SYNOPSIS

Name of Sponsor/Company:		*(For National Authority Use only)*
Baxalta US Inc. One Baxter Way Westlake Village, CA 91362 USA	and	**Baxalta Innovations GmbH** Industriestrasse 67 A-1221 Vienna, AUSTRIA
Name of Investigational Product (IP)	Onivyde®	
Name(s) of Active Ingredient(s)	BAX2398 (Irinotecan hydrochloride encapsulated in liposomal particles)	
CLINICAL CONDITION(S)/INDICATION(S) Metastatic pancreatic cancer which progressed or recurred after prior gemcitabine-based therapy		
PROTOCOL IDENTIFIER	331501	
PROTOCOL TITLE	Phase II Randomized Study of BAX2398 in Combination with 5-Fluorouracil and Calcium Levofolinate in Japanese Patients with Metastatic Pancreatic Cancer, Which Progressed or Recurred After Prior Gemcitabine-Based Therapy	
Short Title	Phase II of BAX2398/5-FU/Calcium Levofolinate in Pancreatic Cancer	
STUDY PHASE	Phase II	

INVESTIGATORS AND STUDY SITE(S):
Sixteen study sites in Japan participated in this study:

01 [redacted]
02 [redacted]
03 [redacted]
04 [redacted]
05 [redacted]
06 [redacted]
07 [redacted]
08 [redacted]
09 [redacted]
10 [redacted]
11 [redacted]
12 [redacted]
13 [redacted]

14	[redacted]
15	[redacted]
16	[redacted]

PUBLICATION (REFERENCE): None

STUDY PERIOD

Initiation	2016 MAR 30
Study Completion	2018 JAN 31 (estimated)
Duration	approximately 22 months

STUDY OBJECTIVES AND PURPOSE

Study Purpose

Part 1: The aim of Part 1 was to characterize the pharmacokinetics (PK) of BAX2398 in combination with 5-Fluorouracil (5-FU)/calcium levofolinate (LV) in Japanese patients treated with the same dose regimen as in the reference trial NAPOLI-1 and to assess the safety and to confirm the tolerability of the combination in Japanese patients.

Part 2: The aim of Part 2 was to compare the efficacy of BAX2398 in combination with 5-FU/LV with 5-FU/LV after prior gemcitabine-based therapy, and to further evaluate the safety and PK characteristics of BAX2398 in combination with 5-FU/LV.

Primary Objectives

Part 1: To assess the safety and tolerability, and to characterize the PK of BAX2398 in combination with 5-FU/LV in Japanese patients.

Part 2: To compare the efficacy of BAX2398 in combination with 5-FU/LV versus 5-FU/LV alone as assessed by Progression Free Survival (PFS) using Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).

Secondary Objective(s)

Part 1: To evaluate PFS, and Overall Survival (OS).

Part 2: To further characterize the PK profile of BAX2398 in combination with 5-FU/LV and to compare the following efficacy and safety parameters after treatment with BAX2398 in combination 5-FU/LV versus treatment with 5-FU/LV:

- OS
- Time to Treatment Failure (TTF)
- Tumor-marker response using CA 19-9
- Objective Response Rate (ORR) per RECIST 1.1
- Disease Control Rate (DCR) per RECIST 1.1
- Safety and tolerability of BAX2398
- Patient-reported outcomes (PROs) using the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Core Questionnaire (EORTC-QLQC30) and a patient diary for clinical benefit evaluation

STUDY DESIGN	
Study Type/ Classification/ Discipline	Efficacy, Safety, and Pharmacokinetic
Control Type	Concurrent (Active)
Study Indication Type	Treatment
Intervention model	Parallel (Two Arms)
Blinding/Masking	Open-label
Study Design	This study was a Phase II, prospective, open-label, randomized, comparative, multicenter study in Japanese patients with metastatic pancreatic cancer which progressed or recurred after prior gemcitabine-based therapy. The study was conducted in 2 parts. In Part 1, the safety of BAX2398 in combination with 5-FU/LV was assessed to confirm the tolerability of the same dosing regimen as in pivotal NAPOLI-1 trial, and the PK of BAX2398 in combination with 5-FU/LV was characterized in Japanese patients. After the Independent Data Monitoring Committee (IDMC) had reviewed all safety data, Part 2 was opened to further assess the safety of the combination, the PK of BAX2398, and to compare the efficacy of BAX2398 in combination with 5-FU/LV versus 5-FU/LV. Patients in Part 1 continued in the study until progressive disease (radiologic or symptomatic deterioration) or the occurrence of unacceptable toxicity. During the 28-day screening period, all patients were assessed for eligibility and characterized for the presence of UGT1A1*28 and UGT1A1*6 alleles to determine the starting dose. *In Part 1*, six evaluable patients were enrolled in a staggered fashion with the next patient to be commenced at least 72 hours after the previous patient's first dose. When the first 2-week cycle of treatment with BAX2398 in combination with 5-FU/LV was completed in all 6 evaluable patients, the IDMC reviewed all safety data (adverse events [AEs], results of physical examination, electrocardiogram [ECGs], laboratory tests, and vital signs) and made the recommendation to move into Part 2. *In Part 2*, a total of 74 patients were planned to be enrolled and randomized with a 1:1 allocation between the 2 arms after stratification for the Karnofsky Performance Status (KPS; 70 and 80 *vs* ≥90) and baseline albumin levels (≥4.0 g/dL *vs* <4.0 g/dL). A patient who screened homozygous for the UGT1A1*28 or UGT1A1*6 alleles, or had both alleles received an adjusted reduced starting dose. Patients randomized in Arm A received BAX2398 + 5-FU/LV and patients enrolled in Arm B received 5-FU/LV alone. Patients were treated until progressive disease (radiologic or symptomatic deterioration) or the occurrence of unacceptable toxicity.

	Tumor responses were measured and recorded every 6 weeks using the RECIST guidelines (version 1.1). Tumor marker response was evaluated by the change in CA19-9 serum levels as measured at baseline and every 6 weeks after enrollment, even if the dose was delayed or interrupted. A quality-of-life (QoL) assessment and review of the patient diary for clinical benefit was performed monthly. Safety data were collected on a continuous basis from the consent of the patient through 30 days after the last dose or before initiation of a new antineoplastic treatment. Assessments of PK included blood sample collection for determination of plasma exposures to BAX2398 at specified intervals in all patients in Part 1 and only in patients receiving BAX2398 in Part 2. Plasma samples were collected at 14 timepoints during the first cycle in Part 1, and at 8 timepoints during the first cycle of Part 2. For the assessment of potential effect of BAX2398 on QTcF interval, triplicate digital 12-lead ECG measurements were performed within an hour prior to the first dose in all patients in both Part 1 and Part 2, and at specified times post dose:

CRITERIA FOR EVALUATION

Primary Outcome Measures

The primary efficacy outcome measure in the study was PFS in Part 2, defined as the time from randomization to the first documented disease progression based on the independent central review board's assessment using RECIST 1.1 or death due to any cause, whichever occurred first. Kaplan-Meier methods were used to estimate median PFS for each treatment arm. Results from the investigator's assessment also were evaluated. In case of a discrepancy between the assessment of the independent central review board and that of the investigator, the independent board's assessment took precedence.

Secondary Outcome Measures

Efficacy

- PFS in Part 1, defined as the time from the date of first dose of study drug to the first documented disease progression based on the independent central review board's assessment using RECIST 1.1 or to death due to any cause, whichever occurred first.
- OS defined as the time from the date of first dose of study drug (Part 1) or from randomization (Part 2) to date of death due to any cause or the date of last known alive.
- TTF (Part 2), defined as the time from randomization to disease progression according to RECIST 1.1, death due to any cause, discontinuation of treatment due to toxicity, or for symptomatic deterioration, or start of another anticancer therapy.
- ORR (Part 2), defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR).
- DCR (Part 2), defined as the proportion of patients with a best overall response of CR, PR, or stable disease lasting ≥24 weeks.

- Tumor marker response (Part 2), evaluated by the change in CA19-9 serum levels at baseline and every 6 weeks after enrollment, even if the dose was delayed or interrupted.
- PROs using EORTC-QLQ-C30 general questionnaire and clinical benefit using patient's diary for two primary parameters (pain intensity and analgesic consumption) clinic visit data for 1 primary and 1 secondary parameters (KPS and weight, respectively).

Safety

- SAEs
- Incidence and intensity of nonserious AEs (coded to preferred term and system organ class using MedDRA, v18.1 and graded according to the NCI CTCAE v4.03)
- Physical examination
- Vital signs
- Laboratory tests classified for severity using NCI CTCAE v4.03
- Triplicate 12-lead ECGs were recorded to evaluate the heart rate, atrial ventricular conduction, QR and QTcF, and possible arrhythmias.

Pharmacokinetics

In Part 1, PK parameters for total irinotecan (encapsulated + unencapsulated), the primary metabolite of irinotecan, SN-38 (encapsulated + unencapsulated), and SN-38-glucuronide (SN‑38G) were to include maximum plasma concentration (C_{max}), time of maximum concentration (t_{max}), terminal half-life ($t_{1/2}$), area under the curve (AUC), systemic clearance (CL), volume of distribution (V), and volume of distribution at steady-state (V_{ss}), as applicable.

In Part 2, PK parameters for total irinotecan (encapsulated + unencapsulated), total SN-38 (encapsulated + unencapsulated), and SN-38-glucuronide (SN-38G) were to be calculated using population PK modeling (combined analysis of Part 1 and Part 2 data). Parameters to be calculated included $t_{1/2}$, AUC, CL, V and V_{ss}.

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION

Investigational Product(s)	BAX2398 was to be administered at a dose of 80 mg/m^2 by intravenous (IV) infusion over 90 minutes (±10) every 2 weeks. The first cycle Day 1 was a fixed day; subsequent doses were administered on the first day (±3 days) of each cycle. LV was to be administered at a dose of 200 mg/m^2 as an IV infusion over 2 hours, every 2 weeks before 5-FU. 5-FU was to be administered at a dose of 2400 mg/m^2 as an IV infusion over 46 (±3) hours continuous infusion, every 2 weeks.
Control/ Comparator	LV was to be administered at a dose of 200 mg/m^2 as an IV infusion over 2 hours, every 2 weeks before 5-FU. 5-FU was to be administered at a dose of 2400 mg/m^2 as an IV infusion over 46 (±3) hours continuous infusion, every 2 weeks.
Duration of treatment:	Treatment duration of individual patients was anticipated to be approximately 6 to 12 months.

SUBJECT SELECTION	
Planned	Targeted Accrual: Approximately 80 patients
Analyzed	The Safety Analysis Set included a total of 84 patients: 6 patients who received BAX2398 +5-FU/LV in Part 1, 40 patients in Part 2, Arm A (who received BAX2398 +5-FU/LV), and 38 patients in Part 2, Arm B (who received 5-FU/LV). In both parts of the study combined, the Safety Analysis Set includes 46 patients treated with BAX2398 +5-FU/LV and 38 patients treated with 5-FU/LV. The Full Analysis Set (FAS) population included the 78 patients who received at least 1 dose of study treatment in Part 2 of this study. The Intent-to-Treat (ITT) Analysis Set included the 79 patients randomized in Part 2 (including 1 patient randomized but not treated). The Per-Protocol Population (PP) Analysis Set included the 78 patients randomized in Part 2 who received at least 1 dose of the study treatment and had no major protocol deviations. The Evaluable Patient Analysis Set consisted of the 78 patients randomized in Part 2 who received at least 1 dose of the study treatment. The PK Analysis Set included the 46 patients treated with BAX2398 in both parts of the study who had valid data for at least 1 postdose PK assessment, and who did not have major or significant number of other protocol deviations or other events (e.g., dose reduction, incomplete dose administered, etc.) that affected PK. The Tumor Marker Response Evaluable Population (TMREP) included the 56 patients in Part 2 who had elevated CA-19-9 levels (>30 µ/mL) at baseline. The Clinical Benefit Response Evaluable Population (CBREP) included the 67 patients in Part 2 who met the protocol-defined baseline criteria for pain intensity, morphine consumption, and Karnofsky Performance Status. The Patient-Reported Outcomes Evaluable Population (PROEP) included the 73 patients from the ITT population that provided baseline and at least one subsequent assessment on the EORTC QLQ-C30 instrument. Finally, the All Screened Population included all 101 patients who signed informed consent.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Patients who met all of the following criteria were eligible for this study:

1. Patient was 20 years of age or older at the time of screening
2. Histologically or cytologically confirmed adenocarcinoma of exocrine pancreas
3. Documented metastatic disease according to TNM Classification of Malignant Tumours (TNM) staging of American Joint Committee on Cancer (AJCC)
4. Metastatic disease with at least one measurable lesion as defined by RECIST 1.1 guidelines
5. Documented disease progression after prior gemcitabine or any gemcitabine containing therapy but excluding irinotecan, for locally advanced or metastatic setting. Prior chemotherapy must have been stopped for at least 21 days before the first dose. Examples of prior therapies included, but were not limited to:
   - Single agent gemcitabine
   - Any gemcitabine-based regimen, with or without maintenance gemcitabine
   - Single agent gemcitabine to which a platinum agent, a fluoropyrimidine, or erlotinib was subsequently added
   - Gemcitabine administered in the adjuvant setting if disease recurrence occurred within 6 months of completing the adjuvant therapy
6. KPS ≥70
7. Adequate bone marrow reserves as evidenced by meeting all of the following requirements:
   - Absolute neutrophil count (ANC) >1,500 cells/µl without the use of hematopoietic growth factors; and
   - Platelet count >100,000 cells/µl; and
   - Hemoglobin >9 g/dL
8. Adequate hepatic function as evidenced by meeting all of the following requirements:
   - Serum total bilirubin within normal range for the institution (biliary drainage is allowed for biliary obstruction)
   - Serum albumin levels ≥3.0 g/dL
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN) without liver metastases (≤5 × ULN was acceptable if liver metastases were present)
9. Adequate renal function as evidenced by a serum creatinine ≤1.5 × ULN
10. Normal ECG including QTcF <440 ms within 7 days prior to first dose of study drug
11. Recovered from the effects of any prior surgery, radiotherapy or other anti neoplastic therapy with no residual AEs of Grade ≥2
12. Able to understand and sign an informed consent (or had a legal representative who was able to do so)
13. If female of childbearing potential (excluding women who had undergone surgical sterilization or menopause; menopause is defined as the status where no menstrual periods continue for 1 year or more without any other medical reasons), patient presented with a negative pregnancy test (either urine or serum, per investigator discretion), and agreed to employ adequate birth control measures during the study dosing period and for 3 months following the last dose of study drug
14. Patient was willing and able to comply with the requirements of the protocol

Patients who met any of the following criteria were not eligible for this study:

1. Active and uncontrolled CNS metastases (indicated by clinical symptoms, cerebral edema, steroid and anticonvulsant requirement, or progressive disease); for controlled CNS metastases, patients were to have been off steroids for at least 28 days prior to starting study therapy
2. History of any second malignancy in the previous 5 years; patients with prior history of in-situ cancer or basal or squamous cell skin cancers were eligible. Patients with other malignancies were eligible if they had been continuously disease free for at least 5 years.
3. Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion
4. Could not stop medications that are potent human cytochrome P450 3A4 isoenzyme (CYP3A4) inducers within 2 weeks and inhibitors within 1 week before start of treatment
5. Significant cardiac conduction abnormalities, including a history of long QTcF syndrome and/or pacemaker
6. New York Heart Association (NYHA) Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure
7. Active infection, including active hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV), or an unexplained fever >38.5°C during screening visits or on the first scheduled day of dosing (at the discretion of the investigator, patients with tumor fever could be enrolled), which in the investigator's opinion might have compromised the patient's participation in the study or affected the study outcome
8. Known hypersensitivity to any of the components of BAX2398, other liposomal products, fluoropyrimidines, or LV
9. Any other medical or social condition deemed by the investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results
10. Patient had been exposed to an investigational product (IP) within 30 days prior to the first dose of the study drug or was scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
11. Patient was a family member or employee of the investigator.
12. Patient was pregnant or lactating at the time of enrollment. Lactating mothers could resume breast feeding 30 days following the last dose of the study treatment

Sample Size Calculation

For the purpose of the sample size calculation, the median PFS in the BAX2398 plus 5-FU/LV treatment arm and the 5-FU/LV treatment arm were estimated as 3.0 months and 1.5 months, respectively. Assuming a drop-out rate of 10%, approximately 74 patients were to be randomized in a 1:1 allocation to the 2 treatment arms in 12 months and followed up for up to 3 months which would correspond to the time when all randomized patients completed the second scheduled tumor assessment. A total of 53 events (disease progression or death) would allow the study to have an approximate 88% power to detect a 1.5 month improvement in PFS based on a 0.5 hazard ratio using a 2-sided log-rank test at a significance level of alpha=0.2.

Taking into account the 6 patients enrolled in Part 1, the total sample size was plannedto be 80 patients.

Planned Statistical Analysis

PFS was to be estimated using the KM method for each treatment arm. The primary analysis was to compare the PFS of patients randomized to the 2 treatment arms using log-rank test. The primary analysis population was the ITT population which comprised all the randomized patients. This analysis only included patients from Part 2. A sensitivity analysis of PFS was performed using log-rank test on the PP population which included patients in the ITT population who received at least 1 dose of the study treatment and had no major protocol deviations.

The primary analysis of the secondary efficacy outcome measures was based on the primary efficacy analysis set. OS and TTF were estimated using the KM method and comparisons between the treatment arms were performed using log-rank test. For each of the outcome measures, tumor marker response of CA 19-9, and PROs (EORTC QLQ-C30 and patient diary), the analysis was based on a subset of the primary efficacy analysis set which is evaluable for the outcome measure, as described in the protocol. Fisher's exact test was used to compare ORR, DCR, and tumor marker response of CA 19-9.

A sensitivity analysis of all the efficacy outcome measures was based on the FAS population, which includes all the patients receiving at least 1 dose of the study treatment in Part 2.

The PK population comprised all treated patients with at least 1 PK assessment on treatment. PK data were analyzed using noncompartmental methods (data from Part 1 only, and any patients with full PK sampling in Part 2) and population PK modeling (all data from Parts 1 and 2 combined). PK concentrations and parameters were summarized using descriptive statistics.

All safety analyses of AEs and other safety data were based on the Safety population including all patients receiving at least 1 dose of the study treatment. Physical examination, including vital signs, and triplicate 12-lead ECG recorded at screening and before and after administration of study treatment are presented. Each ECG parameter was summarized by descriptive statistics per timepoint, and changes from baseline were calculated. A categorical analysis was performed for QTcF data.

SUMMARY – CONCLUSIONS

Efficacy Results:

Primary Efficacy Outcome:

Median PFS was similar between BAX2398+5-FU/LV and 5-FU/LV as evaluated by independent assessment at 1.7 months and 1.6 months (p= 0.376; HR=0.79), respectively. It should be noted that tumor assessments are scheduled at discrete times which increases the likelihood that estimates are numerically similar. Median PFS as evaluated by Investigator assessment was statistically significant favoring BAX2398+5-FU/LV versus 5-FU/LV alone at 2.7 months and 1.5 months, respectively (p=0.039; HR=0.60).

Secondary Efficacy Outcome(s):

Secondary Endpoints in Part 1 (BAX2398+5-FU/LV):

The best overall responses observed in Part 1 of the study were 1 CR (16.7%), 2 PR (33.3%) and 2 stable disease (33.3%) as evaluated by the independent assessment. The best overall response observed, as evaluated by the investigator assessment, were 2 PR (33.3%) and 3 stable disease (50%).

The majority of patients (4 of 6 patients, 66.6%) discontinued treatment due to disease progression.

Secondary Endpoints in Part 2 (BAX2398+5-FU/LV vs. 5-FU/LV):

- ORR: The BAX2398+5-FU/LV treatment arm achieved an ORR by independent assessment of 17.5% (95% CI: 5.72, 29.28) compared to 0% in the 5-FU/LV control arm (p=0.012). In the BAX2398+5-FU/LV treatment arm, 2 (5.0%) of 40 patients achieved CR and 5 (12.5%) of 40 patients achieved PR; no patients in the 5-FU/LV control arm achieved any CR or PR. In addition, 14 (35.0%) of 40 patients in the BAX2398+5-FU/LV treatment arm achieved stable disease, versus 10 (25.6%) of 39 patients in the 5-FU/LV control arm. While no CR was observed by investigator assessment, the BAX2398+5-FU/LV treatment arm achieved an ORR of 20.0% (95% CI: 7.60, 32.40) compared to 2.6% (95% CI: 0.00, 7.72) in the 5-FU/LV control arm (p=0.029) by investigator assessment in the ITT analysis set.
- DCR: A total of 8 (20.0%) of 40 patients in the BAX2398+5-FU/LV treatment arm achieved disease control, versus 2 (5.1%) of 39 patients in the 5-FU/LV control arm (p=0.087) based on both independent and investigator assessments.
- OS: Median OS for BAX2398+5-FU/LV treatment arm was 6.3 months (95% CI: 5.22, -), and the median was not reached in the 5-FU/LV control arm at the primary analysis (hazard ratio: 1.67 [95% CI: 0.884, 3.158]). The OS data were considered insufficiently mature at the time of the primary analyses. The number of patients receiving post anticancer therapies was observed to be higher in the 5-FU/LV control arm (28 patients;71.8%) compared to the BAX2398+5-FU/LV treatment arm (22 patients; 55.0%); this difference may have impacted the OS for both arms in the study. The OS data were based on the data cut-off for the primary analysis and will continue to be collected for the final survival analysis.
- TTF: Median TTF in both the ITT and PP analysis sets was numerically greater (1.7 months) in the BAX2398+5-FU/LV treatment arm versus the 5-FU/LV control arm (1.5 months). The primary unstratified log-rank analysis of TTF was not statistically significant (p=0.134), but with a corresponding hazard ratio of 0.70 favoring the BAX2398+5-FU/LV treatment.
- Tumor Marker Response (CA-19-9): In the BAX2398+5-FU/LV treatment arm, 5 of 28 (17.9%) patients had a ≥50% decrease from baseline of CA-19-9 versus 1 of 28 (3.6%) patients in the 5-FU/LV control arm.
- CBR: The BAX2398+5-FU/LV treatment arm showed a CBR rate of 17.6% (6 of 34 patients in the CBREP) compared to 12.1% (4 of 33 patients in the CBREP) in the 5-FU/LV control arm (p=0.492).
- Patient-Reported Outcomes:
    - HRQoL measured by the EORTC-QLQ-C30 was maintained in patients treated with either BAX2398+5FU/LV or 5-FU/LV alone. There were no notable differences between treatment groups in change from baseline for all functional and symptom scales of the EORTC-QLQ-C30.
    - Overall, the impact on KPS of BAX2398+5-FU/LV was negligible and not notably different from 5-FU/LV treatment.

Safety Results:

All (100%) patients treated with BAX2398+5-FU/LV had treatment-emergent adverse events (TEAEs), as did 86.8% of patients treated with 5-FU/LV. Grade 3 or 4 TEAEs were more frequent in patients treated with BAX2398+5-FU/LV than in patients treated with 5-FU/LV (78.3% versus 36.8%, respectively).

As expected, SAEs were more common in patients treated with BAX2398+5-FU/LV (47.8%) than in patients treated with 5-FU/LV (23.7%).

The 5 most common TEAEs by preferred term (PT) were nausea, neutrophil count decreased, decreased appetite, white blood cell count decreased, and diarrhea, all of which occurred more frequently in patients treated with BAX2398+5-FU/LV. The 5 most common treatment-related TEAEs by PT were nausea, neutrophil count decreased, decreased appetite, white blood cell count decreased, and diarrhea, all of which occurred more frequently in patients treated with BAX2398+5-FU/LV (as is expected for this class of drug).

Forty-two deaths were reported during the study. The majority of deaths occurred >30 days after the last dose of study medication. The main cause of death was pancreatic cancer. Six patients experienced a TEAE with a fatal outcome, 5 of which were due to pancreatic carcinoma. There were no treatment related deaths in the study.

The incidence of TEAEs leading to dose delay, dose reduction, and treatment discontinuation was higher in patients treated with BAX2398+5-FU/LV, as was expected for this line of treatment. The number of patients discontinuing treatment due to gastrointestinal events was low (1 out of 46 patients), thus the protocol-defined dose modification and supportive care instructions are appropriate. Dose delay, dose reduction, and colony stimulating factors were used to manage myelosuppression. Treatment discontinuation due to myelosuppression was seen in 4 of 46 patients receiving BAX2398+5FU/LV treatment.

Three patients homozygous for UGT1A1*28, UGT1A1*6 or heterozygous for UGT1A1*28 and UGT1A1*6 who were treated with BAX2398+5-FU/LV experienced a higher incidence of neutrophil count decrease, WBC count decrease, nausea and diarrhea (3 of 3 for all events) during the course of study as compared to patients treated with5-FU/LV.

Changes in laboratory evaluations, vital signs, and ECGs were as expected for this population and treatment regimen.

Conclusion:

The BAX2398+5-FU/LV treatment regimen in Japanese patients is safe as assessed in this Study 331501 and evaluated by the IDMC. No new safety signal was identified in Japanese patients and the observed safety profile in this study is consistent with the global NAPOLI-1 study. The PK parameters of Part 1 patients are similar to those observed in the global NAPOLI-1 study. The efficacy measures favor the BAX2398+5-FU/LV treatment regimen.

In conclusion, the totality of safety, PK, and efficacy data in Study 331501 provides support for the clinical benefit of BAX2398+5-FU/LV regimen in metastatic pancreatic cancer patients who have progressed after prior gemcitabine-based therapy.

Date of Report: 2017 DEC 15