Abstract

**Purpose:** Rigosertib, a dual non-ATP inhibitor of polo-like kinase 1 (Plk1) and phosphoinositide 3-kinase pathways (PI3K), and gemcitabine have synergistic antitumor activity when combined in preclinical studies. This phase I study aimed to determine the recommended phase II dose (RPTD) of the combination of rigosertib and gemcitabine in patients with cancer.

**Experimental Design:** Patients with solid tumors who failed standard therapy or were candidates for gemcitabine-based therapy were eligible. Gemcitabine was administered on days 1, 8, and 15 on a 28-day cycle and rigosertib on days 1, 4, 8, 11, 15, and 18. Pharmacokinetic studies were conducted during an expansion cohort of patients with advanced pancreatic ductal adenocarcinoma (PDA).

**Results:** Forty patients were treated, 19 in the dose-escalation phase and 21 in the expansion cohort. Dose levels evaluated were (gemcitabine/rigosertib mg/m²): 750/600 (n = 4), 750/1,200 (n = 3), 1,000/600 (n = 3), 1,000/1,200 (n = 3), and 1,000/1,800 (n = 6). One dose-limiting toxicity (death) occurred at the highest dose level (1,000/1,800) tested. Non–dose-limiting grade II/III toxicities included neutropenia, lymphopenia, thrombocytopenia, fatigue, and nausea. Grade III/IV neutropenia, thrombocytopenia, and fatigue were seen in two, one, and two patients in the expansion cohort. Partial responses were observed in PDA, thymic cancer, and Hodgkin lymphoma, including gemcitabine-pretreated PDA. The pharmacokinetic profile of rigosertib was not affected by gemcitabine.

**Conclusion:** The RPTD established in this study is rigosertib 1,800 mg/m² and gemcitabine 1,000 mg/m². This regimen is well tolerated with a toxicity profile of the combination similar to the profile of gemcitabine alone. Antitumor efficacy was observed in patients who previously progressed on gemcitabine-based therapy. *Clin Cancer Res; 18(7); 2048–55. ©2012 AACR.*

Introduction

Cell-cycle dysregulation is a hallmark of cancer (1). Polo-like kinase 1 (Plk1) is a key mitotic regulator that modulates the G2–M transition by affecting the activation of phosphatase CDC25C and cyclin B1 (2–4). Plk1 is overexpressed in a number of malignancies including lung, head and neck, ovary, prostate, and pancreas. Approaches targeting this checkpoint modulator achieved antitumor effects in preclinical studies (5). Rigosertib (ON 01910.Na; rigosertib sodium) is a non–ATP-binding small molecule that disrupts Plk1-mediated G2–M cell-cycle transition, thereby inducing mitotic arrest and apoptosis. In addition, rigosertib was recently found to exhibit phosphoinositide 3-kinase (PI3K) inhibitory activity (6). The PI3K pathway was first described more than 25 years ago when certain viral oncoproteins required PI3K to cause malignant transformation in target cells (7, 8). Since that discovery, an elaborate signaling cascade has been described in which PI3K plays an important role in cellular processes critical to both normal tissue growth and metabolism, as well as oncogenesis and tumor survival (9). There are multiple PI3K inhibitors undergoing clinical development with diverse selectivity both within PI3K subunits and with other targets such as mTOR or Akt (10), but rigosertib is the sole dual PI3K and Plk1 pathway inhibitor undergoing development.
In the first-in-human phase I single-agent trial of rigosertib, the recommended phase II dose (RPTD) was 3,120 mg [based on body surface area (BSA) 1.7 mg/m²] administered intravenously as a 2-hour infusion on days 1, 4, 8, 11, 15, and 18 of a 28-day cycle (11). Rigosertib toxicity profile minimally overlaps that of gemcitabine and includes fatigue, abdominal, tumor, and joint pain, and diarrhea.

Given the relevance of Plk1 in pancreatic ductal adenocarcinoma (PDA; refs. 12, 13), in vivo experiments in mice bearing patient-derived tumors showed that rigosertib exhibited single-agent efficacy (14). However, given the complexity of pancreatic cancer (15), it is unlikely that single-gene alterations will help design therapies for broad subsets of patients. In preclinical work, leading to this clinical trial, we hypothesized that interrogating the integrative response of a tumor to a pharmacologic insult with gemcitabine would provide rationale for combinatorial strategies. Using a dynamic, fine-needle aspirate–based ex vivo gemcitabine exposure assay on 11 PDA cases with known gemcitabine sensitivity, we found that the common feature of resistant cases was the inability of gemcitabine to induce a downregulation of Plk1 mRNA expression (16). Further mechanistic studies indicate that Plk1 was a mediator of gemcitabine susceptibility and cotreatment with siRNA against Plk1 gene synergized the in vitro antiproliferative effects of gemcitabine. Again, using mice bearing patient-derived pancreatic tumors, rigosertib synergized the antitumor effect of gemcitabine and induced tumor shrinkage in gemcitabine-resistant tumors when coadministered with gemcitabine. Thus, as opposed to many PDA studies where new agents are combined with gemcitabine simply because it is a standard of care, there is a strong rationale to combine these agents based on advanced human tumor models.

This phase I study was conducted to determine the RPTD of rigosertib administered in combination with gemcitabine in patients with advanced solid tumors. The study included an expansion cohort enriched with patients with advanced pancreatic cancer who could potentially benefit from treatment with this combination to further characterize the tolerability and toxicity profile of the regimen and examine preliminary efficacy. Blood samples and archival tumor blocks were also obtained for pharmacokinetic and biomarker studies, respectively.

**Patients and Methods**

**Patient eligibility**

The eligibility criteria included patients with histologically confirmed solid malignancy (including Hodgkin lymphoma) for which standard curative or palliative measures did not exist or were no longer effective or patients with a clinical rationale for a gemcitabine-based therapy; life expectancy at least 12 weeks; Eastern Cooperative Oncology Group (ECOG) performance status ≤1; ≥18 years of age; must have evaluable disease, either with tumor markers or with measurable disease in imaging by Response Evaluation Criteria in Solid Tumors (RECIST); must have adequate bone marrow, hepatic, and renal function as defined by absolute neutrophil count (ANC) ≥1,500/mm³, platelet count ≥100,000/mm³, hemoglobin ≥9 g/dL, serum creatinine ≤2× upper limit of normal (ULN), total bilirubin ≤2× ULN, and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤3× ULN (patients with primary or metastatic hepatic malignancy were eligible if total bilirubin ≤1.5 mg/dL, ALT or AST ≤5× ULN). Patients should have completed radiotherapy and/or chemotherapy more than 4 weeks before study drug initiation and without residual toxicity. Patients with active, clinically significant, and/or uncontrolled medical conditions were excluded. The study protocol was reviewed and approved by the Institutional Review Boards of respective centers, and written informed consent was mandatory.

**Treatment plan**

Rigosertib was supplied by Onconova Therapeutics Inc., as a sterile concentrate solution diluted with aqueous infusion solutions. Gemcitabine (Gemzar; Eli Lilly) was obtained commercially as a lyophilized powder and was reconstituted with normal saline to a final volume of 250 mL. Treatment consisted of rigosertib administered intravenously as a 2-hour infusion on days 1, 4, 8, 11, 15, and 18 and gemcitabine intravenously as a 30-minute infusion on days 1, 8, and 15 of a 28-day cycle. On days when patients received both drugs, gemcitabine was infused first and followed immediately by rigosertib. The starting dose for rigosertib was 600 mg/m², about 33% of the RPTD for single-agent treatment. The planned dose levels to be explored were as per Table 1. Prophylactic antiemetics included 5-HT3 antagonist and dexamethasone administered 30 minutes before all study drug infusions. Treatment was administered until disease progression, intercurrent illness, unacceptable adverse event(s), withdrawal of...
consent, noncompliance, or treatment delay due to toxicity for more than 3 weeks. Retreatment required adequate laboratory parameters on every evaluation, ANC/plt $\leq 1,000/\mu L$ or platelets $\leq 100,000/\mu L$ and resolution of all nonhematologic adverse events to $\leq$ grade II. Gemcitabine dose was reduced by 25% for ANC from 500 to 999/µL. Administration of both study drugs was withheld for $\geq$ grade III nonhematologic adverse events, where ANC $< 500/\mu L$ or platelets $< 50,000/\mu L$.

### Assessments, follow-up, and monitoring

Following consent, patients underwent a clinical and physical examination, ECOG performance assessment, complete blood count (CBC), chemistries, urine analysis, pregnancy test, tumor markers, and disease assessment by computed tomography (CT) for screening. CBC and chemistries were conducted weekly and before each infusion. CT evaluation was repeated every 2 cycles with tumor markers (if applicable) every cycle. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria of Adverse Events (version 1.0) and disease response by RECIST (version 1.0). Patients were considered evaluable for toxicity once therapy started and for efficacy if at least one cycle was administered.

### Definition of DLT, MTD, and dose-escalation plan

Dose-limiting toxicity (DLT) was defined as any treatment-related adverse event occurring during cycle 1 that corresponded to any of the following criteria: grade IV neutropenia lasting more than 7 days; febrile neutropenia, neutropenia associated with bacteremia or sepsis or $\geq$ grade III neutropenia associated with treatment-related fever or infection; grade IV thrombocytopenia or grade 3 thrombocytopenia accompanied by clinically significant bleeding; $\geq$ grade 3 nonhematologic toxicity lasting more than 7 days or any grade III or IV toxicity considered clinically significant, except suboptimally managed nausea, vomiting, and diarrhea; grade IV vomiting or diarrhea that persisted despite maximal prophylaxis and treatment with antiemetic and anti-diarrheal therapy; missing 2 or more doses of rigosertib within 1 cycle for rigosertib-related toxicity; missing gemcitabine dose on both days 8 and 15 for treatment-related toxicity; and treatment delay for more than 21 days after last scheduled dose because of treatment-related toxicity from which the patient failed to recover. Patients were evaluable for dose-escalation decision if they completed cycle 1 without missing more than one dose of rigosertib for nontreatment-related reason(s). Nonevaluable patients were replaced. The maximum tolerated dose (MTD) was defined as the highest dose level at which 1 or less of 6 patients experienced DLT during cycle 1.

The trial used the standard 3 + 3 dose-escalation design. The study drug dose was escalated to the next higher level if none of the first 3 patients developed DLTs. If 1 of the first 3 patients developed DLTs, up to 3 additional patients were to be enrolled for treatment at the same dose level. If no further DLT was encountered, dose-escalation resumed. If more than 1 patient developed DLT, the next cohort of 3 patients were to be treated at the next lower dose level. Once the MTD was determined or escalation finalized, an expanded cohort enriched with patients with pancreatic cancer was enrolled and treated at the MTD to further characterize the safety and tolerability of the study regimen to declare the RPTD.

### Pharmacokinetic sampling and analytic assay

Plasma samples were obtained from patients enrolled to the expansion cohort (dose level 3) for pharmacokinetic studies. Venous blood samples were collected into tubes containing potassium EDTA anticoagulant for the determination of rigosertib concentrations. The blood samples were collected at predose, 0.25, 0.5, 1, and 2 hours during the infusion, and at 10, 20, and 30 minutes, followed by 1, 3, and 6 hours postinfusion. Blood samples were collected on days 1 and 11 of the treatment cycle. Blood samples were centrifuged within 30 minutes of collection at 1,000 x g for 10 minutes. Plasma samples were stored at $-80^\circ$C before analysis. The plasma concentration of rigosertib was measured by a validated high-performance liquid chromatography/tandem mass spectrometry (LC/MS-MS) assay (11, 17).

### Pharmacokinetic analysis

Rigosertib plasma data (concentration vs. time) were analyzed by noncompartmental analysis. Pharmacokinetic parameters were generated through WinNonlin (version 5.3; Pharsight Corporation). Area under the concentration versus time curve ($AUC_{0-\infty}$) from time 0 to the last blood collection time point ($T_{\text{last}}$) was determined using the linear trapezoidal rule with extrapolation to infinity using the formula $\frac{T_{\text{last}}}{k}$ where $k$ is the elimination rate constant. Standard pharmacokinetic equations were used to calculate

### Table 1. Patient characteristics (N = 40)

<table>
<thead>
<tr>
<th>Sex</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Male</td>
<td>14</td>
</tr>
<tr>
<td>Female</td>
<td>26</td>
</tr>
</tbody>
</table>

### Primary tumor site

| Pancreas (adenocarcinoma) | 25  |
| Ovary                  | 6   |
| Lung (non–small cell)  | 2   |
| Neuroendocrine         | 1   |
| Cervix                 | 1   |
| Lymphoma (Hodgkin)    | 1   |
| Thymus                 | 1   |
| Colon                  | 1   |
| Anus                   | 1   |
| Esophagus              | 1   |

### Pharmacokinetic calculation

Rigosertib plasma data (concentration vs. time) were analyzed by noncompartmental analysis. Pharmacokinetic parameters were generated through WinNonlin (version 5.3; Pharsight Corporation). Area under the concentration versus time curve ($AUC_{0-\infty}$) from time 0 to the last blood collection time point ($T_{\text{last}}$) was determined using the linear trapezoidal rule with extrapolation to infinity using the formula $\frac{T_{\text{last}}}{k}$ where $k$ is the elimination rate constant. Standard pharmacokinetic equations were used to calculate
the elimination half-life \((0.693/k)\), clearance, and volume of distribution at steady state.

**Tumor genomic analyses**
Archival baseline formalin-fixed, paraffin-embedded tumor tissues from expansion cohort pancreatic cancer were used in SNaPshot tests evaluating 68 discrete mutational loci from 15 genes (Akt, APC, Braf, O-catenin, EGFR, FLT3, JAK2, KIT, KRAS, ME, NOTCH, NRAS, PI3KCA, PTEN, and TP53).

**Results**

**Patient characteristics**
A total of 46 patients with advanced solid tumors and lymphoma were consented and 40 patients received treatment between November 2008 and May 2011: 19 patients were treated in the dose-escalation phase and 21 treated at the MTD in the expansion cohort. All 40 treated patients were evaluable for safety evaluation. Thirty-two patients had received prior chemotherapy whereas 8 had not. Among patients who had received prior therapy, 19 had 3 or more prior regimens. Thirty-two patients were evaluable for response. Demographic and clinical characteristics of the enrolled patients are listed in Table 1. The study enrolled a total of 25 patients with PDA, of whom 19 metastatic patients were evaluable for response by RECIST.

**Dose-escalation process**
Three patients were enrolled to dose level 1 (see Table 2) at the beginning of the study and no DLT was observed. However, 2 patients developed grade III thrombocytopenia without bleeding and 1 of whom had grade III thrombocytopenia during week 3 of cycle 1 that recovered by the start of cycle 2. As such, cohorts of 4 and 3 patients were enrolled to lower dose levels, \(-1a\) and \(-1b\), respectively, to gather more safety data. As there were no dose-limiting and/or clinically significant toxicities observed at these 2 dose levels, escalation was continued to starting dose level 2 in which 3 patients were treated with no DLT observed. At dose level 3, 1 of 6 patients experienced a grade V fall of unknown etiology that was felt to be possibly related to the study drug during cycle 1 constituting a DLT. No other patients treated at this dose level developed DLT but no further escalation was attempted, as there were no dose-limiting and/or clinically significant toxicities observed at these 2 dose levels.

### Table 2. Dose-escalation schema

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Gemcitabine, a mg/m²</th>
<th>Rigosertib, b mg/m²</th>
<th>No. of patients</th>
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<tbody>
<tr>
<td>(-1a)</td>
<td>750</td>
<td>600</td>
<td>4</td>
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<tr>
<td>(-1b)</td>
<td>750</td>
<td>1,200</td>
<td>3</td>
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<td>1</td>
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<td>3</td>
<td>1,000</td>
<td>1,800</td>
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*Intravenously on days 1, 8, and 15 every 28 days.

### Table 3. Grade II and above treatment-related adverse events during cycle 1 (N = 40)

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<th>Adverse events</th>
<th>GII</th>
<th>GIII/IV</th>
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<td>Fatigue</td>
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<td>Hyponatremia</td>
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<td>Tumor pain</td>
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<td>Vomiting</td>
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aGrade V
this was the highest planned dose level with rigosertib at its full single-agent dose and gemcitabine at a clinically significant dose. Treatment of 21 additional patients at this dose level was confirmed as safe, and hence dose level 3 was declared the RPTD for the study combination.

Safety
The toxicity profile observed with the study combination was similar to that reported for gemcitabine alone. Forty patients received at least 1 dose of treatment and were evaluable for toxicities, including 19 who were evaluated for DLT during the dose-escalation phase. Grade II or higher treatment-related adverse events are summarized in Table 3. The median number of cycles received was 2 and the mean was 4. There was 1 death, classified as DLT, at dose level 3 that occurred in a patient with esophageal cancer following a fall. The death was attributed as possibly related to the study treatment due to the temporal relationship but the patient was showing clinical indication of rapid clinical progression. Other \( \geq \) grade III non–dose-limiting treatment–related toxicities observed during cycle 1 of the dose-escalation phase included neutropenia, lymphopenia, thrombocytopenia, fatigue, nausea, and vomiting. Common \( \geq \) grade II treatment-related adverse events during cycle 1 in all patients include neutropenia, anemia, thrombocytopenia, and fatigue. In the expansion cohort of 21 patients, grade III/IV neutropenia was observed in 2 (10%) patients, grade III/IV thrombocytopenia in 1 (5%) patient, grade III/IV fatigue in 2 (10%) patients, and grade III/IV hyponatremia in 1 (5%) patient.

Efficacy
Partial responses by RECIST were observed in 3 patients (Fig. 1): 1 gemcitabine-pretreated Hodgkin lymphoma, 1 thymic cancer, and 1 gemcitabine-pretreated PDA. Another patient with gemcitabine-naive PDA had an unconfirmed response. One patient with non–small cell lung cancer achieved stable disease for 48 weeks. Two heavily pretreated patients with ovarian cancer, including one previously treated with gemcitabine, achieved more than 50% decrease in CA-125 level.

Of the 19 evaluable patients with PDA, one had a partial response (PR; \(-55\%\) by RECIST) and 11 had stable disease (SD) as best response (Fig. 2). Minor response (MR; defined as \(-10\%\) to \(-30\%\) by RECIST) was observed in 5 of 19 evaluable in patients with PDA including one previously treated PR (\(-55\%\); Fig. 2). Among the subset of patients with PDA who had previously received gemcitabine, 4 of the 12 evaluable subjects had shrinkage including the confirmed PR. Decrease in CA19-9 (\(\geq 50\%\)) was observed in 10 of 16 evaluable patients; 1 had PR, 4 SD/MR, 1 SD, and 4 PD by RECIST. The median duration of stable disease at the RPTD was 113 days (range, 52–215 days). When analyzed according to the dose of rigosertib received, a trend was observed with the median survival of the 1,800-mg/m² dose group being longer than 1,200 mg/m² and 600 mg/m² (42, 31, and 9.5 weeks, respectively), that was not significant statistically. The overall survival of patients with PDA at the RPTD was 42 weeks (Supplementary Fig. S1).

Pharmacokinetics and genomics
Rigosertib plasma concentration versus time on days 1 and 11 are shown in Fig. 3, and the pharmacokinetic parameters are summarized in Table 4. The plasma concentration reached a maximum at the end of 2-hour infusion and then declined very rapidly, in concordance with the data from the first-in-human experience with rigosertib (11). The functional half-life of the drug was determined to be relatively short (~1 hour). The systemic clearance of rigosertib at the dose of 1,800 mg/m² is 3.66 ± 1.20 L/h/m², similar to the reported clearance of 2.5 L/h/m² at the flat dose of 3,120 mg (11). The volume of distribution at steady state is 4.39 ± 0.64 L/m², suggesting that the drug is moderately distributed. There were no differences in the pharmacokinetic parameters of rigosertib between days 1 (rigosertib given with gemcitabine) and 11 (rigosertib alone). No PIK3CA mutations were detected in 8 pancreatic cancer samples.
Phase I of Rigosertib in Combination with Gemcitabine

Figure 2. Tumor (A) and CA19-9 (B) response in patients with PDA treated in the study. The discrepancies between the number of patients in each dose levels between (A) and (B) is because some patients were evaluable for CA19-9 but not tumor response and vice versa.

Discussion

The RPTD for rigosertib by 2-hour infusion on days 1, 4, 8, 11, 15, and 18 is 1,800 mg/m² when combined with gemcitabine 1,000 mg/m² on days 1, 8, and 15 in patients with solid tumors, administered in 28-day cycles. This dose is equivalent to the previously reported rigosertib single-agent full RPTD dose assuming an average 1.7 m² BSA. Rigosertib hematologic toxicity was infrequent and mild during single-agent rigosertib phase I evaluation (11), and coadministration of rigosertib with gemcitabine did not significantly potentiate the hematologic impact of gemcitabine alone. Preliminary efficacy was observed in patients with cancers of the pancreas, thymus, ovary, and Hodgkin lymphoma. In accordance with findings from preclinical studies, we observed clinical benefit in patients who had previously received and/or progressed while on gemcitabine treatment.

Pharmacokinetic studies were conducted in the expansion cohort on patients receiving 1,000 mg/m² gemcitabine and 1,800 mg/m² rigosertib. The dosing of rigosertib according to BSA achieved similar pharmacokinetic profile as the flat dosing strategy used during single-agent phase I evaluation (11). Combining with gemcitabine did not affect rigosertib pharmacokinetics. In addition, repeat dosing did not seem to alter the pharmacokinetic profile of rigosertib. The pharmacokinetic profile of gemcitabine when combined with rigosertib will be evaluated in an ongoing study.

The dual inhibitory activity of rigosertib is noteworthy, as it enables blocking key pathways that dictate susceptibility to agents targeting DNA replication and/or escape pathways that become activated during cytotoxic chemotherapy. Interestingly, wortmannin, a known PI3K inhibitor, was also recently shown to have Plk1-inhibitory activity leading to the hypothesis that a shared structure exists between putative inhibitors for both molecules (18). Inhibition of Plk1 has been postulated as one of the last cell-cycle arrest checkpoints (3). Elegant mechanistic studies provided the biologic framework explaining our preclinical data. While in undamaged cells, several redundant pathways can promote the onset of mitosis, this redundancy is lost in cells recovering from a DNA damage–induced arrest (19). Plk1 is crucial for mitotic entry following recovery from DNA damage and supports the observation that cells, where Plk1 function does not decrease after gemcitabine-induced insults, are ultimately resilient to arrest and senescence/death.

The PI3K signaling axis has a well-established role in treatment resistance to EGF inhibitors (20) and is likely to be involved in escape mechanisms to other therapies (10). Although PI3K is not frequently mutated in pancreatic cancer (15), it is downstream of KRAS that is frequently altered in PDA. However interesting, PI3K mutations are relatively rare in human cancers at large, and only specific types of tumors may exhibit an oncogene addiction phenotype to components of the PI3K pathway. Inhibition of
PI3K alone has generally resulted only in stable disease, not disease regression, with the exception of dual PI3K-mTOR inhibitors where isolated responses have been communicated (10). Thus, it is likely that PI3K inhibitors will need to be combined with other therapies, and rigosertib dual activity may be a significant benefit.

The efficacy and a median overall survival of 42 weeks documented in this study warrant further evaluation, particularly considering patients who had been previously treated with gemcitabine. Accordingly, a randomized phase II/III study in gemcitabine-naive PDA (ONTRAC) has been initiated at multiple sites. PDA remains a highly fatal disease despite recent advances (21, 22). The addition of erlotinib to gemcitabine only marginally improved the 1-year survival rate to 23% versus 17% for gemcitabine alone, and the regimen has not been widely adopted by oncologists (23). In a recent report, FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) achieved an impressive survival improvement over gemcitabine alone in metastatic PDA. However, patients receiving FOLFIRINOX reported a higher frequency of toxicities including alopecia and diarrhea. In this study, rigosertib was safely administered in combination with gemcitabine-refractory patients, supporting the notion that the combined inhibition could sensitize to and/or reverse acquired gemcitabine resistance. Comparative clinical trials are underway to confirm the validity of this provocative observation. Finally, this work is notable considering the rapid translation from preclinical mechanistic studies with an advanced patient–derived animal model to phase I study completion in a 3-year period.

Disclosure of Potential Conflicts of Interest
A. Jimeno has commercial research grants from Onconova Therapeutics, Inc. and Infinity Pharmaceuticals. No potential conflicts of interests were disclosed by other authors.

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Table 4. Pharmacokinetic parameters of rigosertib on days 1 and 11 obtained from patients enrolled to the expansion cohort

<table>
<thead>
<tr>
<th>Day 1</th>
<th>T_{1/2}, h</th>
<th>C_{max}, μg/mL</th>
<th>AUC_{0–24 h}, μg h/mL</th>
<th>V_{ss}, L/m²</th>
<th>CI, L/h/m²</th>
<th>V_{ss}, L/m²</th>
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<tbody>
<tr>
<td>Mean</td>
<td>0.97</td>
<td>214.24</td>
<td>561.28</td>
<td>4.69</td>
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<td>SD</td>
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<td>41.46</td>
<td>181.66</td>
<td>0.96</td>
<td>1.07</td>
<td>0.64</td>
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<td>Day 11</td>
<td>Mean 0.94</td>
<td>204.69</td>
<td>524.55</td>
<td>4.85</td>
<td>3.81</td>
<td>4.47</td>
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<tr>
<td>SD</td>
<td>0.22</td>
<td>37.14</td>
<td>166.68</td>
<td>0.96</td>
<td>1.35</td>
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References


Phase I Study of Rigosertib, an Inhibitor of the Phosphatidylinositol 3-Kinase and Polo-like Kinase 1 Pathways, Combined with Gemcitabine in Patients with Solid Tumors and Pancreatic Cancer

Wen Wee Ma, Wells A. Messersmith, Grace K. Dy, et al.


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