A Phase Ib study of ruxolitinib + gemcitabine ± nab-paclitaxel in patients with advanced solid tumors

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Purpose: Aberrant activation of the Janus-associated kinase (JAK)/signal transducer and activator of transcription (STAT) pathway is associated with increased malignant cell proliferation and survival. This Phase Ib study evaluated ruxolitinib, a potent JAK1/2 inhibitor, in combination with gemcitabine with or without nab-paclitaxel in patients with advanced solid tumors.

Patients and methods: Patients received ruxolitinib + gemcitabine (regimen A) or ruxolitinib + gemcitabine + nab-paclitaxel (regimen B). The objective of the dose-finding phase was to identify the maximum tolerated doses (MTDs) of ruxolitinib plus gemcitabine with or without nab-paclitaxel.

Results: Among 42 patients enrolled, the median age was 62.5 years, 81.0% had pancreatic cancer, and almost 62% had received prior systemic therapy. Regimen A was tolerated with standard doses of gemcitabine; regimen B was tolerated with reduced doses of gemcitabine/nab-paclitaxel or concomitant granulocyte colony-stimulating factor. The sponsor decided to terminate the study early due to the interim analysis results of the Phase III JANUS 1 study. Discontinuations were mainly due to radiologic or clinical disease progression (81.0% of patients). Median treatment durations were 55.5 days (cohort A0) and 150.5 days (pooled B cohorts). Four patients (pooled B cohorts) had dose-limiting toxicities: grade 3 pneumonia (n=1), grade 4 neutropenia (n=1), and grade 4 thrombocytopenia (n=2). The most common grade 3/4 hematologic adverse events (AEs) were anemia, thrombocytopenia, and neutropenia. Serious AEs occurring in ≥2 patients in cohort A0 or pooled B cohorts were abdominal pain, sepsis (cohort A0), dehydration, anemia, and asthenia (pooled B cohorts). Overall response rates (ORRs) were 12.5% in cohort A0 and 38.5% in pooled B cohorts. Among patients with pancreatic cancer, ORR was 23.5% (14.0% cohort A0 30.0% pooled B cohorts).

Conclusion: The study was terminated early prior to reaching MTDs per sponsor decision; although ruxolitinib plus gemcitabine with or without nab-paclitaxel was generally safe and well tolerated in patients with advanced solid tumors, this combination will not be pursued further.

Keywords: Janus kinase inhibitor, pancreatic cancer

Introduction

The Janus-associated kinase (JAK) family comprises 4 non-receptor protein tyrosine kinases (JAK1–3 and tyrosine kinase 2) that transduce cytokine-mediated signaling via the JAK/signal transducer and activator of transcription (STAT) pathway.1 Aberrant activation of this pathway is associated with increased malignant cell proliferation and survival1,2 and has been observed in various tumor types.3–5 Furthermore, JAK kinases are key mediators of downstream signaling for various cytokine and/or growth factor
receptors that play a role in systemic inflammation, leading
to cancer cachexia that increases cancer-associated morbidity
and mortality.1,6–8

Ruxolitinib, an orally bioavailable, potent, and selective
inhibitor of JAK1 and 2 enzymes, has been approved by the
US Food and Drug Administration and European Medicines
Agency for the treatment of intermediate- to high-risk pri-
mary or secondary myelofibrosis.9,10 By selectively inhibiting
JAK2 V617F, STAT5, and ERK1/2 phosphorylation, ruxoli-
tinib reduces cellular proliferation and induces apoptosis of
JAK2 V617F Ba/F3 cells.11 Ruxolitinib has also been shown
to possess activity in solid tumors. In a previous Phase II
study of Ruxolitinib in Pancreatic Cancer Patients (RECAP),
early evidence of ruxolitinib in combination with capecta-
tabine suggested an association with improved survival com-
pared with placebo and capectabine in a subset of patients
with metastatic pancreatic cancer and systemic inflammation,
evidenced by elevated C-reactive protein levels.12

In addition to approvals in other solid tumor settings,
gemcitabine is indicated as a single agent for pancreatic
cancer and in combination with nab-paclitaxel as a first-line
therapy for metastatic adenocarcinoma of the pancreas;13,14
however, myelosuppression is a common and sometimes
dose-limiting adverse event (AE) associated with both
gemcitabine and nab-paclitaxel.13,14 Ruxolitinib has dem-
onstrated the ability to reduce levels of pro-inflammatory
cytokines (thought to be associated with the development
of cachexia) in patients with myelofibrosis.15–17 Ruxolitinib
is generally known to be well tolerated and may augment
the activity of gemcitabine in patients with pancreatic
cancer. Indeed, in a murine model of pancreatic cancer,
the combination of gemcitabine plus a JAK2 inhibitor
(fedratinib) substantially reduced the rate of tumor growth
and significantly improved overall survival compared with
either agent alone.18 Overlapping hematologic toxicities
associated with gemcitabine and ruxolitinib may be a
concern clinically.

The current Phase Ib, dose-finding study was conducted
to evaluate the safety and tolerability of ruxolitinib in com-
bination with gemcitabine with or without nab-paclitaxel in
patients with advanced pancreatic cancer and other advanced
solid tumors. Our study was terminated early by the sponsor
after an interim analysis from a Phase III trial of ruxolitinib
plus capectabine (JANUS 1) showed no additional benefit
over capectabine alone in patients with advanced pancreatic
cancer and high systemic inflammation as measured by the
modified Glasgow prognostic score.19

Patients and methods

Patients

Eligible patients were aged ≥18 years, had radiographically
measurable advanced or metastatic pancreatic adenocar-
cinoma or another advanced solid tumor, and an Eastern
Cooperative Oncology Group (ECOG) performance status
of ≤1.

The study was conducted in accordance with the study
protocol, Declaration of Helsinki, Good Clinical Practices
as defined in the Code of Federal Regulations Title 21,
International Conference of Harmonisation—Good Clinical
Practice consolidated guidelines, and applicable regulatory
requirements. All patients provided written informed consent
before study participation. The study protocol and its amend-
ments and patients’ informed consent were reviewed and
approved by institutional review boards or independent ethics
committees (IntegReview Ethical Review Board, Austin, TX,
USA; Western Institutional Review Board, Puyallup, WA,
USA; Western Institutional Review Board, Olympia,
WA, USA; and Duke University Health System Institutional
Review Board, Durham, NC, USA).

Study design

The Phase Ib open-label study (NCT01822756) was designed
to be conducted in 2 parts. Part 1 comprised a dose-finding
phase to identify the maximum tolerated dose (MTD) of
ruxolitinib when administered with gemcitabine with or
without nab-paclitaxel to patients with advanced or meta-
static pancreatic cancer and other advanced solid tumors;
safety, tolerability, and pharmacokinetics would be assessed
in part 1. Part 2 was to explore the safety, tolerability, phar-
macokinetics, pharmacodynamics, and preliminary clinical
activity of ruxolitinib, at the dose identified in part 1, in
combination with gemcitabine with or without nab-paclitaxel.
Part 2 of the study was not conducted following a sponsor
decision not to pursue the combinations of ruxolitinib +
gemcitabine or ruxolitinib + gemcitabine/nab-paclitaxel, and
therefore, to stop further enrollment during part 1 before the
MTD was reached.

Part 1 was a 3 + 3 dose-finding design in which patients
were assigned to 1 of 2 treatment regimens, regimen A or B,
based on prior chemotherapy exposure (Figure 1). Patients
who had received no more than 1 prior chemotherapy regi-
men for advanced or metastatic disease (excluding neoadju-
vant or adjuvant disease) were eligible to receive ruxolitinib +
gemcitabine (regimen A). Patients who had not received prior
chemotherapy for advanced or metastatic disease (excluding
neoadjuvant or adjuvant disease) were eligible to receive ruxolitinib + gemcitabine + nab-paclitaxel (regimen B).

The first patients enrolled to regimen A were assigned to the starting dose cohort A0, consisting of ruxolitinib 15 mg twice daily (BID) and gemcitabine 1,000 mg/m² on days 1, 8, and 15 every 28 days (Q28D). The first patients enrolled to regimen B were assigned to the starting dose cohort B0, consisting of ruxolitinib 10 mg BID, gemcitabine 1,000 mg/m², and nab-paclitaxel 100 mg/m² on days 1, 8, and 15 Q28D. Cohort B0 administered with prophylactic granulocyte colony-stimulating factor (GCSF) support could be repeated in patients with pancreatic cancer if any of the dose-limiting toxicities (DLTs) observed were due to myelosuppression. If a DLT was observed in 1 patient, then that cohort was expanded to at least 6 patients. If no additional DLTs were observed in those 3 additional patients, then dose finding could proceed or result in cohort expansion. If a DLT occurred in 2 patients or more of the total cohort, then the MTD was deemed to be exceeded, and the lower dose level was to be expanded to at least 6 patients to evaluate safety. If the regimen in cohort B0 was not tolerated, then an additional cohort (B1) was added to test a reduced dose of gemcitabine at 750 mg/m², without the addition of prophylactic GCSF support. In addition, ruxolitinib 5 mg BID, gemcitabine 1,000 mg/m², and nab-paclitaxel 100 mg/m² on days 1, 8, and 15 Q28D were tested in cohort B (-1) to evaluate the effects of GCSF with the expectation of re-escalating doses.

Treatment for all patients in regimens A and B consisted of repeating 28-day cycles, with treatment cycles continuing for as long as the regimen was tolerated and the patient did not meet discontinuation criteria. The expected duration was 4–6 months.

End points
The primary end points were the determination of the MTD of ruxolitinib in combination with gemcitabine with or without nab-paclitaxel, and the safety and tolerability of the treatment regimens. Secondary end points were pharmacokinetics and pharmacodynamics. Because of the early termination of the study, samples for pharmacokinetics and pharmacodynamics, and computed tomography for tumor burden were collected but not analyzed. The exploratory end point was antitumor effects assessed as overall response rate (ORR).

Assessments and statistical methods
Safety and tolerability were assessed by monitoring AEs, measuring vital signs and 12-lead electrocardiograms, and evaluating physical examinations and clinical laboratory blood tests. The severity of AEs was graded using the National Cancer Institute Common Terminology Criteria for AEs v4.03. Safety data were compared over time to assess change from baseline, during treatment, and follow-up. The safety population, including all enrolled patients who received at least 1 dose of ruxolitinib (treatment group defined according to actual treatment received regardless of assigned study drug treatment), was used for all safety analyses. Response was determined by radiographic disease assessments per Response Evaluation Criteria in Solid Tumors version 1.1 by investigator assessment and was exploratory in nature with descriptive statistics (eg, mean, standard deviation, and range) provided. The intent-to-treat
(ITT) population, including all patients who received at least 1 dose of ruxolitinib (treatment group defined according to assigned treatment regardless of actual study drug received), was used for all efficacy analyses.

**Results**

**Patients**

A total of 42 patients with advanced solid tumors (predominantly pancreatic cancer; 81.0%) were enrolled in part 1 of the study (ITT and safety population; Table 1). The median age at the time of enrollment was 62.5 years, and all patients had an ECOG performance status of either 0 (57.1%) or 1 (42.9%) at baseline. Almost 62% of patients had received prior systemic therapy for their primary cancer; ~19% had received prior gemcitabine; and ~40% had received prior radiation therapy. Of the 16 patients who had received prior radiation therapy, 8 received radiation therapy at the same time as chemotherapy as an add-on, 3 received neoadjuvant radiation therapy, and 5 received adjuvant radiation therapy.

**Exposure, safety, and efficacy**

**MTD and exposure**

Ruxolitinib + gemcitabine (regimen A) was tolerated with standard doses of gemcitabine (1,000 mg/m²). Ruxolitinib + gemcitabine/nab-paclitaxel (regimen B) was tolerated with reduced doses of gemcitabine (750 mg/m²)/nab-paclitaxel (100 mg/m²) or with concomitant GCSF. MTDs were not defined, as the study was terminated after cohort B1 when the sponsor decided not to pursue these combinations further based on the interim results from another Phase III trial.

A total of 40 patients (95.2%) discontinued treatment, primarily due to radiologic or clinical disease progression (n=34 [81.0%]; Table 2). Other reasons included AE (7.1%), death (4.8%), and patient decision (2.4%). Overall, the median duration of ruxolitinib exposure was 97.5 days (55.5 days in cohort A0; 150.5 days in the pooled B cohorts); a median of 8.5 (range, 1–46) intravenous gemcitabine treatments were administered.

**Safety**

There were no DLTs experienced in cohort A0. Four patients in the B0 cohorts experienced DLTs; 2 patients from cohort B0 without GCSF, including 1 case of grade 4 neutropenia, 1 case of grade 4 thrombocytopenia, and 2 patients from cohort B0 with GCSF, including a serious event of grade 3 pneumonia (which resolved with treatment 6 days after onset) and 1 case of grade 4 thrombocytopenia.

All patients experienced at least 1 treatment-emergent AE (TEAE), with the most common nonhematologic TEAEs of any grade (occurring in ≥50% of patients in cohort A or pooled B cohorts) being fatigue, nausea, alopecia, and peripheral edema (Table 3). A lower percentage of infections and infestations occurred in patients who did not receive GCSF compared with patients who did receive GCSF (28.6% vs 57.1%). Grade 3/4 TEAEs were reported in >80% of patients in both cohort A0 and pooled B cohorts. The most common grade 3/4 nonhematologic AEs (occurring in ≥10% of patients in cohort A or pooled B cohorts) were abdominal pain, fatigue, sepsis, and hypokalemia (Table 3); the most common grade 3/4 hematologic AEs (new/worsening laboratory abnormalities occurring in ≥10% of patients in cohort A or pooled B cohorts) were anemia, thrombocytopenia, and neutropenia (Table 4).

Treatment-emergent serious AEs (SAEs) were experienced in 62.5% of patients in cohort A and 34.6% of patients in pooled B cohorts. Treatment-emergent SAEs occurring in ≥2 patients in either cohort A or pooled B cohorts were abdominal pain (25% cohort A0), sepsis (12.5% cohort A0), dehydration, anemia, and asthenia (7.7% each, pooled B cohorts). One death occurred in cohort A0 due to sepsis (without neutropenia), which was not considered related to ruxolitinib; no deaths occurred in pooled B cohorts.

**Efficacy**

ORRs were 12.5% (2/16) in cohort A0 and 38.5% (10/26) in the pooled B cohorts (Table 5). Among the patients with pancreatic cancer, ORR was 23.5% (14.0% in cohort A0 and 30.0% in pooled B cohorts). A complete response (CR) occurred in 1 patient (2.4%) overall with non-small cell lung cancer in cohort B0 without GCSF, and a partial response (PR) occurred in 11 patients overall (26.2%). Among patients who achieved a PR, the median duration of response ranged from 33.0 days in cohort B (1) to 225.0 days in cohort B1. The majority of PRs (82.0%) occurred in patients treated with ruxolitinib for a median of >140 days. Clinical benefit rate (ORR + stable disease for ≥7 weeks) was 37.5% (6/16) in cohort A0 and 73.0% (19/26) for the pooled B cohorts. The largest percentage reduction of target lesions occurred in a patient with PR in cohort B (1) and in a patient with CR in cohort B0 (Figure 2).

**Discussion**

In patients with chemotherapy-naive metastatic pancreatic adenocarcinoma, the combination of gemcitabine and nab-paclitaxel has previously demonstrated improved survival
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cohort A</th>
<th>Cohort B (−1)</th>
<th>Cohort B0</th>
<th>Cohort B0</th>
<th>Cohort B1</th>
<th>Total (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RUX 5 mg BID + GCSF + gemcitabine 1,000 mg/m² + nab-paclitaxel 100 mg/m² (N=16)</td>
<td>RUX 15 mg BID - GCSF + gemcitabine 1,000 mg/m² (N=4)</td>
<td>RUX 10 mg BID + GCSF + gemcitabine 1,000 mg/m² + nab-paclitaxel 100 mg/m² (N=10)</td>
<td>RUX 10 mg BID - GCSF + gemcitabine 1,000 mg/m² + nab-paclitaxel 100 mg/m² (N=4)</td>
<td>RUX 10 mg BID - GCSF + gemcitabine 750 mg/m² + nab-paclitaxel 100 mg/m² (N=8)</td>
<td></td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>60.5 (48–78)</td>
<td>59.5 (56–70)</td>
<td>63.5 (44–75)</td>
<td>72.5 (59–76)</td>
<td>64.0 (51–76)</td>
<td>62.5 (44–78)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>8 (50.0)</td>
<td>0</td>
<td>4 (40.0)</td>
<td>4 (100.0)</td>
<td>6 (75.0)</td>
<td>22 (52.4)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>13 (81.3)</td>
<td>4 (100.0)</td>
<td>10 (100.0)</td>
<td>4 (100.0)</td>
<td>4 (50.0)</td>
<td>35 (83.3)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>3 (18.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4 (50.0)</td>
<td>7 (16.7)</td>
</tr>
<tr>
<td>Mean BSA, m² (SD)</td>
<td>1.911 (0.3141)</td>
<td>1.663 (0.2069)</td>
<td>1.792 (0.2453)</td>
<td>2.063 (0.2329)</td>
<td>1.941 (0.3198)</td>
<td>1.879 (0.2911)</td>
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<tr>
<td>ECOG PS, n (%)</td>
<td></td>
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<td></td>
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<tr>
<td>0</td>
<td>6 (37.5)</td>
<td>2 (50.0)</td>
<td>8 (80.0)</td>
<td>3 (75.0)</td>
<td>5 (62.5)</td>
<td>24 (57.1)</td>
</tr>
<tr>
<td>1</td>
<td>10 (62.5)</td>
<td>2 (50.0)</td>
<td>2 (20.0)</td>
<td>1 (25.0)</td>
<td>3 (37.5)</td>
<td>18 (42.9)</td>
</tr>
<tr>
<td>Tumor type, n (%)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>14 (87.5)</td>
<td>3 (75.0)</td>
<td>8 (80.0)</td>
<td>1 (25.0)</td>
<td>8 (100.0)</td>
<td>34 (81.0)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0</td>
<td>1 (25.0)</td>
<td>2 (20.0)</td>
<td>0</td>
<td>0</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>1 (6.3)</td>
<td>0</td>
<td>0</td>
<td>1 (25.0)</td>
<td>0</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Others</td>
<td>1 (6.3)</td>
<td>0</td>
<td>0</td>
<td>2 (50.0)</td>
<td>0</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>Metastatic disease, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (37.5)</td>
<td>1 (25.0)</td>
<td>3 (30.0)</td>
<td>1 (25.0)</td>
<td>5 (62.5)</td>
<td>16 (38.1)</td>
</tr>
<tr>
<td>1</td>
<td>7 (43.8)</td>
<td>3 (75.0)</td>
<td>6 (60.0)</td>
<td>2 (50.0)</td>
<td>3 (37.5)</td>
<td>21 (50.0)</td>
</tr>
<tr>
<td>2</td>
<td>3 (18.8)</td>
<td>0</td>
<td>1 (10.0)</td>
<td>1 (25.0)</td>
<td>0</td>
<td>5 (11.9)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BID, twice daily; BSA, body surface area; ECOG PS, Eastern Cooperative Oncology Group performance status; GCSF, granulocyte colony-stimulating factor; NSCLC, non-small cell lung cancer; RUX, ruxolitinib; SD, standard deviation.
### Table 2 Patient disposition

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Cohort A0</th>
<th>Cohort B (−1)</th>
<th>Cohort B0</th>
<th>Cohort B0</th>
<th>Cohort B1</th>
<th>Total (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUX 15 mg BID − GCSF + gemcitabine 1,000 mg/m² (N=16)</td>
<td>16 (100.0)</td>
<td>10 (100.0)</td>
<td>4 (100.0)</td>
<td>7 (87.5)</td>
<td>4 (100.0)</td>
<td>40 (95.2)</td>
</tr>
<tr>
<td>RUX 5 mg BID + GCSF + gemcitabine 1,000 mg/m² + nab-paclitaxel 100 mg/m² (N=4)</td>
<td>3 (75.0)</td>
<td>2 (50.0)</td>
<td>1 (10.0)</td>
<td>2 (50.0)</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>RUX 10 mg BID − GCSF + gemcitabine 1,000 mg/m² + nab-paclitaxel 100 mg/m² (N=4)</td>
<td>10 (100.0)</td>
<td>5 (50.0)</td>
<td>2 (10.0)</td>
<td>6 (75.0)</td>
<td>0</td>
<td>23 (54.8)</td>
</tr>
<tr>
<td>RUX 10 mg BID − GCSF + gemcitabine 1,000 mg/m² + nab-paclitaxel 100 mg/m² (N=4)</td>
<td>1 (100.0)</td>
<td>1 (10.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>RUX 10 mg BID − GCSF + gemcitabine 1,000 mg/m² + nab-paclitaxel 100 mg/m² (N=4)</td>
<td>4 (100.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
</tbody>
</table>

#### Patients who discontinued treatment

<table>
<thead>
<tr>
<th>Reason for treatment discontinuation</th>
<th>Cohort A0</th>
<th>Cohort B (−1)</th>
<th>Cohort B0</th>
<th>Cohort B0</th>
<th>Cohort B1</th>
<th>Total (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression</td>
<td>8 (50.0)</td>
<td>5 (50.0)</td>
<td>2 (50.0)</td>
<td>2 (50.0)</td>
<td>6 (75.0)</td>
<td>23 (54.8)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>0</td>
<td>1 (10.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (6.3)</td>
<td>1 (10.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Patient decision</td>
<td>0</td>
<td>1 (10.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Other (clinical progression)</td>
<td>7 (43.8)</td>
<td>2 (20.0)</td>
<td>0</td>
<td>1 (12.5)</td>
<td>11 (26.2)</td>
<td>11 (26.2)</td>
</tr>
</tbody>
</table>

#### Abbreviations:
- BID: twice daily
- GCSF: granulocyte colony-stimulating factor
- rUX: ruxolitinib

### Table 3 Most common treatment-emergent nonhematologic adverse events

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Cohort A0</th>
<th>Pooled B cohorts (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(MedDRA preferred term)</td>
<td>RUX 15 mg BID − GCSF + gemcitabine 1,000 mg/m² (N=16)</td>
<td>All grades, n (%)</td>
</tr>
<tr>
<td>All grades, n (%)</td>
<td>10 (62.5)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Grade ≥3, n (%)</td>
<td>2 (12.5)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8 (50.0)</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (31.3)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 (31.3)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5 (31.3)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>4 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4 (25.0)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3 (18.8)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (12.5)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (12.5)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (12.5)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1 (6.3)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Notes:
- Most common (≥30%) all-grade events.
- Most common (≥10%) grade ≥3 events.

#### Abbreviations:
- BID: twice weekly
- GCSF: granulocyte colony-stimulating factor
- MedDRA: Medical Dictionary for Regulatory Activities
- rUX: ruxolitinib
### Table 4 Worsening of hematologic toxicity

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Cohort A0 RUX 15 mg BID - GCSF + gemcitabine 1,000 mg/m² (N=16)</th>
<th>Pooled B cohorts (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Anemia</td>
<td>9 (56.3)</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (25.0)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (18.8)</td>
<td>2 (12.5)</td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice weekly; GCSF, granulocyte colony-stimulating factor; MedDRA, Medical Dictionary for Regulatory Activities; RUX, ruxolitinib.

### Table 5 Tumor response

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Cohort A0 RUX 15 mg BID - GCSF + gemcitabine 1,000 mg/m² (N=16)</th>
<th>Cohort B (−1) RUX 5 mg BID + GCSF + gemcitabine 1,000 mg/m² + nab-paclitaxel 100 mg/m² (N=4)</th>
<th>Cohort B0 RUX 10 mg BID + GCSF + gemcitabine 1,000 mg/m² + nab-paclitaxel 100 mg/m² (N=10)</th>
<th>Cohort B0 RUX 10 mg BID - GCSF + gemcitabine 1,000 mg/m² + nab-paclitaxel 100 mg/m² (N=4)</th>
<th>Cohort B1 RUX 10 mg BID - GCSF + gemcitabine 750 mg/m² + nab-paclitaxel 100 mg/m² (N=8)</th>
<th>Pooled B cohorts Total (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>2 (12.5)</td>
<td>1 (25.0)</td>
<td>5 (50.0)</td>
<td>1 (25.0)</td>
<td>3 (37.5)</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (25.0)</td>
<td>0</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>PR</td>
<td>2 (12.5)</td>
<td>1 (25.0)</td>
<td>5 (50.0)</td>
<td>0</td>
<td>3 (37.5)</td>
<td>9 (34.6)</td>
</tr>
<tr>
<td>Stable disease for ≥7 weeks</td>
<td>4 (25.0)</td>
<td>3 (75.0)</td>
<td>2 (20.0)</td>
<td>2 (50.0)</td>
<td>2 (25.0)</td>
<td>9 (34.6)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>6 (37.5)</td>
<td>0</td>
<td>1 (10.0)</td>
<td>0</td>
<td>3 (37.5)</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1 (6.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>3 (18.8)</td>
<td>0</td>
<td>2 (20.0)</td>
<td>1 (25.0)</td>
<td>0</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Median duration of response, days (range)</td>
<td>132.0 (NE–NE)</td>
<td>33.0 (NE–NE)</td>
<td>113.0 (57.0–533.0)</td>
<td>244.0 (NE–NE)</td>
<td>225.0 (57.0–225.0)</td>
<td>169.0 (33.0–505.0)</td>
</tr>
</tbody>
</table>

**Note:** Not evaluable and missing patients are included in the denominator, even if these patients did not have a response assessment.

**Abbreviations:** BID, twice daily; CR, complete response; GCSF, granulocyte colony-stimulating factor; NE, not estimated; ORR, overall response rate; PR, partial response; RUX, ruxolitinib.
Figure 2. Waterfall plot of best percent change in sum of target lesions (ITT population).

Note: For patients who only had increases in target lesion size from baseline, the smallest increase was considered as the best change from baseline.

Abbreviations: BC, breast cancer; CCOC, clear cell odontogenic cancer; CUP, cancer of unknown primary (likely gallbladder); GCSF, granulocyte colony-stimulating factor; ITT, intent-to-treat; NSCLC, non-small cell lung cancer; PC, pancreatic cancer.

and tumor response compared with gemcitabine alone; however, this combination was also found to increase the rates of peripheral neuropathy and myelosuppression observed.\(^{21,22}\) In the Phase II RECAP study in patients with metastatic pancreatic cancer who had failed prior gemcitabine therapy, the combination of ruxolitinib and capecitabine demonstrated clinical activity, especially in patients with systemic inflammation, evidenced by elevated C-reactive protein levels.\(^{12}\) These results suggest that the modulation of inflammatory cytokine signaling may be important in these patients and highlight a potential role for JAK inhibition as a therapeutic target.\(^{12}\)

The combination of ruxolitinib and gemcitabine, with and without nab-paclitaxel, in patients with advanced solid tumors, 81% of whom had pancreatic cancer, at the doses investigated were generally safe and well tolerated. The combination of ruxolitinib and gemcitabine was tolerated with standard doses of gemcitabine; however, the combination of ruxolitinib, gemcitabine, and nab-paclitaxel was tolerated with reduced doses of gemcitabine/nab-paclitaxel or with concomitant GCSF. Dose reductions of gemcitabine and/or nab-paclitaxel were required in up to 47% of patients in the pivotal study of gemcitabine versus gemcitabine plus nab-paclitaxel in patients with metastatic pancreatic cancer, and 15%–26% of patients received growth factor support.\(^{22}\) Although the overall number of patients treated was relatively small and any results from a comparison between groups must be interpreted with caution, the addition of GCSF to the ruxolitinib combination suggested no apparent clinical advantage, as a higher percentage of patients in cohorts receiving GCSF reported more infections than cohorts who did not receive GCSF. The most frequently reported TEAE was fatigue, which occurred in at least 50% of patients across all cohorts, and the most frequently reported grade ≥3 TEAEs were anemia, thrombocytopenia, and neutropenia, consistent with the prescribing information for ruxolitinib.\(^{9,10}\)

In 2 randomized double-blind Phase III trials, JANUS 1 and JANUS 2, ruxolitinib, when combined with capecitabine, also had a reasonably well-tolerated safety profile in patients with refractory advanced/metastatic pancreatic cancer. However, the addition of ruxolitinib to capecitabine did not improve clinical or quality of life outcomes, and the studies were terminated early based on efficacy findings of the planned interim analysis of JANUS 1.\(^{19}\)

In our study, objective responses were noted in 23.5% of 34 patients with pancreatic cancer. These results correlate well with response rates determined from recent studies in patients with advanced/metastatic pancreatic cancer (7%–35%) depending on the treatment regimen used.\(^{22–27}\)

**Conclusion**

In this Phase I study of ruxolitinib in combination with gemcitabine with or without nab-paclitaxel in patients with advanced solid tumors, assessment of the safety data revealed that no new safety concerns were identified, and the doses investigated were generally well tolerated. The study was
terminated early prior to reaching the MTDs per sponsor decision. The combinations of ruxolitinib and gemcitabine or ruxolitinib, gemcitabine, and nab-paclitaxel will not be pursued further.

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Disclosure
Both AA and YD are employees of Incyte Corporation and have stock ownership. The authors report no other conflicts of interest in this work.

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