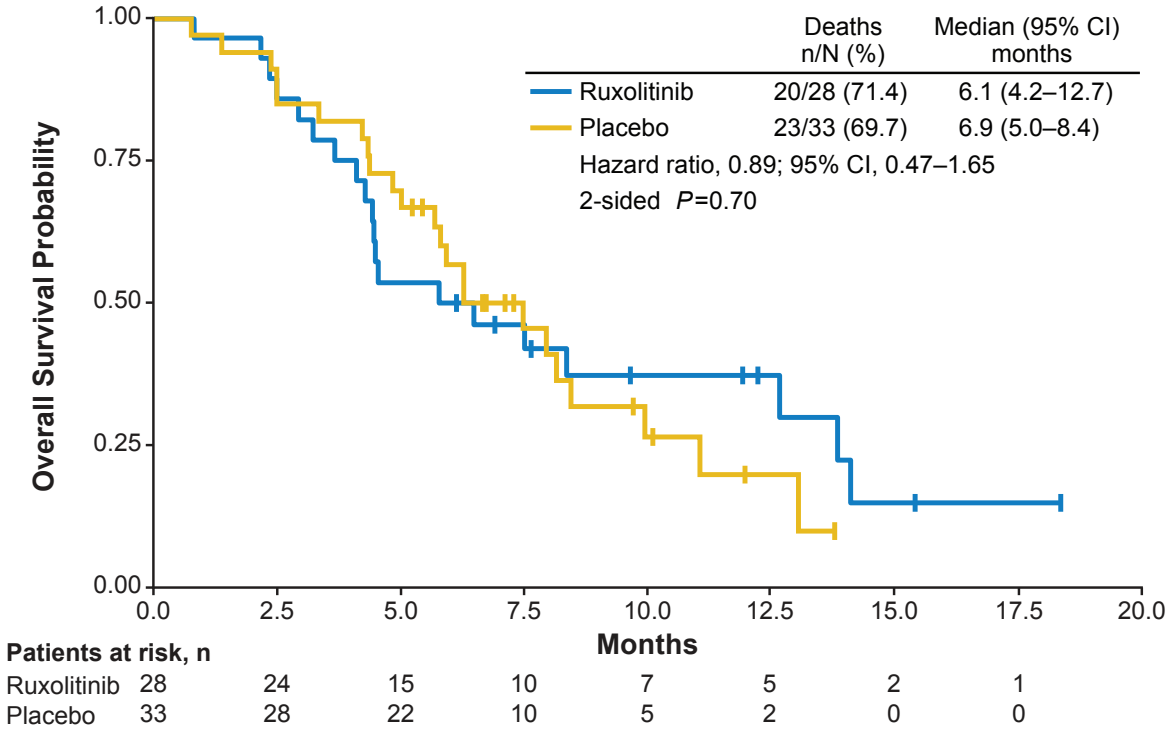
Supplementary Figure 4. Waterfall plot of the largest percentage reduction in the sum of target lesions in the ITT population (A), patients with CRP above the median of the study population (CRP >13 mg/L) at baseline (B), and patients with CRP ≤13 mg/L at baseline (C). Four patients in the ruxolitinib group were included in the ITT population (panel A) but could not be categorized by CRP and are not captured in panels B or C. CRP=C-reactive protein; ITT=intent-to-treat.

Supplementary Figure 5. Proportion of patients with ≥0% or ≥5% weight gain. Responders included patients with 2 consecutive weight assessments displaying a ≥0% or ≥5% increase in weight from baseline without worsening of edema or ascites. CRP=C-reactive protein; ITT=intent-to-treat.

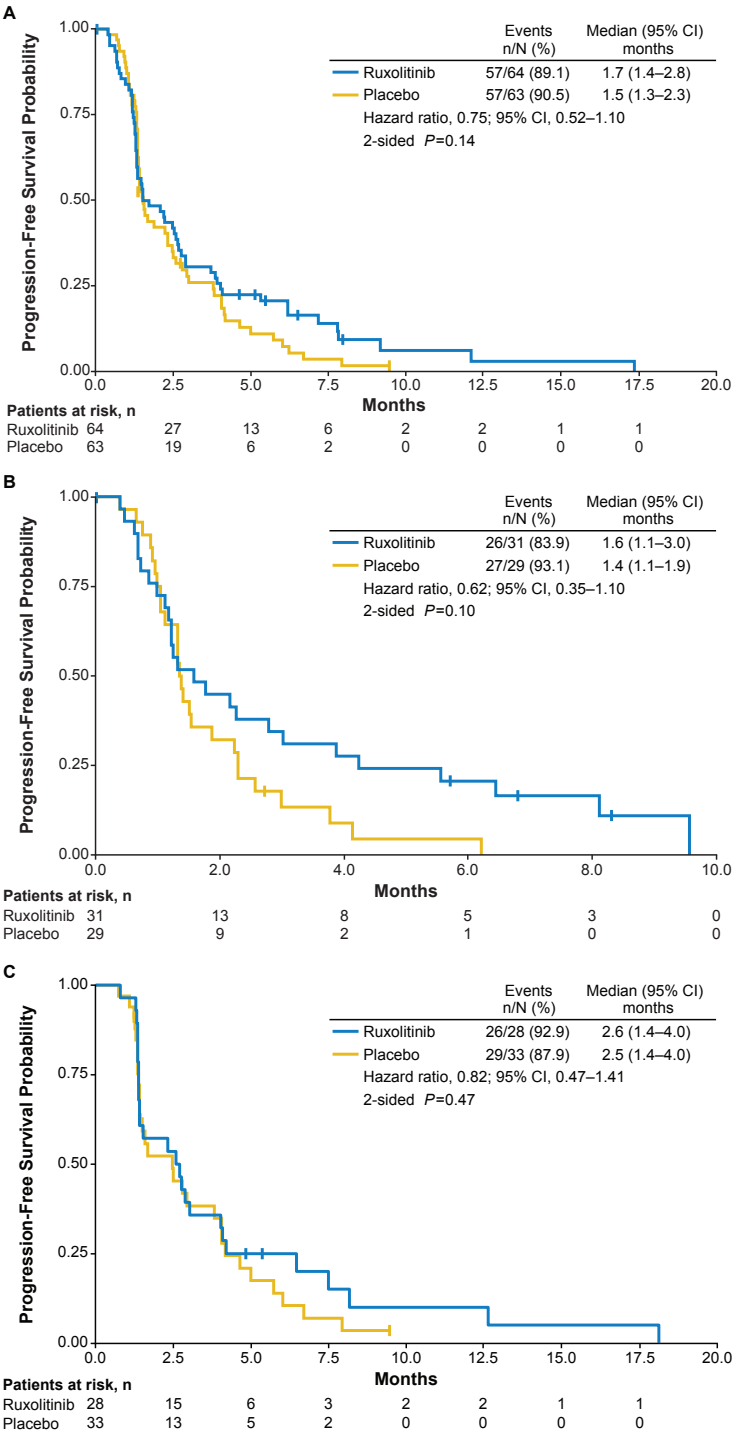
Supplementary Figure 6. Change from baseline in EORTC QLQ-C30 global health status/quality-of-life score (A) and FAACT-A total score (B). EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FAACT-A= Functional Assessment of Anorexia Cachexia Therapy.

Supplementary Figure 7. Time to thromboembolic event (A), grade ≥2 stomatitis (B), and pneumonia (C). Thrombotic event terms included portal vein thrombosis, deep vein thrombosis, pulmonary embolism, thrombosis, Trousseau syndrome, or embolism. Terms for pneumonia included pneumonia, pneumonia klebsiella, and pneumonia aspiration.

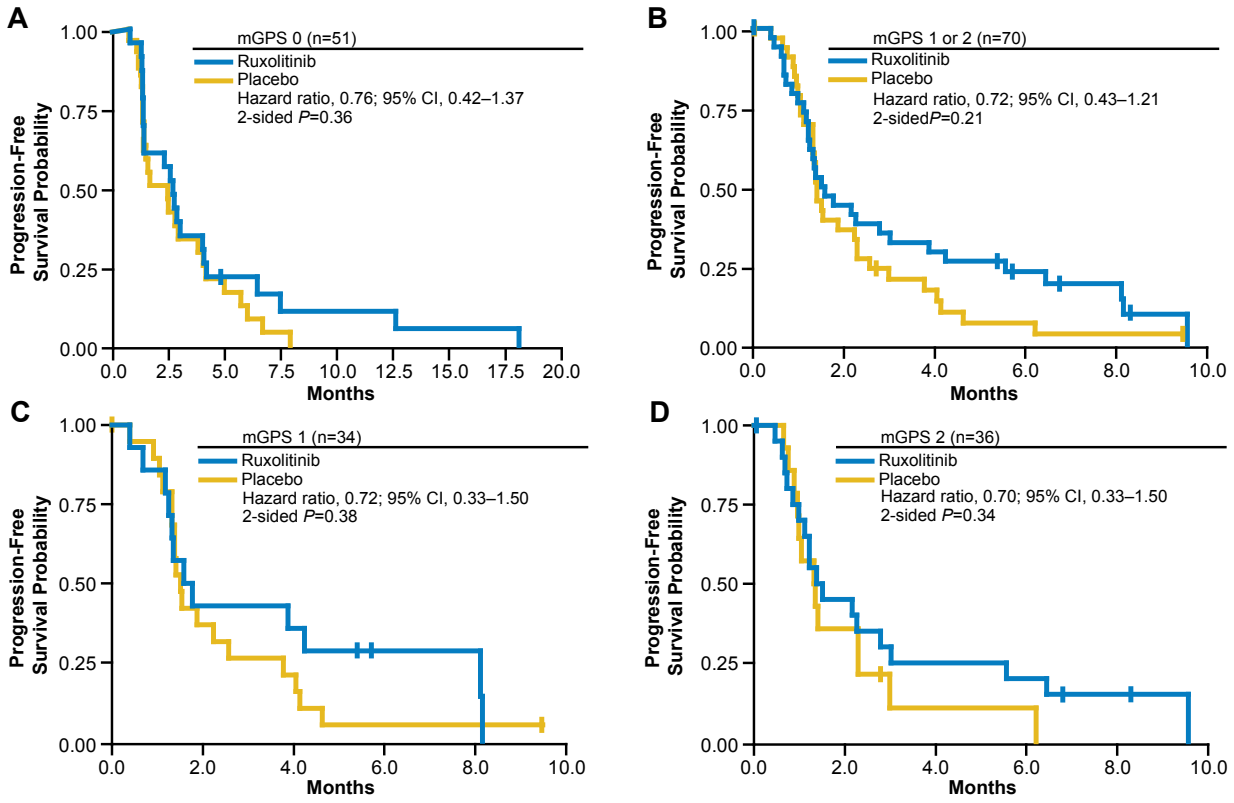
Supplementary Figure 1. Kaplan-Meier curves of overall survival in patients with CRP below the median of the study population (CRP ≤13 mg/L) at baseline.



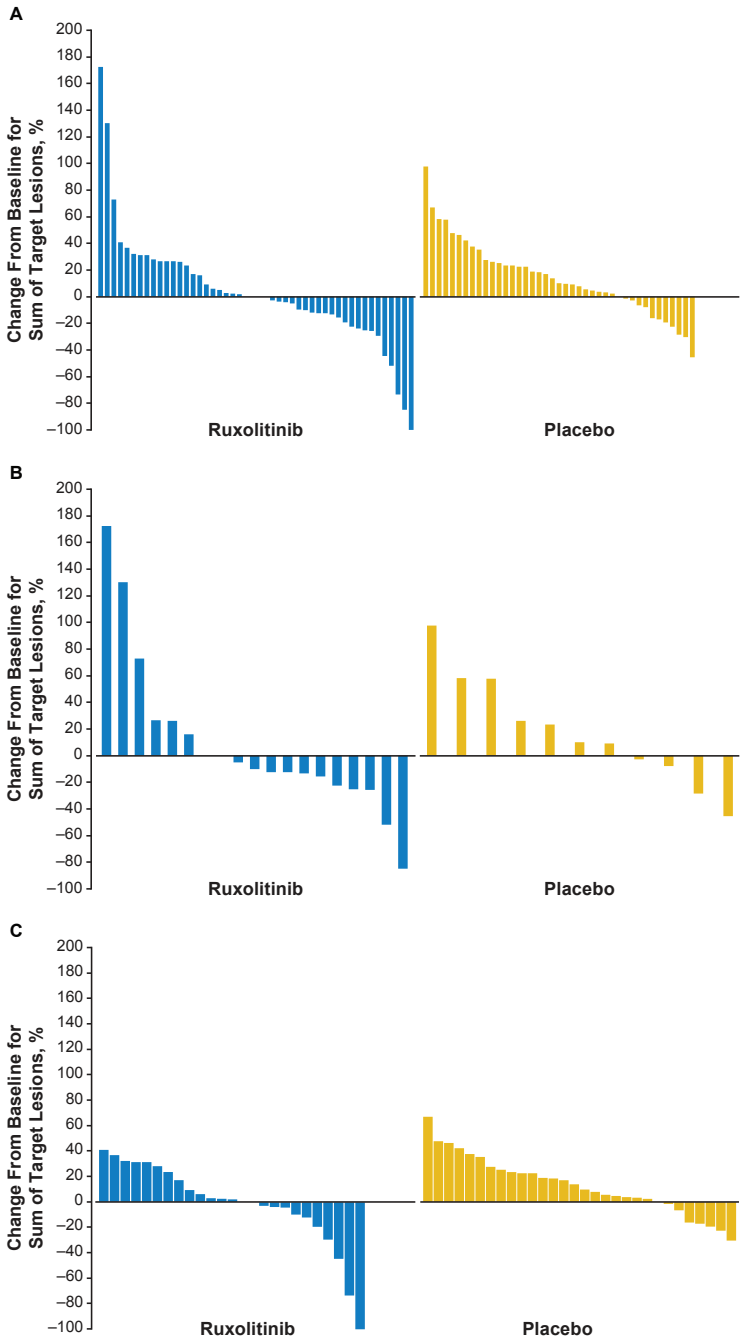
Supplementary Figure 2. Kaplan-Meier curves of progression-free survival in the ITT population (A), patients with CRP above the median of the study population (CRP >13 mg/L) at baseline (B), and patients with CRP ≤13 mg/L at baseline (C).



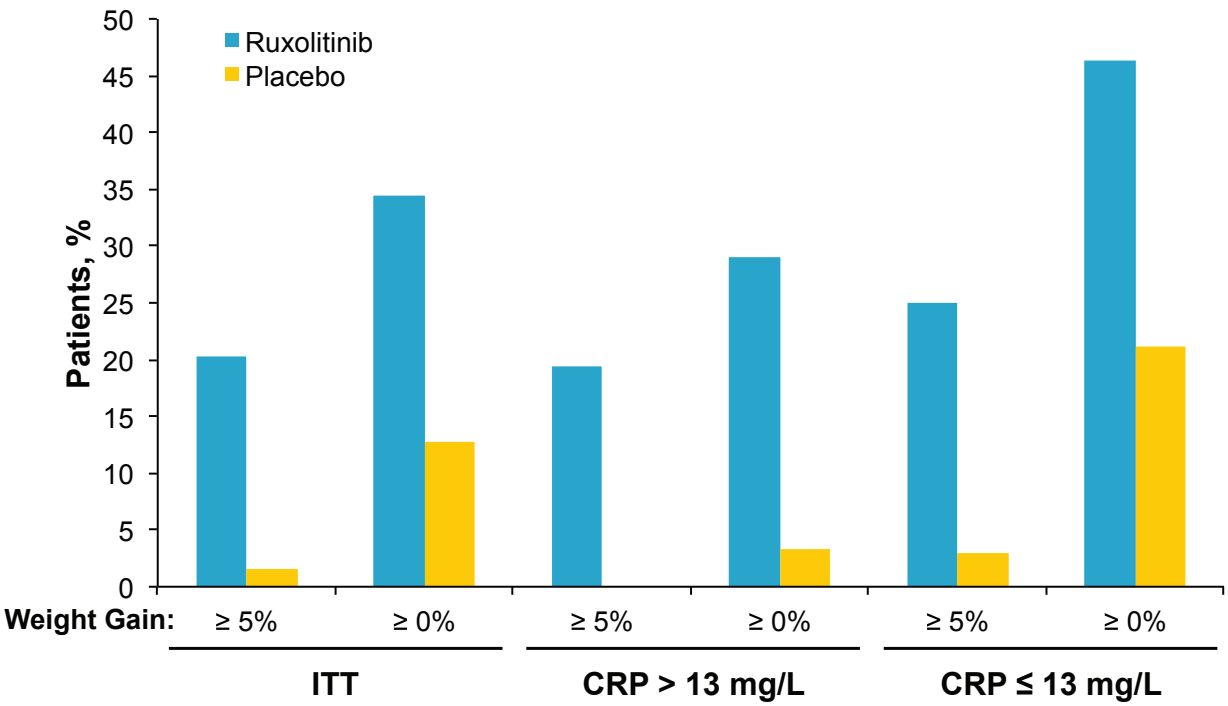
Supplementary Figure 3. Kaplan Meier curves of progression-free survival by mGPS.



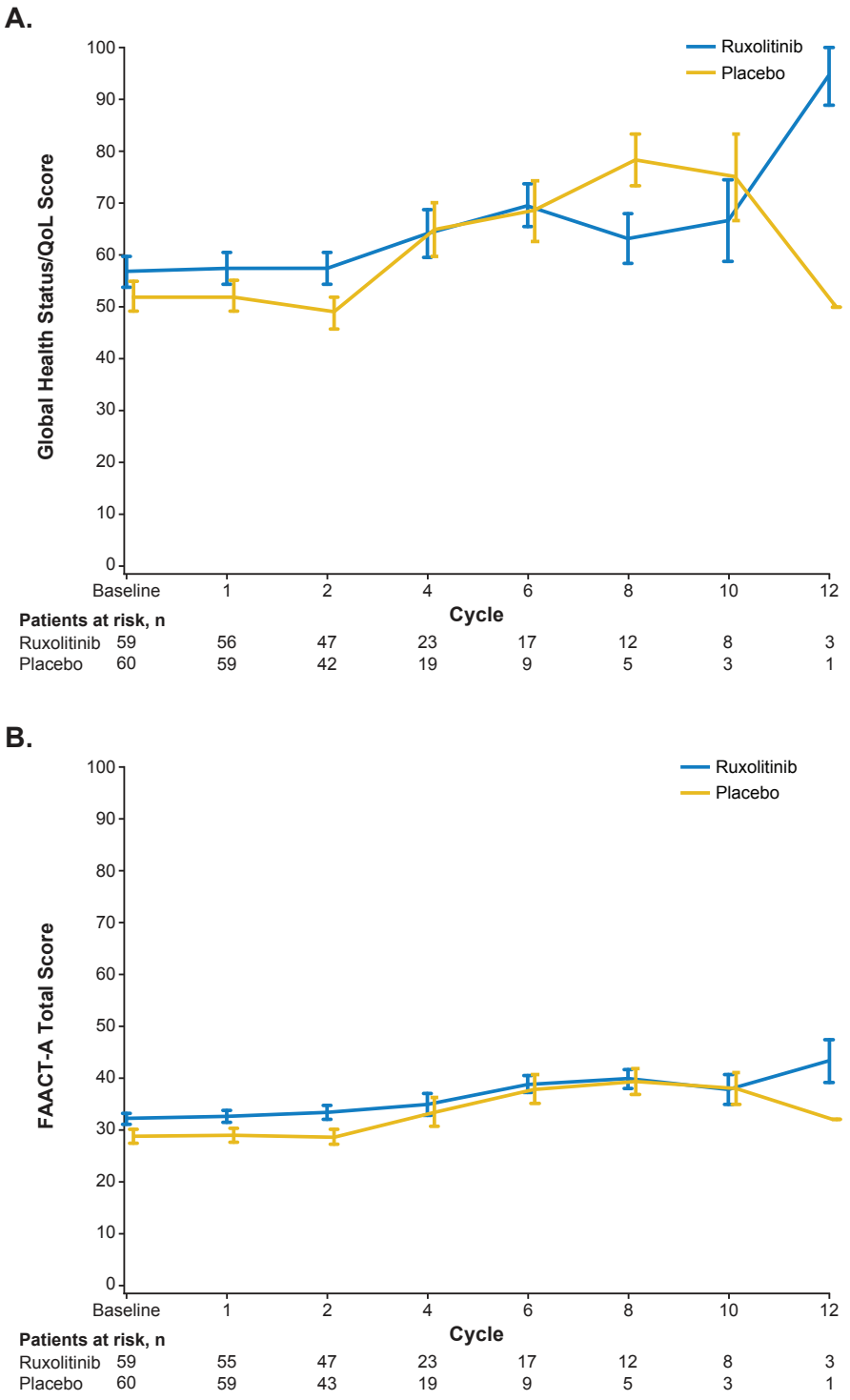
Supplementary Figure 4. Waterfall plot of the largest percent reduction in the sum of target lesions in the ITT population (A), patients with CRP above the median of the study population (CRP >13 mg/L) at baseline (B), and patients with CRP ≤13 mg/L at baseline (C).



Supplementary Figure 5. Proportion of patients with ≥0% or ≥5% weight gain.



Supplementary Figure 6. Change from baseline in EORTC QLQ-C30 global health status/quality-of-life score (A) and FAACT-A total score (B).



Supplementary Figure 7. Time to thromboembolic event (A), grade ≥2 stomatitis (B), and pneumonia (C).