Name of Sponsor/Company: Astellas Pharma Global Development, Inc (APGD) on Behalf of OSI Pharmaceuticals, LLC		
Name of Finished Product: Tarceva		
Name of Active Ingredient: Erlotinib		

SYNOPSIS

Title of Study: A Phase 1b Study of Erlotinib in Combination with Gemcitabine and Nab-Paclitaxel in Patients with Previously Untreated Advanced Pancreatic Cancer (ISN OSI-774-108)

Investigators/Coordinating Investigator: [redacted]

Study Center(s): 5 centers in the United States

Publication Based on the Study: None.

Study Period: Approximately 2 years

Study Initiation Date (Date of First Enrollment): 03-Feb-2010

Study Completion Date (Date of Last Evaluation): 25-Jan-2012

Phase of Development: Phase 1b

Objectives: The primary objective of this study was to define the maximum tolerated dose (MTD) for the combination of gemcitabine, nab-paclitaxel, and erlotinib. The secondary objectives of this study were to 1) assess the safety of the combination of gemcitabine, nab-paclitaxel, and erlotinib; 2) evaluate limited erlotinib pharmacokinetic profiling in combination with gemcitabine and nab-paclitaxel; and 3) perform a preliminary evaluation of efficacy of the 3-drug combination (objective response rate, progression-free survival, and overall survival).

Methodology: This was a multicenter, open-label, phase 1b study of erlotinib in combination with gemcitabine and nab-paclitaxel on an outpatient basis. Treatment was in 28-day cycles as follows:

- Erlotinib: once daily oral; days 1 through 28 continuous dosing
- Gemcitabine (following nab-paclitaxel): iv over 30 minutes; days 1, 8 and 15 every 28 days
- Nab-paclitaxel: iv over 30 minutes; days 1, 8 and 15 every 28 days

No more than 20 dose-limiting toxicity (DLT)-evaluable patients were to be enrolled into this protocol. All patients were considered evaluable for DLT unless they could not complete cycle 1 because of withdrawal of consent, adverse event (AE) unrelated to study treatment (per Amendment 1) or disease progression. Patients who were not DLT-evaluable were replaced. Intrapatient dose escalation was not allowed.

Potential dose levels were as follows:

Dose Level	Gemcitabine (mg/m²)	Nab-paclitaxel (mg/m²)	Erlotinib (mg)
1†	1,000	125	100
2	1,000	125	150
−1‡	1,000	100	100
−2a‡	1,000	100	75
−2b‡	1,000	75	100
−3	1,000	75	75

Footnotes appear on next page

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†Starting level

‡If dose level −1 exceeded the MTD, further accrual was to proceed to dose level −2a or −2b, depending on whether excessive toxicity was attributed to chemotherapy (e.g., myelosuppression) or erlotinib (e.g., diarrhea, rash). Protocol-mandated dose level changes did not go into effect until the investigator or designate presented data to the appropriate representatives of the sponsor. Upon agreement to change dose levels, the investigator or designate notified participating [redacted] institutions.

Number of Patients (Planned, Enrolled and Analyzed):

No more than 20 DLT-evaluable patients were to be enrolled to this protocol. A total of 19 patients were enrolled; all patients were evaluable for safety, 94.7% (18 of 19 patients) were evaluable for DLT, and 73.7% (14 of 19 patients) were evaluable for efficacy.

Diagnosis and Main Criteria for Inclusion:

- Histologically or cytologically confirmed measurable, locally advanced, unresectable or metastatic pancreatic adenocarcinoma
- No prior therapy for pancreatic cancer
- Nonsmokers (no cigarette smoking for at least 14 days before enrollment or a positive cotinine at baseline). Patients also had to agree to not smoke while on study.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Adequate organ and marrow function as follows:
  - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
  - Platelets $\geq 100 \times 10^9$/L
  - Total bilirubin $\leq$ institutional upper limits of normal
  - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leq 2 \times$ institutional upper limits of normal
  - Serum creatinine $< 1.5 \times$ institutional upper limits of normal

Test Product, Dose and Mode of Administration, Batch Numbers:

Erlotinib lot numbers: 25 mg tablet (8686701, 1022101), 100 mg erlotinib tablet (8758801) and 150 mg erlotinib tablet (7634301), taken orally.

Duration of Treatment (or Duration of Study, if applicable):

Until disease progression or intolerable toxicity.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Nab-paclitaxel administered once weekly iv over 30 minutes on days 1, 8 and 15, every 28 days (window ± 1 day). Commercially purchased.

Gemcitabine administered once weekly iv over 30 minutes on days 1, 8 and 15, every 28 days (window ± 1 day). Commercially purchased.

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Criteria for Evaluation:

Efficacy

An exploratory analysis of objective response rate, progression-free survival (PFS) and overall survival (OS) was undertaken.

Pharmacokinetics

Plasma samples for pharmacokinetic analysis were collected from all patients. Dose time and meal time (either 1 hour before or 2 hours after dosing) were recorded on the pharmacokinetic sampling days. Plasma samples were analyzed by a validated high performance liquid chromatography (HPLC) assay with triple quadrupole mass spectrometric detection (LC/MS/MS) for both erlotinib and its major metabolites. Since the bioanalytical method could not distinguish between OSI-420 (the primary metabolite of erlotinib) and OSI-413, the plasma concentrations were collectively referred to as OSI-420/413 or OSI-420. The limit of quantitation for both analytes was 1 ng/mL.

Safety

The MTD, defined as the highest dose tested at which ≤ 1 of the first 6 patients enrolled at that dose level experience DLT within their first cycle of therapy, was determined.

The AEs of all patients were graded at scheduled intervals according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) (version 4.0). Patients were monitored continually throughout the study for the occurrence of AEs. All AEs that occurred from the time of protocol therapy administration until the completion of the study were recorded on the electronic case report form as an AE, regardless of the potential relationship to the protocol therapy. The date of onset, stop date, severity, action taken and investigator's opinion of potential relationship of the event to protocol therapy were recorded.

Hematology tests were performed on each day of gemcitabine and nab-paclitaxel administration prior to dosing. Chemistry tests were performed within 24 hours prior to the administration of the day 1 dose for each cycle. Tests were repeated more frequently, if clinically indicated.

Statistical Methods:

Efficacy

Response was based on the Response Evaluation Criteria in Solid Tumors (version 1.1) criteria. While patients with both locally advanced and metastatic adenocarcinoma of the pancreas were enrolled into this trial, all patients were required to have measurable disease. All of the patients who met the eligibility criteria and who had received at least 1 dose of any of the study drug(s) were included in the analysis of the response rate. Patients with partial response (PR) and complete response (CR) were classified as "responders." A secondary analysis included those eligible patients who completed the first course of therapy and who had been assessed for response, or who terminated treatment early for reasons of toxicity or disease progression.

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The best overall response and responders were summarized with the number and percentage of patients for the safety population. A secondary analysis was performed for the efficacy evaluable population.

All patients who received at least 1 dose of any of the study drug(s) were included in the analysis of PFS. PFS was calculated as the time from start of treatment until disease progression or death; patients who were still alive and free of progression at their last follow-up were censored at that time.

All patients who received at least 1 dose of any of the study drug(s) were included in the analysis of OS. Survival was calculated as the time from start of treatment until death of any cause; patients who were still alive at their last follow-up were censored at that time.

PFS and OS were analyzed using the method of Kaplan-Meier for all cohorts in the safety population.

Pharmacokinetics

For pharmacokinetic assessment of potential drug-drug interaction, only patients that had received 5 consecutive doses of erlotinib prior to the days of pharmacokinetic sampling on days 29 and 30 were included in the evaluation. Erlotinib trough concentrations (C_{24h}) at steady state were collected on day 29 (cycle 2, day 1), day 30 (each approximately 24 hours following the previous day's erlotinib dose) and just prior to administration of that day's erlotinib dose. These data were analyzed to estimate the intrapatient geometric mean ratio of C_{24h}, which compared the trough concentration taken following the combination of the 3 study drugs to the trough concentration of erlotinib taken as a single agent.

C_{24h} was summarized for each dose cohort using descriptive statistics (n, median, minimum, maximum and geometric mean). The ratio of cycle 2 day 2 to cycle 2 day 1 were summarized to assess the effect of concomitant administration of gemcitabine and nab-paclitaxel on C_{24h}. The median ratio and geometric mean ratio of those individual ratios, as well as the 90% CI for the geometric mean, were reported in the table for each treatment cohort. Analysis of the pharmacokinetic data were documented separately and performed independently of other study data. Details of the pharmacokinetic analyses were provided in a separate pharmacokinetic statistical analysis plan.

Safety

All AEs were graded according to the NCI CTCAE (version 4.0). Adverse events were coded to the lower-level term and mapped to the preferred term (PT) and primary system organ class (SOC) using MedDRA (version 12.1). Signs and symptoms reported at baseline were coded and mapped in the same manner as AEs. Summary tabulations of all AEs, serious adverse events (SAEs), related AEs, and related SAEs by PT and SOC were generated for each initial dose cohort, as well as for the maximum dose achieved. Patients who reported more than 1 AE within a SOC or a PT were counted only once within that SOC or PT as the worst grade of the AE reported. Summary tabulations and data listings were generated to support each of these summary tables. Data summaries and listings of patient baseline signs and symptoms and AEs that resulted in withdrawal were generated.

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Data listings were generated for all laboratory parameters for each patient. Values outside of the normal ranges were flagged. Normal ranges from each clinical laboratory were used to determine whether or not a value was out of range. In addition, a NCI CTCAE (version 4.0) grade was reported for applicable hematology and biochemistry parameters. Shift tables from baseline to the maximum grade of postbaseline results, including unscheduled assessments, were generated for hematology and biochemistry laboratory results. Baseline was defined as the last assessment prior to the first study drug dose. Vital sign parameters included pulse, systolic and diastolic blood pressure, weight, body surface area, temperature, and mean arterial pressure. A data listing was generated for vital sign parameters for each patient. A separate listing was generated for physical exams and ECOG performance status for each patient.

Summary of Results/Conclusions:

Efficacy Results:

Overall Best Response

All of the patients who met the eligibility criteria and who received at least 1 of the study drugs were included in the analysis of the response rate. For the Safety population, the best overall response was a PR in 36.8% (7 of 19) of patients (66.7% [4 of 6] of patients in the 1000/125/100 cohort, 33.3% [1 of 3] of patients in the 1000/75/100 cohort and 28.6% [2 of 7] of patients in the 1000/75/75 cohort) and SD in 26.3% (5 of 19) of patients (33.3% [1 of 3] of patients in the 1000/100/100 cohort and 57.1% [4 of 7] of patients in the 1000/75/75 cohort. No patient had a CR and 10.5% (2 of 19) of patients had PD [Table 3].

For the Efficacy population, the best overall response was a PR in 50.0% (7 of 14) of patients (80.0% [4 of 5] of patients in the 1000/125/100 cohort, 50.0% [1 of 2] of patients in the 1000/75/100 cohort and 33.3% [2 of 6] of patients in the 1000/75/75 cohort) and SD in 35.7% (5 of 14) of patients (100.0% [1 of 1] of patient in the 1000/100/100 cohort and 66.7% [4 of 6] of patients in the 1000/75/75 cohort). No patient had a CR and 14.3% (2 of 14) of patients had progressive disease (20.0% [1 of 5] of patients in the 1000/125/100 cohort and 50.0% [1 of 2] of patients in the 1000/75/100 cohort).

Progression-free Survival

For the Safety population, the median PFS was 5.3 months overall: 4.6 months for patients in the 1000/125/100 cohort, 8.9 months for patients in the 1000/100/100 cohort, 4.4 months for patients in the 1000/75/100 cohort and 7.2 months for patients in the 1000/75/75 cohort. For the Efficacy population, the median PFS was 5.4 months overall: 5.1 months for patients in the 1000/125/100 cohort, 10.6 months for patients in the 1000/100/100 cohort, 4.4 months for patients in the 1000/75/100 cohort and 7.2 months for patients in the 1000/75/75 cohort.

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Overall Survival

For the Safety population, the median time to death was 9.3 months overall: 9.3 months in the 1000/125/100 cohort, 8.9 months in the 1000/100/100 cohort, 9.4 months in the 1000/75/100 cohort and 10.3 months in the 1000/75/75 cohort. For the efficacy population, the median time to death was 9.3 months overall: 9.3 months in the 1000/125/100 cohort, not quantifiable in the 1000/100/100 cohort (only 1 patient in the cohort), 9.4 months in the 1000/75/100 cohort and 10.3 months in the 1000/75/75 cohort.

Pharmacokinetic Results:

A total of 13 patients received 5 consecutive doses of erlotinib prior to pharmacokinetic sampling on study days 29 and 30. To assess the effect of concomitant administration of gemcitabine and nab-paclitaxel on erlotinib $C_{24,}$ the ratio of cycle 2, day 2 to cycle 2, day 1 was summarized [Table 4]. The median ratios and geometric mean ratios, as well as the 90% CI for the geometric means, suggest no potential drug-drug interaction when erlotinib is concomitantly administered with gemcitabine and nab-paclitaxel.

Safety Results:

Study Drug Exposure

Overall, the median duration of treatment (treatment duration reflects the total number of days that the drug was administered) was 81 days for erlotinib (given once daily, days 1 through 28), 7 days for gemcitabine (given on days 1, 8, and 15 every 28 days) and 7 days for nab-paclitaxel (given on days 1, 8, and 15 every 28 days). The mean total dose intensity was 89.28 mg/day for erlotinib, 874.95 mg/m^2/day for gemcitabine and 92.62 mg/m^2/day for nab-paclitaxel. Treatment compliance, as measured by mean relative dose intensity, was 97.61% for erlotinib, 87.49% for gemcitabine and 97.61% for nab-paclitaxel.

Evaluation of MTD

The MTD was defined in the protocol as the highest dose tested at which ≤ 1 of the 6 patients enrolled at that dose level experienced a DLT within their first cycle of therapy. Four dose cohorts were evaluated during this study: Dose Level 1 (1000/125/100); Dose Level –1 (1000/100/100); Dose Level –2b (1000/75/100) and Dose Level –3 (1000/75/75). The MTD was declared to be Dose Level –3 (1000/75/75).

Adverse Events

All patients experienced AEs and almost all (94.7%) had AEs that were considered by the investigator to be related to treatment. The most common AEs in all treated patients combined were diarrhea (78.9%), nausea (63.2%), fatigue (57.9%), neutropenia (57.9%), rash (57.9%), anemia (52.6%) and alopecia (52.6%). Across cohorts, the percentage of patients experiencing AEs appeared to be similar.

Overall, 12 (63.2%) patients had SAEs, of which 7 patients (36.8%) had study treatment-related SAEs. Thirteen (68.4%) patients permanently discontinued multi-drug study treatment because of study treatment-related AEs. One patient in the 1000/75/75 dose cohort died of multi-organ failure due to progressive disease

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within 30 days following the last dose of study drug. This event was not, in the opinion of the investigator, related to any of the study drugs. Changes in laboratory parameters, vital signs and weight observed in the study revealed no pattern suggestive of dose-cohort effects.

Protocol-defined DLTs occurred in a total of 8 patients and resulted in 3 dose-group de-escalations; however, no pattern of specific dose-group–related DLTs was discerned. A majority of these DLTs were attributed by the investigator to gemcitabine/nab-paclitaxel/erlotinib or to gemcitabine/nab-paclitaxel. Decisions made in cohort review meetings were based on available data, including investigator identification of DLTs. Subsequent data reviews, using protocol-defined criteria, identified additional DLTs, however, no changes to DLT data were identified that would have had an impact on the dose cohort decisions.

Overall, the safety findings were consistent with what might be anticipated for the study population receiving these agents. The administration of multiple drugs did result in DLTs necessitating dose de-escalation; however, no relationship between dose cohort and AEs or laboratory abnormalities was discerned, although all groups were small.

CONCLUSIONS:

The primary objective of this study was to determine the MTD of erlotinib administered in combination with gemcitabine and nab-paclitaxel to patients with untreated, locally advanced, unresectable or metastatic pancreatic adenocarcinoma. The secondary objectives were to evaluate the safety profile, limited pharmacokinetics and preliminary efficacy of this 3-drug combination.

The MTD was evaluated and determined to be 1000/75/75. The number of DLTs in each cohort studied led to dose de-escalation from the initial doses of 1000/125/100. The approved dose of nab-paclitaxel in combination with gemcitabine for the first-line treatment of metastatic adenocarcinoma of the pancreas is 125 mg/m^2, and the approved dose of erlotinib in combination with gemcitabine is 100 mg. Thus, the MTD of the 3-drug regimen evaluated in this Phase 1b study used doses of nab-paclitaxel and erlotinib that are less than their established therapeutic doses in combinatiion with gemcitabine.

Interpretation of efficacy data in this phase 1b study is limited because of the very small sample size at the MTD. The Phase 3 trial of gemcitabine and nab-paclitaxel demonstrated an ORR of 23% (PFS of 5.5 months and OS of 8.5 months) [Von Hoff et al, 2013], whereas the Phase 3 trial of gemcitabine and erlotinib demonstrated an ORR of 8.6% (PFS of 3.8 months and OS of 6.4 months) [Moore et al, 2007]. While responses were seen even at the lowest dose levels tested, and 7 of 19 patients enrolled demonstrated a response, the need to administer both nab-paclitaxel and erlotinib at less than their established dose levels makes further development of this 3-drug regimen challenging.

The safety profile was generally consistent with what might be anticipated for the study population and as a result of the multiple agents administered. The most common AEs across all treatment groups were diarrhea (78.9%), nausea (63.2%), fatigue (57.9%), neutropenia (57.9%), rash (57.9%), anemia (52.6%) and alopecia (52.6%). The administration of multiple drugs did result in DLTs necessitating dose de-escalation; however, no

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relationship between dose-cohort and AEs or laboratory abnormalities was discerned, although all groups were small. There was no potential drug-drug interaction with respect to erlotinib pharmacokinetics when erlotinib was concomitantly administered with gemcitabine and nab-paclitaxel.

In summary, the MTD for the 3-drug regimen utilized doses of erlotinib and nab-paclitaxel that were below their established therapeutic doses in combination with gemcitabine. Further investigation of this regimen is not currently planned.

Date of Report: 28 February 2014

Table 1 Summary of Patient Disposition (Enrolled Population)

Category	Gemcitabine (mg/m^2)/Nab-paclitaxel (mg/m^2) /Erlotinib (mg) Dose				Total n (%)†
	1000/125/100 n (%)†	1000/100/100 n (%)†	1000/75/100 n (%)†	1000/75/75 n (%)†	
Enrolled	6	3	3	7	19
Treated	6 (100.0)	3 (100.0)	3 (100.0)	7 (100.0)	19 (100.0)
Discontinued	6 (100.0)	3 (100.0)	3 (100.0)	7 (100.0)	19 (100.0)
Reason for terminating treatment					
Disease progression	0	0	2 (66.7)	1 (14.3)	3 (15.8)
AE resulting in death	0	0	0	0	0
AE requiring withdrawal from study	4 (66.7)	3 (100.0)	1 (33.3)	2 (28.6)	10 (52.6)
AE—patient missed > 14 days of therapy due to toxicity	1 (16.7)	0	0	0	1 (5.3)
AE—persistent decline in patient's performance status of ECOG ≥ 2	0	0	0	2 (28.6)	2 (10.5)
Medical/ethical reason	0	0	0	1 (14.3)	1 (5.3)
Patient requested	1 (16.7)	0	0	1 (14.3)	2 (10.5)

AE: adverse event; ECOG: Eastern Cooperative Oncology Group.

†Percentages were based on the number of patients in each cohort in the Safety Population (treated).

Source: Table 14.1.1

Table 2 Summary of Demographic Characteristics and Baseline Assessments (Safety Population)

Parameter	Gemcitabine (mg/m^2)/Nab-paclitaxel (mg/m^2) /Erlotinib (mg) Dose				Total (N = 19)
	1000/125/100 (N = 6)	1000/100/100 (N = 3)	1000/75/100 (N = 3)	1000/75/75 (N = 7)	
Gender, n (%)†					
Male	3 (50.0)	1 (33.3)	1 (33.3)	4 (57.1)	9 (47.4)
Female	3 (50.0)	2 (66.7)	2 (66.7)	3 (42.9)	10 (52.6)
Race, n (%)†					
White	5 (83.3)	2 (66.7)	3 (100.0)	7 (100.0)	17 (89.5)
Black or African American	1 (16.7)	1 (33.3)	0	0	2 (10.5)
Ethnic Group, n (%)†					
Hispanic or Latino	0	0	0	2 (28.6)	2 (10.5)
Not Hispanic or Latino	6 (100.0)	1 (33.3)	3 (100.0)	5 (71.4)	15 (78.9)
Not reported, n (%)	0	2 (66.7)	0	0	2 (10.5)
Age Category, n (%)†					
40 to 64 years	4 (66.7)	0	2 (66.7)	5 (71.4)	11 (57.9)
≥ 65 years	2 (33.3)	3 (100.0)	1 (33.3)	2 (28.6)	8 (42.1)
Age (years)					
Median	60.0	69.0	64.0	61.0	63.0
Min, Max	55, 70	66, 71	63, 77	54, 78	54, 78
Height (cm)					
n‡	6	3	2	7	18
Median	168.850	162.000	165.600	168.100	167.800
Min, Max	152.40, 180.34	152.00, 184.00	155.90, 175.30	160.80, 178.60	152.00, 184.00
Weight (kg)					
n‡	6	3	2	7	18
Median	84.570	71.000	65.350	74.470	74.985
Min, Max	55.40, 95.44	57.60, 80.80	52.70, 78.00	44.40, 90.40	44.40, 95.44

Table continued on next page

Parameter	Gemcitabine (mg/m^2)/Nab-paclitaxel (mg/m^2) /Erlotinib (mg) Dose				Total (N = 19)
	1000/125/100 (N = 6)	1000/100/100 (N = 3)	1000/75/100 (N = 3)	1000/75/75 (N = 7)	
ECOG PS, n (%)†					
n‡	6	3	2	7	18
0	4 (66.7)	1 (33.3)	0	2 (28.6)	7 (38.9)
1	2 (33.3)	2 (66.7)	2 (100.0)	5 (71.4)	11 (61.1)
2	0	0	0	0	0
Cotinine Test, n (%)†					
Negative	6 (100.0)	3 (100.0)	3 (100.0)	7 (100.0)	19 (100.0)
Smoking History, n (%)†					
Never smoked cigarettes	0	3 (100.0)	1 (33.3)	2 (28.6)	6 (31.6)
Smoked ≤ 100 cigarettes in a lifetime and stopped	6 (100.0)	0	0	0	6 (31.6)
Smoked > 100 cigarettes in a lifetime and stop	0	0	2 (66.7)	5 (71.4)	7 (36.8)
Currently smoked cigarettes	0	0	0	0	0

ECOG: Eastern Cooperative Oncology Group; Max: maximum; Min: minimum; PS: performance status.

ECOG: 0 = fully active, able to carry on all predisease performance without restriction; 1 = restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, (e.g., light housework, office work); 2 = ambulatory and capable of all self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.

†Percentages were based on the number of patients in each cohort in the Safety Population with nonmissing data.

‡Number of patients (n) is reported only for those parameters where there is not an assessment for all patients in the cohort.

Source: Table 14.1.3.

Table 3 Summary of Overall Best Clinical Response (Safety Population)

Best Clinical Response, n (%)†	Gemcitabine (mg/m^2)/Nab-paclitaxel (mg/m^2) /Erlotinib (mg) Dose				Total (N = 19)
	1000/125/100 (N = 6)	1000/100/100 (N = 3)	1000/75/100 (N = 3)	1000/75/75 (N = 7)	
Complete response (CR)	0	0	0	0	0
Partial response (PR)	4 (66.7)	0	1 (33.3)	2 (28.6)	7 (36.8)
Stable disease (SD)	0	1 (33.3)	0	4 (57.1)	5 (26.3)
Progressive disease (PD)	1 (16.7)	0	1 (33.3)	0	2 (10.5)
Unable to determine/not evaluable	1 (16.7)	2 (66.7)	1 (33.3)	1 (14.3)	5 (26.3)

†Percentages were based on the number of patients in each cohort in the Safety Population.

Source: Table 14.2.1

Table 4 Geometric Mean Ratio of C_{24h} Cycle 2 Day 2 to C_{24h} Cycle 2, Day 1 in Each Dose Cohort

Analyte	Gemcitabine/ Nab-paclitaxel/ Erlotinib	N	C_{24h} (ng/mL)		Median Ratio C2D2/C2D1	Geometric Mean Ratio† (%)	90% CI
			Median C2D2	Median C2D1			
Erlotinib	1000/125/100	5	608	640	1.03	105.3	92.0, 120.4
	1000/100/100	1	819	748	1.09	109.5	NA
	1000/75/100	2	645	317	4.59	230.3	0.1, 920755.7
	1000/75/75	5	639	821	1.00	89.8	63.3, 127.5
OSI-420	1000/125/100	5	63	61	1.16	118.0	104.1, 133.8
	1000/100/100	1	82	72	1.14	113.6	NA
	1000/75/100	2	67	26	3.13	189.5	0.2, 181629.9
	1000/75/75	5	58	83	0.80	83.3	61.8, 112.4

Note: Patient [redacted] was excluded from the analysis because of an incorrect pharmacokinetic sampling date.

C2D1: cycle 2, day 1; C2D2: cycle 2, day 2; NA: not applicable.

†Geometric mean for individual ratios are reported.

Source: Table 2 [Attachment 2]

Table 5 Treatment-emergent Adverse Events (in > 1 Patient Overall) by System Organ Class, Preferred Term and Any Severity Grade (Safety Population)

MedDRA System Organ Class‡ Preferred Term	TEAEs, n (%)† Gemcitabine (mg/m^2)/Nab-paclitaxel (mg/m^2) /Erlotinib (mg) Dose Dose Level 1 1000/125/100 (N = 6)	Dose Level –1 1000/100/100 (N = 3)	Dose Level –2b 1000/75/100 (N = 3)	Dose Level –3 1000/75/75 (N = 7)	Total (N = 19)
Any TEAE	6 (100.0)	3 (100.0)	3 (100.0)	7 (100.0)	19 (100.0)
Blood and Lymphatic System Disorders					
Anaemia	2 (33.3)	2 (66.7)	1 (33.3)	5 (71.4)	10 (52.6)
Leukopenia	1 (16.7)	1 (33.3)	0	4 (57.1)	6 (31.6)
Lymphopenia	2 (33.3)	0	0	1 (14.3)	3 (15.8)
Neutropenia	3 (50.0)	1 (33.3)	2 (66.7)	5 (71.4)	11 (57.9)
Thrombocytopenia	2 (33.3)	1 (33.3)	0	2 (28.6)	5 (26.3)
Eye Disorders					
Visual impairment	0	1 (33.3)	0	1 (14.3)	2 (10.5)
Gastrointestinal Disorders					
Abdominal pain	1 (16.7)	0	1 (33.3)	0	2 (10.5)
Abdominal pain upper	1 (16.7)	0	1 (33.3)	1 (14.3)	3 (15.8)
Constipation	1 (16.7)	0	1 (33.3)	2 (28.6)	4 (21.1)
Diarrhoea	6 (100.0)	2 (66.7)	2 (66.7)	5 (71.4)	15 (78.9)
Dry mouth	2 (33.3)	0	0	0	2 (10.5)
Dyspepsia	1 (16.7)	0	1 (33.3)	0	2 (10.5)
Melaena	2 (33.3)	0	0	0	2 (10.5)
Nausea	4 (66.7)	1 (33.3)	3 (100.0)	4 (57.1)	12 (63.2)
Oral dysaesthesia	2 (33.3)	0	0	0	2 (10.5)
Stomatitis	2 (33.3)	0	0	1 (14.3)	3 (15.8)
Vomiting	4 (66.7)	2 (66.7)	0	2 (28.6)	8 (42.1)
General Disorders and Administration Site Conditions					
Chills	1 (16.7)	0	1 (33.3)	2 (28.6)	4 (21.1)
Fatigue	5 (83.3)	2 (66.7)	1 (33.3)	3 (42.9)	11 (57.9)
Gait disturbance	1 (16.7)	0	0	1 (14.3)	2 (10.5)
Oedema peripheral	0	1 (33.3)	0	1 (14.3)	2 (10.5)
Performance status decreased	0	0	0	2 (28.6)	2 (10.5)
Pyrexia	2 (33.3)	0	1 (33.3)	2 (28.6)	5 (26.3)
Hepatobiliary Disorders					
Hyperbilirubinaemia	0	0	1 (33.3)	1 (14.3)	2 (10.5)
Infections and Infestations					
Urinary tract infection	1 (16.7)	0	1 (33.3)	0	2 (10.5)
Investigations					
ALT increased	0	0	2 (66.7)	2 (28.6)	4 (21.1)
AST increased	0	0	2 (66.7)	2 (28.6)	4 (21.1)
Blood alkaline phosphatase increased	0	0	1 (33.3)	2 (28.6)	3 (15.8)
Lymphocyte count decreased	0	0	1 (33.3)	1 (14.3)	2 (10.5)
Weight decreased	3 (50.0)	2 (66.7)	1 (33.3)	0	6 (31.6)
WBC count decreased	2 (33.3)	0	1 (33.3)	0	3 (15.8)
Metabolism and Nutrition Disorders					
Decreased appetite	5 (83.3)	2 (66.7)	0	2 (28.6)	9 (47.4)
Dehydration	2 (33.3)	1 (33.3)	3 (100.0)	2 (28.6)	8 (42.1)
Hypoalbuminaemia	0	0	0	3 (42.9)	3 (15.8)
Hyponatraemia	1 (16.7)	0	0	2 (28.6)	3 (15.8)
Musculoskeletal and Connective Tissue Disorders					
Pain in extremity	1 (16.7)	0	0	1 (14.3)	2 (10.5)
Nervous System Disorders					
Dizziness	3 (50.0)	0	0	0	3 (15.8)
Dysgeusia	2 (33.3)	1 (33.3)	0	0	3 (15.8)
Peripheral sensory neuropathy	1 (16.7)	0	1 (33.3)	0	2 (10.5)

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MedDRA System Organ Class‡ Preferred Term	TEAEs, n (%)† Gemcitabine (mg/m^2)/Nab-paclitaxel (mg/m^2) /Erlotinib (mg) Dose Dose Level 1 1000/125/100 (N = 6)	Dose Level –1 1000/100/100 (N = 3)	Dose Level –2b 1000/75/100 (N = 3)	Dose Level –3 1000/75/75 (N = 7)	Total (N = 19)
Psychiatric Disorders					
Anxiety	1 (16.7)	1 (33.3)	0	1 (14.3)	3 (15.8)
Depression	0	0	1 (33.3)	1 (14.3)	2 (10.5)
Renal and Urinary Disorders					
Urinary incontinence	0	1 (33.3)	1 (33.3)	0	2 (10.5)
Respiratory, Thoracic and Mediastinal Disorders					
Dyspnoea	2 (33.3)	0	0	0	2 (10.5)
Epistaxis	2 (33.3)	0	0	1 (14.3)	3 (15.8)
Hiccups	1 (16.7)	0	0	1 (14.3)	2 (10.5)
Skin and Subcutaneous Tissue Disorders					
Alopecia	5 (83.3)	0	1 (33.3)	4 (57.1)	10 (52.6)
Dermatitis acneiform	1 (16.7)	1 (33.3)	1 (33.3)	1 (14.3)	4 (21.1)
Pruritus	1 (16.7)	1 (33.3)	1 (33.3)	0	3 (15.8)
Rash	5 (83.3)	1 (33.3)	1 (33.3)	4 (57.1)	11 (57.9)
Vascular Disorders					
Hypotension	3 (50.0)	0	0	1 (14.3)	4 (21.1)

A patient who experienced multiple events within a system organ class (SOC) or preferred term was counted once for that class and once for the preferred term.

This table classifies patients using initial dose cohorts.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; TEAE: treatment-emergent adverse event.

†Percentages were based on the number of patients in each cohort in the Safety Population.

‡Adverse events were coded using MedDRA, version 12.1.

Source: Table 14.3.3.4

Table 6 Serious Adverse Events by System Organ Class, Preferred Term and Any Severity Grade (Safety Population)

MedDRA System Organ Class‡ Preferred Term	SAEs, n (%)† Gemcitabine (mg/m^2)/Nab-paclitaxel (mg/m^2) /Erlotinib (mg) Dose 1000/125/100 (N = 6)	1000/100/100 (N = 3)	1000/75/100 (N = 3)	1000/75/75 (N = 7)	Total (N = 19)
Any SAE	**4 (66.7)**	**2 (66.7)**	**2 (66.7)**	**4 (57.1)**	**12 (63.2)**
Blood and Lymphatic System Disorders					
Anaemia	1 (16.7)	0	0	0	1 (5.3)
Leukopenia	1 (16.7)	0	0	0	1 (5.3)
Neutropenia	2 (33.3)	0	0	0	2 (10.5)
Thrombocytopenia	1 (16.7)	0	0	0	1 (5.3)
Cardiac Disorders					
Atrial fibrillation	1 (16.7)	0	0	0	1 (5.3)
Sinus tachycardia	1 (16.7)	0	0	0	1 (5.3)
Eye Disorders					
Optic neuropathy	0	1 (33.3)	0	0	1 (5.3)
Gastrointestinal Disorders					
Constipation	0	0	0	1 (14.3)	1 (5.3)
Diarrhoea	3 (50.0)	0	0	0	3 (15.8)
Duodenal obstruction	0	0	1 (33.3)	0	1 (5.3)
Duodenal ulcer	0	0	1 (33.3)	0	1 (5.3)
Gastric ulcer	1 (16.7)	0	0	0	1 (5.3)
Nausea	1 (16.7)	0	0	1 (14.3)	2 (10.5)
Oesophagitis	0	0	1 (33.3)	0	1 (5.3)

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MedDRA System Organ Class‡ Preferred Term	SAEs, n (%)† Gemcitabine (mg/m^2)/Nab-paclitaxel (mg/m^2)/Erlotinib (mg) Dose 1000/125/100 (N = 6)	1000/100/100 (N = 3)	1000/75/100 (N = 3)	1000/75/75 (N = 7)	Total (N = 19)
Stomatitis	1 (16.7)	0	0	0	1 (5.3)
Vomiting	0	0	0	1 (14.3)	1 (5.3)
General Disorders and Administration Site Conditions					
Fatigue	1 (16.7)	0	1 (33.3)	0	2 (10.5)
Multi-organ failure	0	0	0	1 (14.3)	1 (5.3)
Pyrexia	0	0	0	1 (14.3)	1 (5.3)
Infections and Infestations					
Cellulitis streptococcal	0	0	0	1 (14.3)	1 (5.3)
Enterococcal bacteraemia	0	0	0	1 (14.3)	1 (5.3)
Entercolitis infectious	0	0	0	1 (14.3)	1 (5.3)
Pneumonia	0	0	0	1 (14.3)	1 (5.3)
Sepsis	1 (16.7)	0	0	0	1 (5.3)
Urinary tract infection	1 (16.7)	0	0	0	1 (5.3)
Urosepsis	0	0	0	1 (14.3)	1 (5.3)
Investigations					
Blood bilirubin increased	0	0	1 (33.3)	0	1 (5.3)
Metabolism and Nutrition Disorders					
Decreased appetite	1 (16.7)	0	0	0	1 (5.3)
Dehydration	2 (33.3)	0	1 (33.3)	1 (14.3)	4 (21.1)
Failure to thrive	0	0	0	1 (14.3)	1 (5.3)
Hypokalaemia	0	0	0	1 (14.3)	1 (5.3)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)					
Malignant pleural effusion	0	0	0	1 (14.3)	1 (5.3)
Nervous System Disorders					
Peripheral sensory neuropathy	1 (16.7)	0	0	0	1 (5.3)
Transient ischaemic attack	0	1 (33.3)	0	0	1 (5.3)
Reproductive System and Breast Disorders					
Prostatitis	0	0	0	1 (14.3)	1 (5.3)
Respiratory, Thoracic and Mediastinal Disorders					
Dyspnoea	2 (33.3)	0	0	0	2 (10.5)
Interstitial lung disease	1 (16.7)	0	0	0	1 (5.3)
Skin and Subcutaneous Tissue Disorders					
Stasis dermatitis	0	0	1 (33.3)	0	1 (5.3)
Vascular Disorders					
Hypotension	2 (33.3)	0	0	0	2 (10.5)
Venous insufficiency	0	0	1 (33.3)	0	1 (5.3)

A patient who experienced multiple events within a SOC or preferred term was counted once for that class and once for the preferred term.

This table classifies patients using initial dose cohorts.

SAE: serious adverse event.

†Percentages were based on the number of patients in each cohort in the Safety Population.

‡Adverse events were coded using MedDRA, version 12.1.

Source: Table 14.3.3.9