Name of Company: Onconova Therapeutics, Inc. **Name of Finished Product:** rigosertib (ON 01910.Na) **Name of Active Ingredient:** sodium salt of (E)-2,4,6-trimethoxystyryl-3-carboxymethylamino-4-methoxybenzyl sulfone	Location of Full Report in the Submission	(For National Authority Use Only)

Title of Study: A Phase III Multi-center, Randomized, Controlled Study to Compare the Efficacy and Safety of Gemcitabine Alone vs. ON 01910.Na Combined with Gemcitabine in Patients with Previously Untreated Metastatic Pancreatic Cancer (Title Modified per Amendment 3)

Investigators and Study Centers: Multicenter

Name and Address of Sponsor:	**Name and Address of Medical Monitor**
Onconova Therapeutics, Inc. 375 Pheasant Run Newtown, PA 18940	Bernard Brownstein, MD 375 Pheasant Run Newtown, PA 18940

Date of the Report: March 16, 2016

Study Period (years):	**Development Phase:** III
First Patient's Baseline Visit: July 18, 2011 Data cut-off: December 09, 2013	

Objectives:

Primary objective: To compare overall survival in chemotherapy-naive patients with metastatic pancreatic cancer receiving gemcitabine 1000 mg/m^2 weekly combined with rigosertib (ON 01910.Na) at 1800 mg/m^2 via 2-hour continuous intravenous infusions administered twice weekly for 3 weeks of a 4-week cycle vs. gemcitabine alone at 1000 mg/m^2 weekly for 3 weeks of a 4-week cycle.

Secondary objectives: To compare the gemcitabine + rigosertib group to the gemcitabine-only group with respect to:

- Progression-free survival time
- Objective response rates using Response Evaluation Criteria In Solid Tumors (RECIST)
- Safety/tolerability
- Quality of life (QOL).

Additional secondary objectives included:

- Rigosertib population pharmacokinetics (combined treatment group only)
- Full rigosertib and gemcitabine pharmacokinetics in a subset of 10 patients in the combined treatment group only
- Biomarker analysis (to include markers of the PI3K/AKT and PLK1 pathways) performed on archival tissue from all patients with available tissue who gave consent; results were to be correlated with efficacy outcomes.

Methodology:

This was an open-label, randomized, controlled, multi-center Phase III study with an interim analysis for futility. The study was designed to enroll a total of 364 patients to observe 268 deaths, with sample size recalculation after 125 deaths in 150 patients had occurred.

In the first portion of the study, a total of 150 patients with metastatic pancreatic cancer who received no prior chemotherapy for this disease were recruited from 60 to 80 centers and randomized in a 2:1 fashion to 1 of the 2 following treatment regimens:

- Arm A: Gemcitabine 1000 mg/m^2 weekly for 3 weeks of a 4-week cycle plus rigosertib 1800 mg/m^2 via 2-hr CIV infusions administered twice weekly for 3 weeks of a 4-week cycle (gem + rigo: approximately 100 patients)
- Arm B: Gemcitabine only, 1000 mg/m^2 weekly for 3 weeks of a 4-week cycle (gem-only: approximately 50 patients).

Patients were stratified at entry using the Eastern Cooperative Oncology Group (ECOG) performance status (ECOG scores of 0-1 vs. ECOG scores of 2; patients with higher scores were not enrolled).

Patients remained on study until disease progression or death from any cause, whichever came first. Moreover, after treatment discontinuation for any cause, all patients were followed until death.

After 150 patients were enrolled, accrual was to pause and patients were to be followed until 100 deaths occurred (37% of the total 268 deaths planned). At that time, the Data Safety Monitoring Committee (DSMC) was to oversee a formal interim analysis to compare safety and OS between the 2 groups.

Patients in the gemcitabine-only arm (Arm B) were not allowed to cross over to the combined treatment arm (Arm A). In addition, no palliative radiotherapy was allowed during the trial.

The primary analysis compared OS in the rigosertib + gemcitabine arm (Arm A) vs. gemcitabine-only arm (Arm B) once an appropriate number of events had been reached. There were 2 secondary efficacy outcomes: PFS and objective response.

Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03). Grade 3 and 4 hematologic toxicities and > Grade 2 non-hematologic toxicities were monitored.

Number of Patients:

Up to 800 patients could be enrolled per protocol; 203 patients were screened and 160 were enrolled.

Diagnosis/Criteria for Inclusion:

Patients ≥ 18 years of age with a histopathologically or cytologically confirmed metastatic adenocarcinoma of the pancreas; metastatic disease defined as disease which had spread beyond the peri-pancreatic lymph nodes; received no prior chemotherapy for pancreatic cancer, including adjuvant chemotherapy; measurable disease, defined as lesions at least 1 dimension with longest diameter (LD) ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral computed tomography (CT) scan; measurable lymph nodes ≥ 15 mm in the short axis; ECOG Performance Status of ≤ 2; adequate renal function and serum creatinine ≤2.0 mg/dL, with a minimum calculated glomerular filtration rate (GFR) of 40 mL/min (Cockcroft-Gault method); adequate liver function as defined by total bilirubin ≤ 2.0 mg/dL and transaminase levels no higher than 3.0 times the institution's upper limit of normal (ULN). Patients with hepatic metastases had transaminase levels of up to 5.0 times the ULN; serum albumin ≥ 3.0 g/dL; adequate bone marrow (BM) function as defined by a granulocyte count ≥ 1,500/mm^3, a platelet count ≥ 100,000/mm^3, and hemoglobin >9 g/dL; disease-free period of more than 5 years from prior malignancies other than pancreas (except curatively treated basal cell carcinoma, squamous cell carcinoma of the skin, or carcinoma in situ of the cervix and ductal carcinoma in situ [DCIS] breast

disease). If female, negative screening for pregnancy. Women of child-bearing potential and men had to agree to use adequate contraception prior to study entry (hormonal or barrier method of birth control; abstinence) and for the duration of study participation; Signature of informed consent and agreement to adhere to the terms of the protocol.

Test Product, Dose, Batch Number:

Rigosertib sodium (ON 01910.Na) was supplied by Onconova Therapeutics Inc. (Onconova thereafter) as a sterile, concentrated solution in labeled, sealed glass vials, which was stored between 2°C and 8°C. Just prior to dosing, the rigosertib concentrate was diluted with aqueous infusion solution. Reconstituted rigosertib was kept at room temperature and administered on the day of reconstitution via an infusion set with an in-line 1.2 micron filter. Gemcitabine (Gemzar®, Eli Lilly and Company, Indianapolis, Indiana, USA) was obtained commercially.

Patients randomized to Arm A (combination) received gemcitabine 1000 mg/m^2 weekly for 3 weeks of a 4-week cycle plus rigosertib 1800 mg/m^2 via 2-hr CIV infusions administered twice weekly for 3 weeks of a 4-week cycle:

- The starting dose of gemcitabine was 1000 mg/m^2 IV as a 30-min infusion on Day 1, Day 8, and Day 15 every 28 days.
- The starting dose of rigosertib was 1800 mg/m^2 as a 2-hr CIV infusion on Days 1, 4, 8, 11, 15 and 18 of a 28-day cycle.
- A cycle was defined as 4 weeks (28 days) in length.

Patients randomized to Arm B (gemcitabine only) received gemcitabine 1000 mg/m^2 weekly for 3 weeks of a 4-week cycle, with dosing on Day 1, Day 8, and Day 15.

Rigosertib lot numbers: EMK684, ZBL005, ZBM007, ZBM018 and ZBM039

Duration of Treatment:

Treatment was to continue until the disease progression or death.

Evaluation of Efficacy:

The following efficacy outcomes were assessed: overall survival, progression-free survival, and objective tumor response using RECIST v1.1; quality of life as measured by the EORTC QLQ C30 version 3 questionnaire.

Evaluation of Pharmacokinetics:

Blood samples for measurement of rigosertib were taken in Cycle 1 in all patients in Arm A at pre-dose, 1 hour after starting the rigosertib infusion, and just before the end of rigosertib infusion on Day 1 and Day 15 for population pharmacokinetics.

At a limited number of sites, blood samples for measurement of rigosertib and gemcitabine were obtained at Cycle 1 Day 1 only, in a subset of 10 patients in Arm A, at the following time-points: predose, ie, before starting gemcitabine infusion; 15 min after starting gemcitabine infusion; 30 min, immediately before ending gemcitabine infusion; 45 min, approximately 15 min after starting rigosertib infusion; 60 min (= 1 hr), approximately 30 min after rigosertib infusion start; 2 hr 30 min, immediately before ending rigosertib infusion ;2 hr 45 min; 3 hr; 3 hr 30 min; 4 hr 30 min; 6 hr 30 min; 10 hr 30 min.

Blood samples obtained at these time-points were split for gemcitabine and rigosertib measurements.

Evaluation of Safety:

Safety assessments included treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, physical examination findings, and vital signs. In the combination treatment arm (Arm A), ECGs were performed at baseline, at the end of infusion on Cycle 1 Day 1 just before the population PK blood sampling, at the end-of-study visit, and as clinically indicated.

Evaluation of Biomarkers:

Biomarker and Fresh Biopsy Studies: Archival tissue was collected when available and analyzed in order to identify molecular characteristics of pancreas tumors, which may have conferred susceptibility or resistance to gemcitabine alone or in combination with rigosertib. The analysis was performed by Colorado Molecular Correlates Laboratory (CMOCO), a state-of-the-art facility located within the University of Colorado's Department of Pathology.

Depending on the amount of available tissue (and deoxyribonucleic acid [DNA]), the following assays were performed on archival tissue in order of priority:

- SNaPshot (detects >100 mutations), potentially with confirmatory polymerase chain reaction (PCR) studies
- DxS for PI3K and phosphatase and tensin homolog (PTEN) sequencing
- Immunohistochemistry for members of the PI3K and PLK pathways
- Other molecular assays depending on ongoing preclinical experiments.

After initial mutation analysis on archival tissue samples, fresh tumor biopsies may have been obtained in a subpopulation of up to 25 patients in order to permit molecular analysis of tumor tissue obtained just prior to treatment, as well as tumor tissue obtained under highly controlled circumstances permitting the analysis of messenger ribonucleic acid (mRNA).

Tumor biopsies were performed as per local institutional guidelines.

Statistical Methods:

Analyses were performed on the 3 populations: *intent-to-treat* (ITT; all randomized patients), *per-protocol* (all patients who received at least one dose of either study drug and completed the study without major protocol violations), *safety population* (all patients who received at least one dose of either gemcitabine or rigosertib). The analysis of the primary efficacy outcome and the secondary efficacy outcomes were performed on the ITT population according to the randomized treatment regimen. Sensitivity analyses of the primary and secondary outcomes were performed on the PP population according to the randomized treatment regimen. The safety analyses were performed on the safety population according to the actual treatment regimen received.

The primary analysis was the primary efficacy outcome of OS assessed in the ITT population comparing the rigosertib + gemcitabine group to gemcitabine alone. Kaplan-Meier survival curves were compared using a stratified log-rank test (stratified by ECOG performance status: 0-1 vs. 2). Hazard ratios and 95% confidence intervals were estimated using stratified Cox proportional hazards models.

Efficacy analyses using response data included all data from investigator assessments. If the study proceeded to the second stage, sensitivity analyses were to be based on independent radiology assessments using the following:

- Independent assessment data, from independent radiology assessment only,
- Combined assessment data, from independent radiology assessments when available, and investigator assessments for participants without an independent radiology assessment.

Summaries presented the concordance between the investigator and independent radiology assessments.

The primary efficacy outcome was overall survival. The duration of survival was defined as the time from randomization to death from any cause. The secondary outcomes were to compare the gemcitabine + rigosertib group to the gemcitabine-only group with respect to: progression-free survival time; objective response rates using Response Evaluation Criteria in Solid Tumors (RECIST); safety and tolerability; and Quality of life (QOL) (EORTC QLQ-C30 version 3 questionnaire).

Site investigators performed tumor assessment according to RECIST criteria, resulting in an overall response assessment of complete remission (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Patients who had discontinued treatment and not progressed were still followed for progressive disease. Kaplan-Meier curves for PFS were compared using a stratified log-rank test (stratified by ECOG status: 0-1 vs. 2). Hazard ratios and nominal 95% confidence intervals were estimated using stratified Cox proportional hazard models.

Objective response: The proportion of patients achieving objective response, defined as a complete or partial response as defined by RECIST criteria, was summarized. The odds ratio estimate and 95% confidence interval were computed using logistic regression stratified for ECOG status.

Exploratory analyses included biomarker analyses (to include markers of the PI3K/AKT and PLK1 pathways) performed on archival tissue from all patients; results were correlated with efficacy outcomes.

All adverse event (AE) presentations summarized treatment-emergent adverse events (TEAEs) defined as adverse events with onset on or after randomization or onset prior to randomization but with worsened severity post-randomization. Presentations included all AEs through 30 days after a patient discontinued from the study. TEAEs were tabulated using the Medical Dictionary for Regulatory Activities (MedDRA, version 9.0) by system organ class (SOC), preferred term (PT), severity (using NCI CTCAE grading), and relationship to treatment. Similar presentations were provided for SAEs and AEs leading to withdrawal from the study.

Change from baseline was summarized for laboratory results and vital signs.

Demographics and Baseline Characteristics:

A total of 160 patients were enrolled (106 gem + rigo, 54 gem-only). The mean age in the ITT population was 62.7 years, with 63% of patients being male, 71% White, and 95% with an ECOG performance status of 0 or 1. Patients had a mean (SD) of 7.1 (12.6) weeks from pancreatic cancer diagnosis to randomization. Most patients (85%) had liver metastases.

Efficacy Results:

An interim analysis was performed after 100 deaths had occurred, at which time the DSMC recommended stopping the study for futility according to the stopping rule.

Overall survival in the ITT population (N=160) is shown in the table below.

	Gem + rigo N=106	Gem only N=54	Hazard ratio (95% CI)	Z statistic
Overall survival			1.24 (0.85, 1.81)	1.12
Number of deaths	92 (87%)	40 (74%)		
Median (months)	6.1	6.4		
95% CI	(4.4, 7.0)	(4.2, 8.7)		

Column header counts are the number of patients randomized. Duration of survival is defined as the time from randomization to death from any cause. The hazard ratio (gem + rigo vs. gem-only) and 95% CI are estimated using a Cox proportional hazard model stratified by ECOG performance (0-1 vs. 2) status at baseline.
Data cutoff: 09DEC2013 / data received: 10OCT2014

Median progression-free survival was 3.4 months in both arms (CI: 2.5, 3.8 for the gem + rigo group and CI: 2.5, 4.8 in the gem-only group), with a HR of 0.96 (CI: 068, 1.36).

There were no complete responses in either group. Both groups had a disease control rate of 69% among evaluable patients: for gem + rigo, 15 patients (19%) had PR and 40 patients (50%) had SD; for gem-only group, 5 patients (13%) had PR and 22 patients (56%) had SD.

Safety Results:

In the overall safety population, patients in the gem + rigo group (N=106) received a mean of 3.6 weeks of treatment and patients in the gem-only group (N=47) received a mean of 4.0 weeks of treatment. The mean cumulative dose of rigosertib administered was 58.8 g. Treatment-emergent adverse events (TEAEs) for the safety population (N=153) are summarized below.

Treatment-Emergent Adverse Events	Gem + rigo N=106 n (%)	Gem only N=47 n (%)	Total N=153 n (%)
Number (%) of Patients			
With any TEAE	106 (100)	45 (96)	151 (99)
With possible, probable, or definite drug-related TEAEs	91 (86)	31 (66)	122 (80)
With severity grade 3, 4 or 5 TEAEs	78 (74)	26 (55)	104 (68)
With grade 3, 4 or 5 possible, probable, or definite drug-related TEAEs	54 (51)	12 (26)	66 (43)
With any serious TEAEs	49 (46)	15 (32)	64 (42)
With any serious, drug-related TEAEs	17 (16)	0	17 (11)
Discontinued drug due to TEAEs	35 (33)	9 (19)	44 (29)
Died due to TEAEs	12 (11)	4 (7)	16 (10)

The most frequently reported AEs by PT in the gem + rigo group were anemia (42%), fatigue (39%) nausea (35%), abdominal pain, decreased appetite and hyponatremia (30%), constipation (28%), vomiting and diarrhea (27% each) and odema peripheral (25%). In the gem-only group, the most frequently reported AEs by PT were fatigue (40%), nausea (36%), anemia (34%), abdominal pain (30%), vomiting (28%), constipation (26%) and odema peripheral (23%).

The most frequently reported drug-related AEs were anemia (28%), fatigue (27%), and nausea and hyponatremia (25% each) for gem + rigo and anemia and nausea (28% each), fatigue (26%), and vomiting (21%) for gem-only.

The most frequently reported AEs ≥ Grade 3 were hyponatremia (19%), anemia (13%), neutropenia (10%), and fatigue, abdominal pain, and neutrophil count decreased (9% each) in the gem + rigo group and hyponatremia (11%) and neutropenia (9%) for the gem-only group.

The most frequently reported drug-related AEs ≥ Grade 3 for gem + rigo were hyponatremia (17%), neutrophil count decreased (9%), and anaemia and neutropenia (8% each) in the gem + rigo group and neutropenia (6%) in the gem-only group.

Disease progression was the most common cause of death (63% gem + rigo, 50% gem-only) followed by unknown cause (12% gem + rigo, 17% gem-only) and AE/other (11% gem + rigo, 7% gem-only). Four patients (all in the gem + rigo group) had AEs leading to death that were considered possibly related to study drug: 2 death (not otherwise specified; Pts 21004, 30104), 1 renal failure (Pt 20705), 1 sepsis (Pt 21602).

The most frequently reported SAEs were pancreatic carcinoma (8%) and abdominal pain (4%) in the gem + rigo group and pancreatic carcinoma and pulmonary embolism (6% each) in the gem-only group. Possibly-drug-related SAEs were reported in 17 (16%) patients in the gem + rigo group: pancreatitis acute, bladder spasm, supraventricular tachycardia, haematuria, renal failure, death and peptic ulcer haemorrhage, sepsis, anaemia, urinary tract infection and jaundice cholestatic, pyrexia, cellulitis and pyrexia, dysuria, cholecystitis, death, hyponatraemia (2 pts), anaemia and diarrhoea.

The most common AEs leading to discontinuation were fatigue (5%) and pancreatic carcinoma (4%) in the gem + rigo group and neutropenia (4%) in the gem-only group. These events were considered to be drug-related in 15 (14%) patients in the gem + rigo group and 3 (6%) patients in the gem-only group.

Conclusions:

There were no complete responses in either group. Both groups had a disease control rate of 69% among evaluable patients: for gem + rigo, 15 patients (19%) had PR and 40 patients (50%) had SD; for gem-only group, 5 patients (13%) had PR and 22 patients (56%) had SD.

Overall, the safety profile was better in the gem-only group than in the gem + rigo group.

Publication Reference:

O'Neil BH, Scott AJ, Ma WW, et al. A phase II/III randomized study to compare the efficacy and safety of rigosertib plus gemcitabine versus gemcitabine alone in patients with previously untreated metastatic pancreatic cancer. Ann Oncol. 2015 Sep;26(9):1923-9.
