Protocol Registration Receipt
07/25/2013

Grantor: CDER IND/IDE Number: 102175 Serial Number: 0063

Study of GSK1120212 Plus Gemcitabine vs Placebo Plus Gemcitabine in Metastatic Pancreatic Cancer

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01231581

Purpose

GSK1120212 is a potent and highly selective inhibitor of MEK phosphorylation and kinase activity and has demonstrated potent anti-proliferative activity against human pancreatic cancer cell lines. This study is a Phase II, randomized placebo-controlled trial of the MEK inhibitor GSK1120212 plus gemcitabine vs. placebo plus gemcitabine in subjects with metastatic pancreatic cancer. Eligible subjects will receive intravenous gemcitabine with oral GSK1120212 or placebo. Therapy will continue until treatment discontinuation criteria are met. The primary objective will be to compare the overall survival of subjects in the GSK1120212 plus gemcitabine arm vs. subjects in the placebo plus gemcitabine arm. Secondary objectives include comparison of progression free survival, overall response rate, and duration of response between the two arms. Exploratory research objectives include the evaluation of population pharmacokinetics as well as blood and tissue based biomarkers. Safety will also be monitored throughout dosing.

Once the determined number of survival events has occurred, if subjects are eligible, they will have the option to enter MEK114375, an open-label, Phase Ib rollover study of GSK1120212 monotherapy or GSK1120212 in combination with other anti-cancer treatments.

Condition	Intervention	Phase
Cancer	Drug: GSK1120212 Drug: Gemcitabine Drug: Placebo	Phase 2

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Outcomes Assessor), Randomized, Safety/Efficacy Study
Official Title: A Randomized, Double-Blind Placebo-Controlled Phase II Study of the MEK Inhibitor GSK1120212 Plus Gemcitabine vs Placebo Plus Gemcitabine in Subjects With Metastatic Pancreatic Cancer

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Overall Survival [Time Frame: From randomization until death due to any cause or until the data cutoff of 15-March-2013 (up to 24 months)] [Designated as safety issue: No]

  Overall survival is defined as the time from randomization until death due to any cause. For the analysis of overall survival, the last date of known contact was used for those participants who were not dead at the time of analysis; such participants were considered censored.

Secondary Outcome Measures:

- Progression-free Survival (PFS) as Assessed by the Investigator [Time Frame: From randomization until disease progression (PD) or death due to any cause or until the data cutoff of 17-April-2012 (up to 15 months)] [Designated as safety issue: No]

  PFS is defined as the time from randomization until the earliest date of radiological PD or death due to any cause. PD was based on radiographic or photographic evidence, and assessments were made by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm). PD was also based on unequivocal progression of existing non-target lesions. If the participant received subsequent anti-cancer therapy prior to the date of documented progression or death, or did not have a documented date of progression or death, PFS was censored at the last adequate assessment.

- Number of Participants With an Investigator-assessed Best Response, With or Without Confirmation, of Complete Response (CR) or Partial Response (PR) [Time Frame: From randomization until disease progression or death due to any cause or until the data cutoff of 17-April-2012 (up to 15 months)] [Designated as safety issue: No]

  CR is defined as the disappearance of all target and non-target lesions. Any pathological lymph nodes must be <10 mm in the short axis. PR is defined

as at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g., percent change from baseline). CR and PR were evaluated by the Investigator using standard criteria (RECIST version 1.1). Confirmation of response was not required.

- Investigator-Assessed Duration of Response [Time Frame: From the first documented CR or PR until disease progression or death due to any cause or until the data cutoff of 17-April-2012 (up to 13 months)] [Designated as safety issue: No]

  Duration of response is defined, for the subset of participants with a CR or PR, as the time from the first documented evidence of CR or PR until the first documented disease progression or death due to any cause. CR is defined as the disappearance of all target and non-target lesions. Any pathological lymph nodes must be <10 mm in the short axis. PR is defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g., percent change from baseline). PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start).

- Number of Participants With Any Adverse Event (AE) and Any Serious Adverse Event (SAE) [Time Frame: From the start of the first dose of study treatment until 28 days following discontinuation of the study treatment or until the data cutoff of 15-March-2013 (up to 21 months)] [Designated as safety issue: No]

  An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered to be related to the medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, or results in a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury. Per protocol other events were considered SAEs like symptomatic left ventricular ejection fraction (LVEF) decreases or cases of central serous retinopathy (CSR) or retinal vein occlusion (RVO). AE and SAE data were collected from the start of the first dose of study treatment and continued until 28 days following discontinuation of the study treatment or death. Refer to the general AE/SAE module for a complete list of AEs and SAEs.

- Number of Participants (Par.) With a Worst-case Change to Grade 3 or Grade 4 From Baseline Grade in Chemistry Parameters [Time Frame: From the start of the first dose of study treatment until 28 days following discontinuation of the study treatment or until the data cutoff of 17-April-2012 (up to 17 months)] [Designated as safety issue: No]

  A grading (severity) scale is provided for each laboratory toxicity. Grade refers to the severity of the toxicity. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 displays Grades 1 through 5 based on the general guideline: Grade 1, mild toxicity; Grade 2, moderate toxicity; Grade 3, severe toxicity; Grade 4, life-threatening or disabling toxicity; Grade 5, death related to toxicity.

- Number of Participants With Change From Baseline Increase to Grade 3/Grade 4 in Lab Hematology Test Measurements [Time Frame: From the start of the first dose of study treatment until 28 days following discontinuation of the study treatment or until the data cutoff of 17-April-2012 (up to 17 months)] [Designated as safety issue: No]

  A grading (severity) scale is provided for each laboratory toxicity. Grade refers to the severity of the toxicity. The CTCAE version 3.0 displays Grades 1 through 5, with unique clinical descriptions of the severity for each toxicity based on the general guideline: Grade 1, mild toxicity; Grade 2, moderate toxicity; Grade 3, severe toxicity; Grade 4, life-threatening or disabling toxicity; Grade 5, death related to toxicity.

Enrollment: 160
Study Start Date: August 2010

Study Completion Date: February 2013
Primary Completion Date: April 2012

Arms	Assigned Interventions
Experimental: GSK1120212 plus Gemcitabine GSK1120212 administered orally plus gemcitabine IV	Drug: GSK1120212 administered orally starting on day 1 followed by a continuous daily dosing of 2.0 mg Drug: Gemcitabine Intravenous gemcitabine infused over 30 minutes weekly for 7 weeks followed by one week of rest from treatment. Subsequent cycles will consist of 1000 mg/m2 intravenous infusion over 30 minutes on days 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment period.
Active Comparator: Placebo plus Gemcitabine Placebo administered orally plus gemcitabine IV	Drug: Gemcitabine Intravenous gemcitabine infused over 30 minutes weekly for 7 weeks followed by one week of rest from treatment. Subsequent cycles will consist of 1000 mg/m2 intravenous infusion over 30 minutes on days 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment period. Drug: Placebo administered orally starting on day 1 followed by a continuous daily dosing of 2.0 mg

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both

Inclusion Criteria:

- 18 years old or older
- Histologically or cytologically confirmed diagnosis of metastatic (Stage IV) adenocarcinoma of the pancreas with measurable or non-measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
- Performance status score of 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) scale
- All prior treatment related toxicities must be Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.0) ≤ Grade 1 (except alopecia) at the time of randomization
- Adequate baseline organ function
- Able to swallow and retain orally administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels

Exclusion Criteria:

- Prior systemic therapy (i.e., chemotherapy, immunotherapy, hormone therapy, , targeted therapy or any investigational anti-cancer drug) for metastatic pancreatic adenocarcinoma.

(Prior treatment with 5-FU based or gemcitabine administered as a radiation sensitizer during and up to 4 weeks after radiation therapy is allowed. Prior systemic chemotherapy in the adjuvant setting is allowed ; however, prior therapy with gemcitabine is allowed only if tumor recurrence occurred at least 6 months after completing the last dose of gemcitabine)

- History of another malignancy. Exception: Subjects who have been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible. Subjects with second malignancies that are indolent or definitively treated may be enrolled. Consult GSK Medical Monitor if unsure whether second malignancies meet requirements specified above
- Any serious and/or unstable pre-existing medical (aside from malignancy exception above), psychiatric disorder, or other conditions that could interfere with subject’s safety, obtaining informed consent or compliance to the study procedures, in the opinion of the Investigator or GSK Medical Monitor
- History of interstitial lung disease or pneumonitis
- History or current evidence / risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR)
- Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression
- History of acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting within the past 6 months

Contacts and Locations

Locations

Korea, Republic of

GSK Investigational Site

Seoul, Korea, Republic of, 110-744

GSK Investigational Site
Seoul, Korea, Republic of, 120-752
GSK Investigational Site
Seoul, Korea, Republic of, 135-710
GSK Investigational Site
Seoul, Korea, Republic of, 138-736

Taiwan

GSK Investigational Site
Gueishan Township,Taoyuan County, Taiwan, 333
GSK Investigational Site
Tainan, Taiwan, 704
GSK Investigational Site
Taipei, Taiwan, 112

Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Responsible Party:	GlaxoSmithKline
Study ID Numbers:	113487
Health Authority:	United States: Food and Drug Administration

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Study Results

Participant Flow

Reporting Groups

	Description
Trametinib + Gemcitabine	Participants received 2 milligrams (mg) trametinib orally once daily in combination with 1000 mg/m^2 of gemcitabine given as intravenous (IV) infusion over 30 minutes (min). In the first cycle, gemcitabine was

	Description
	infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until progressive disease (PD), unacceptable toxicity, or permanent discontinuation from study treatment for any reason.
Placebo + Gemcitabine	Participants received placebo orally once daily in combination with 1000 mg/m^2 of gemcitabine given as IV infusion over 30 min. In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until PD, unacceptable toxicity, or permanent discontinuation from study treatment for any reason.

Overall Study

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Started	80	80
Ongoing	1 [1]	0
Completed	0	0
Not Completed	80	80
Lost to Follow-up	2	2
Withdrawal by Subject	6	9
Study Closed/Terminated	6	5
Death	65	64
Ongoing	1	0

[1] Participant is continuing treatment with trametinib and gemcitabine under roll over study MEK114375.

Baseline Characteristics

Reporting Groups

	Description
Trametinib + Gemcitabine	Participants received 2 milligrams (mg) trametinib orally once daily in combination with 1000 mg/m^2 of gemcitabine given as intravenous (IV) infusion over 30 minutes (min). In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until progressive disease (PD), unacceptable toxicity, or permanent discontinuation from study treatment for any reason.
Placebo + Gemcitabine	Participants received placebo orally once daily in combination with 1000 mg/m^2 of gemcitabine given as IV infusion over 30 min. In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until PD, unacceptable toxicity, or permanent discontinuation from study treatment for any reason.

Baseline Measures

	Trametinib + Gemcitabine	Placebo + Gemcitabine	Total
Number of Participants	80	80	160
Age, Continuous [units: Years] Mean (Standard Deviation)	62.3 (10.35)	62.2 (9.56)	62.3 (9.93)

	Trametinib + Gemcitabine	Placebo + Gemcitabine	Total
Gender, Male/Female [units: Participants]			
Female	41	34	75
Male	39	46	85
Race/Ethnicity, Customized [units: Participants]			
White - White/Caucasian/European Heritage	50	59	109
Asian - East Asian Heritage	24	13	37
African American Africa	6	5	11
Asian - Central/South Asian Heritage	0	1	1
Asian - South East Asian Heritage	0	1	1
White - Arabic/North African Heritage	0	1	1

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Overall Survival
Measure Description	Overall survival is defined as the time from randomization until death due to any cause. For the analysis of overall survival, the last date of known contact was used for those participants who were not dead at

	the time of analysis; such participants were considered censored.
Time Frame	From randomization until death due to any cause or until the data cutoff of 15-March-2013 (up to 24 months)
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all randomized participants regardless of whether or not treatment was administered

Reporting Groups

	Description
Trametinib + Gemcitabine	Participants received 2 milligrams (mg) trametinib orally once daily in combination with 1000 mg/m^2 of gemcitabine given as intravenous (IV) infusion over 30 minutes (min). In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until progressive disease (PD), unacceptable toxicity, or permanent discontinuation from study treatment for any reason.
Placebo + Gemcitabine	Participants received placebo orally once daily in combination with 1000 mg/m^2 of gemcitabine given as IV infusion over 30 min. In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until PD, unacceptable toxicity, or permanent discontinuation from study treatment for any reason.

Measured Values

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Number of Participants Analyzed	80	80

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Overall Survival [units: months] Median (95% Confidence Interval)	8.4 (7.8 to 10.3)	6.7 (5.3 to 9.9)

Statistical Analysis 1 for Overall Survival

Groups	Trametinib + Gemcitabine
Method	Log Rank
P-Value	0.352
Hazard Ratio (HR)	0.94
95% Confidence Interval	0.66 to 1.32

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

Other relevant estimation information:

Hazard ratios are estimated using a Pike estimator.

2. Secondary Outcome Measure:

Measure Title	Progression-free Survival (PFS) as Assessed by the Investigator
Measure Description	PFS is defined as the time from randomization until the earliest date of radiological PD or death due to any cause. PD was based on

	radiographic or photographic evidence, and assessments were made by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm). PD was also based on unequivocal progression of existing non-target lesions. If the participant received subsequent anti-cancer therapy prior to the date of documented progression or death, or did not have a documented date of progression or death, PFS was censored at the last adequate assessment.
Time Frame	From randomization until disease progression (PD) or death due to any cause or until the data cutoff of 17-April-2012 (up to 15 months)
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Trametinib + Gemcitabine	Participants received 2 milligrams (mg) trametinib orally once daily in combination with 1000 mg/m^2 of gemcitabine given as intravenous (IV) infusion over 30 minutes (min). In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until progressive disease (PD), unacceptable toxicity, or permanent discontinuation from study treatment for any reason.
Placebo + Gemcitabine	Participants received placebo orally once daily in combination with

	Description
	1000 mg/m^2 of gemcitabine given as IV infusion over 30 min. In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until PD, unacceptable toxicity, or permanent discontinuation from study treatment for any reason.

Measured Values

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Number of Participants Analyzed	80	80
Progression-free Survival (PFS) as Assessed by the Investigator [units: weeks] Median (95% Confidence Interval)	16.1 (14.0 to 23.4)	15.1 (8.6 to 21.7)

3. Secondary Outcome Measure:

Measure Title	Number of Participants With an Investigator-assessed Best Response, With or Without Confirmation, of Complete Response (CR) or Partial Response (PR)
Measure Description	CR is defined as the disappearance of all target and non-target lesions. Any pathological lymph nodes must be <10 mm in the short axis. PR is defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g., percent change from baseline). CR and PR were evaluated by the Investigator using standard criteria (RECIST version 1.1). Confirmation of response was not required.

Time Frame	From randomization until disease progression or death due to any cause or until the data cutoff of 17-April-2012 (up to 15 months)
Safety Issue?	No

Analysis Population Description

Measurable Disease (MD) Population: all randomized participants regardless of whether or not treatment was administered who had measurable disease at baseline

Reporting Groups

	Description
Trametinib + Gemcitabine	Participants received 2 milligrams (mg) trametinib orally once daily in combination with 1000 mg/m^2 of gemcitabine given as intravenous (IV) infusion over 30 minutes (min). In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until progressive disease (PD), unacceptable toxicity, or permanent discontinuation from study treatment for any reason.
Placebo + Gemcitabine	Participants received placebo orally once daily in combination with 1000 mg/m^2 of gemcitabine given as IV infusion over 30 min. In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until PD, unacceptable toxicity, or permanent discontinuation from study treatment for any reason.

Measured Values

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Number of Participants Analyzed	77	77

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Number of Participants With an Investigator-assessed Best Response, With or Without Confirmation, of Complete Response (CR) or Partial Response (PR) [units: participants]		
CR	1	0
PR	16	14

4. Secondary Outcome Measure:

Measure Title	Investigator-Assessed Duration of Response
Measure Description	Duration of response is defined, for the subset of participants with a CR or PR, as the time from the first documented evidence of CR or PR until the first documented disease progression or death due to any cause. CR is defined as the disappearance of all target and non-target lesions. Any pathological lymph nodes must be <10 mm in the short axis. PR is defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g., percent change from baseline). PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start).
Time Frame	From the first documented CR or PR until disease progression or death due to any cause or until the data cutoff of 17-April-2012 (up to 13 months)
Safety Issue?	No

Analysis Population Description

MD Population. Duration of response was assessed for only those participants with a CR or PR.

Reporting Groups

	Description
Trametinib + Gemcitabine	Participants received 2 milligrams (mg) trametinib orally once daily in combination with 1000 mg/m^2 of gemcitabine given as intravenous (IV) infusion over 30 minutes (min). In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until progressive disease (PD), unacceptable toxicity, or permanent discontinuation from study treatment for any reason.
Placebo + Gemcitabine	Participants received placebo orally once daily in combination with 1000 mg/m^2 of gemcitabine given as IV infusion over 30 min. In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until PD, unacceptable toxicity, or permanent discontinuation from study treatment for any reason.

Measured Values

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Number of Participants Analyzed	17	14
Investigator-Assessed Duration of Response [units: Weeks] Median (95% Confidence Interval)	23.9 (9.0 to 28.9)	16.1 (8.3 to NA) [1]

[1] There were too few events to provide an estimable upper limit of the confidence interval.

5. Secondary Outcome Measure:

Measure Title	Number of Participants With Any Adverse Event (AE) and Any Serious Adverse Event (SAE)
Measure Description	An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered to be related to the medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, or results in a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury. Per protocol other events were considered SAEs like symptomatic left ventricular ejection fraction (LVEF) decreases or cases of central serous retinopathy (CSR) or retinal vein occlusion (RVO). AE and SAE data were collected from the start of the first dose of study treatment and continued until 28 days following discontinuation of the study treatment or death. Refer to the general AE/SAE module for a complete list of AEs and SAEs.
Time Frame	From the start of the first dose of study treatment until 28 days following discontinuation of the study treatment or until the data cutoff of 15-March-2013 (up to 21 months)
Safety Issue?	No

Analysis Population Description

Safety Population: all participants who were randomized and took at least one dose of study medication. This population was based on the actual treatment received, if it differed from that to which the participant was randomized.

Reporting Groups

	Description
Trametinib + Gemcitabine	Participants received 2 milligrams (mg) trametinib orally once daily in combination with 1000 mg/m^2 of gemcitabine given as intravenous (IV) infusion over 30 minutes (min). In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until progressive disease (PD), unacceptable toxicity, or permanent discontinuation from study treatment for any reason.
Placebo + Gemcitabine	Participants received placebo orally once daily in combination with 1000 mg/m^2 of gemcitabine given as IV infusion over 30 min. In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until PD, unacceptable toxicity, or permanent discontinuation from study treatment for any reason.

Measured Values

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Number of Participants Analyzed	80	80
Number of Participants With Any Adverse Event (AE) and Any Serious Adverse Event (SAE) [units: participants]		
Any AE	80	80
SAE	42	37

6. Secondary Outcome Measure:

Measure Title	Number of Participants (Par.) With a Worst-case Change to Grade 3 or Grade 4 From Baseline Grade in Chemistry Parameters
Measure Description	A grading (severity) scale is provided for each laboratory toxicity. Grade refers to the severity of the toxicity. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 displays Grades 1 through 5 based on the general guideline: Grade 1, mild toxicity; Grade 2, moderate toxicity; Grade 3, severe toxicity; Grade 4, life-threatening or disabling toxicity; Grade 5, death related to toxicity.
Time Frame	From the start of the first dose of study treatment until 28 days following discontinuation of the study treatment or until the data cutoff of 17-April-2012 (up to 17 months)
Safety Issue?	No

Analysis Population Description

Safety Population. Only those par. with laboratory values for worst-case on therapy were analyzed. The same par. were not necessarily analyzed for each laboratory parameter; thus, the number of par. analyzed reflects all par. in the Safety Population. The number of par. analyzed for a particular parameter is included in the parameter title.

Reporting Groups

	Description
Trametinib + Gemcitabine	Participants received 2 milligrams (mg) trametinib orally once daily in combination with 1000 mg/m^2 of gemcitabine given as intravenous (IV) infusion over 30 minutes (min). In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until progressive disease (PD), unacceptable toxicity, or permanent discontinuation from study treatment for any reason.
Placebo + Gemcitabine	Participants received placebo orally once daily in combination with

	Description
	1000 mg/m^2 of gemcitabine given as IV infusion over 30 min. In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until PD, unacceptable toxicity, or permanent discontinuation from study treatment for any reason.

Measured Values

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Number of Participants Analyzed	80	80
Number of Participants (Par.) With a Worst-case Change to Grade 3 or Grade 4 From Baseline Grade in Chemistry Parameters [units: participants]		
Albumin, Grade 3, n=73, 73	7	4
Albumin, Grade 4, n=73, 73	0	0
Alkaline Phosphatase, Grade 3, n=74, 73	7	4
Alkaline Phosphatase, Grade 4, n=74, 73	0	0
Alanine Amino Transferase, Grade 3, n=74, 73	7	7
Alanine Amino Transferase, Grade 4, n=74, 73	0	0
Aspartate Aminotransferase, Grade 3,	6	7

	Trametinib + Gemcitabine	Placebo + Gemcitabine
n=73, 72		
Aspartate Aminotransferase, Grade 4, n=73, 72	0	0
Total Bilirubin, Grade 3, n=74, 73	1	7
Total Bilirubin, Grade 4, n=74, 73	0	1
Calcium (hypercalcemia), Grade 3, n=73, 73	1	1
Calcium (hypercalcemia), Grade 4, n=73, 73	0	0
Calcium (hypocalcemia), Grade 3, n=73, 73	1	2
Calcium (hypocalcemia), Grade 4, n=73, 73	0	0
Creatinine, Grade 3, n=74, 75	0	0
Creatinine, Grade 4, n=74, 75	1	0
Glucose (hyperglycemia), Grade 3, n=74, 72	9	10
Glucose (hyperglycemia), Grade 4, n=74, 72	0	1
Glucose (hypoglycemia), Grade 3, n=74, 72	0	0
Glucose (hypoglycemia), Grade 4, n=74, 72	1	0
Potassium (hyperkalemia), Grade 3,	2	1

	Trametinib + Gemcitabine	Placebo + Gemcitabine
n=74, 72		
Potassium (hyperkalemia), Grade 4, n=74, 72	0	0
Potassium (hypokalemia), Grade 3, n=74, 72	4	1
Potassium (hypokalemia), Grade 4, n=74, 72	0	0
Sodium (hyponatremia), Grade 3, n=74, 74	5	3
Sodium (hyponatremia), Grade 4, n=74, 74	2	0

7. Secondary Outcome Measure:

Measure Title	Number of Participants With Change From Baseline Increase to Grade 3/Grade 4 in Lab Hematology Test Measurements
Measure Description	A grading (severity) scale is provided for each laboratory toxicity. Grade refers to the severity of the toxicity. The CTCAE version 3.0 displays Grades 1 through 5, with unique clinical descriptions of the severity for each toxicity based on the general guideline: Grade 1, mild toxicity; Grade 2, moderate toxicity; Grade 3, severe toxicity; Grade 4, life-threatening or disabling toxicity; Grade 5, death related to toxicity.
Time Frame	From the start of the first dose of study treatment until 28 days following discontinuation of the study treatment or until the data cutoff of 17-April-2012 (up to 17 months)

Safety Issue?	No

Analysis Population Description

Safety Population. Only those par. with laboratory values for worst-case on therapy were analyzed. The same par. were not necessarily analyzed for each laboratory parameter; thus, the number of par. analyzed reflects all par. in the Safety Population. The number of par. analyzed for a particular parameter is included in the parameter title.

Reporting Groups

	Description
Trametinib + Gemcitabine	Participants received 2 milligrams (mg) trametinib orally once daily in combination with 1000 mg/m^2 of gemcitabine given as intravenous (IV) infusion over 30 minutes (min). In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until progressive disease (PD), unacceptable toxicity, or permanent discontinuation from study treatment for any reason.
Placebo + Gemcitabine	Participants received placebo orally once daily in combination with 1000 mg/m^2 of gemcitabine given as IV infusion over 30 min. In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until PD, unacceptable toxicity, or permanent discontinuation from study treatment for any reason.

Measured Values

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Number of Participants Analyzed	80	80
Number of Participants With Change From Baseline Increase to Grade 3/Grade 4 in		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Lab Hematology Test Measurements [units: participants]		
Hemoglobin (Increased), Grade 3, n=80, 79	3	0
Hemoglobin (Increased), Grade 4, n=80, 79	0	0
Hemoglobin (Anemia), Grade 3, n=80, 79	24	13
Hemoglobin (Anemia), Grade 4, n=80, 79	0	0
Lymphocytes (Increased), Grade 3, n=80, 79	1	0
Lymphocytes (Increased), Grade 4, n=80, 79	0	0
Lymphocytes (Decreased), Grade 3, n=80, 79	9	12
Lymphocytes (Decreased), Grade 4, n=80, 79	3	6
Absolute Neutrophil Count, Grade 3, n=80, 79	23	20
Absolute Neutrophil Count, Grade 4, n=80, 79	7	10
Platelet count, Grade 3, n=80, 79	11	10
Platelet count, Grade 4, n=80, 79	1	4
White Blood Cell count, Grade 3, n=80,	15	14

	Trametinib + Gemcitabine	Placebo + Gemcitabine
79		
White Blood Cell count, Grade 4, n=80, 79	1	4

Reported Adverse Events

Reporting Groups

	Description
Trametinib + Gemcitabine	Participants received 2 milligrams (mg) trametinib orally once daily in combination with 1000 mg/m^2 of gemcitabine given as intravenous (IV) infusion over 30 minutes (min). In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until progressive disease (PD), unacceptable toxicity, or permanent discontinuation from study treatment for any reason.
Placebo + Gemcitabine	Participants received placebo orally once daily in combination with 1000 mg/m^2 of gemcitabine given as IV infusion over 30 min. In the first cycle, gemcitabine was infused weekly for 7 weeks followed by a week of rest from treatment and then subsequent cycles on Day 1, 8, and 15 followed by 1 week of rest from treatment for each 28-day treatment cycle until PD, unacceptable toxicity, or permanent discontinuation from study treatment for any reason.

Time Frame

Serious adverse events (SAEs) and non-serious AEs were collected from the time the first dose of study treatment was administered until 28 days following discontinuation of study treatment or until the data cutoff of 15-March-2013 (up to 21 months).

Additional Description

SAEs and non-serious AEs were collected in the Safety Population, comprised of all participants who were randomized and took at least one dose of study medication. This population was based on the actual treatment received, if it differed from that to which the participant was randomized.

Serious Adverse Events

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Total # participants affected/at risk	42/80 (52.5%)	37/80 (46.25%)
Blood and lymphatic system disorders		
Anaemia †[A]		
# participants affected/at risk	3/80 (3.75%)	2/80 (2.5%)
# events		
Febrile neutropenia †[A]		
# participants affected/at risk	1/80 (1.25%)	1/80 (1.25%)
# events		
Leukopenia †[A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Pancytopenia †[A]		
# participants affected/at risk	1/80 (1.25%)	1/80 (1.25%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
# events		
Thrombocytopenia † [A]		
# participants affected/at risk	1/80 (1.25%)	1/80 (1.25%)
# events		
Cardiac disorders		
Angina pectoris † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Atrial fibrillation † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Cardiac failure congestive † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Tachycardia † [A]		
# participants affected/at risk	0/80 (0%)	2/80 (2.5%)
# events		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Ear and labyrinth disorders		
Ear pain †[A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Tympanic membrane perforation †[A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Gastrointestinal disorders		
Abdominal pain †[A]		
# participants affected/at risk	4/80 (5%)	1/80 (1.25%)
# events		
Abdominal pain lower †[A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Abdominal pain upper †[A]		
# participants affected/at	0/80 (0%)	1/80 (1.25%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
risk		
# events		
Aphthous stomatitis †[A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Constipation †[A]		
# participants affected/at risk	2/80 (2.5%)	0/80 (0%)
# events		
Diarrhoea †[A]		
# participants affected/at risk	2/80 (2.5%)	0/80 (0%)
# events		
Duodenal ulcer haemorrhage †[A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Enteritis †[A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Gastrointestinal haemorrhage †[A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Ileus †[A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Intestinal obstruction †[A]		
# participants affected/at risk	2/80 (2.5%)	1/80 (1.25%)
# events		
Melaena †[A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Nausea †[A]		
# participants affected/at risk	3/80 (3.75%)	1/80 (1.25%)
# events		
Obstruction gastric †[A]		
# participants affected/at	1/80 (1.25%)	2/80 (2.5%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
risk		
# events		
Oesophageal ulcer † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Oesophagitis † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Small intestinal obstruction † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Subileus † [A]		
# participants affected/at risk	1/80 (1.25%)	1/80 (1.25%)
# events		
Vomiting † [A]		
# participants affected/at risk	3/80 (3.75%)	2/80 (2.5%)
# events		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
General disorders		
Asthenia † [A]		
# participants affected/at risk	1/80 (1.25%)	1/80 (1.25%)
# events		
Device occlusion † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Fatigue † [A]		
# participants affected/at risk	0/80 (0%)	2/80 (2.5%)
# events		
Mucosal inflammation † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Pyrexia † [A]		
# participants affected/at risk	8/80 (10%)	2/80 (2.5%)
# events		
Stent malfunction † [A]		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Hepatobiliary disorders		
Bile duct obstruction † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Cholangitis † [A]		
# participants affected/at risk	1/80 (1.25%)	2/80 (2.5%)
# events		
Cholestasis † [A]		
# participants affected/at risk	0/80 (0%)	2/80 (2.5%)
# events		
Jaundice † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Jaundice cholestatic † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
# events		
Infections and infestations		
Abdominal sepsis † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Biliary tract infection † [A]		
# participants affected/at risk	2/80 (2.5%)	0/80 (0%)
# events		
Bronchitis † [A]		
# participants affected/at risk	1/80 (1.25%)	1/80 (1.25%)
# events		
Cellulitis † [A]		
# participants affected/at risk	0/80 (0%)	3/80 (3.75%)
# events		
Clostridium difficile colitis † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
# events		
Device related infection † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Diverticulitis † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Enterococcal bacteraemia † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Epstein-Barr virus infection † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Fungal infection † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Liver abscess † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Lung infection † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Otitis media † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Parotitis † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Pneumonia † [A]		
# participants affected/at risk	5/80 (6.25%)	2/80 (2.5%)
# events		
Postoperative abscess † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
# events		
Respiratory tract infection † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Sepsis † [A]		
# participants affected/at risk	3/80 (3.75%)	2/80 (2.5%)
# events		
Sinusitis † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Tonsillitis † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Urinary tract infection † [A]		
# participants affected/at risk	1/80 (1.25%)	1/80 (1.25%)
# events		
Injury, poisoning and		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
procedural complications		
Wound dehiscence † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Investigations		
Alanine aminotransferase increased † [A]		
# participants affected/at risk	4/80 (5%)	0/80 (0%)
# events		
Aspartate aminotransferase increased † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Blood bilirubin increased † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Blood creatinine increased † [A]		
# participants affected/at	0/80 (0%)	1/80 (1.25%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
risk		
# events		
Hepatic enzyme increased † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Neutrophil count decreased † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Metabolism and nutrition disorders		
Dehydration † [A]		
# participants affected/at risk	4/80 (5%)	3/80 (3.75%)
# events		
Hypoalbuminaemia † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Hypoglycaemia † [A]		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Musculoskeletal and connective tissue disorders		
Back pain †[A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Muscular weakness †[A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Colon cancer †[A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Nervous system		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
disorders		
Cerebral ischaemia † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Depressed level of consciousness † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease † [A]		
# participants affected/at risk	0/80 (0%)	1/80 (1.25%)
# events		
Dyspnoea † [A]		
# participants affected/at risk	4/80 (5%)	2/80 (2.5%)
# events		
Hypoxia † [A]		
# participants affected/at	1/80 (1.25%)	0/80 (0%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
risk		
# events		
Interstitial lung disease †[A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Oropharyngeal pain †[A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		
Pneumonitis †[A]		
# participants affected/at risk	2/80 (2.5%)	1/80 (1.25%)
# events		
Pulmonary embolism †[A]		
# participants affected/at risk	1/80 (1.25%)	2/80 (2.5%)
# events		
Respiratory failure †[A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Vascular disorders		
Deep vein thrombosis † [A]		
# participants affected/at risk	1/80 (1.25%)	3/80 (3.75%)
# events		
Thrombosis † [A]		
# participants affected/at risk	1/80 (1.25%)	0/80 (0%)
# events		

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Total # participants affected/at risk	80/80 (100%)	80/80 (100%)
Blood and lymphatic system disorders		
Anaemia † [A]		
# participants affected/at risk	37/80 (46.25%)	34/80 (42.5%)
# events		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Leukopenia † [A]		
# participants affected/at risk	9/80 (11.25%)	8/80 (10%)
# events		
Lymphopenia † [A]		
# participants affected/at risk	1/80 (1.25%)	5/80 (6.25%)
# events		
Neutropenia † [A]		
# participants affected/at risk	28/80 (35%)	22/80 (27.5%)
# events		
Thrombocytopenia † [A]		
# participants affected/at risk	32/80 (40%)	22/80 (27.5%)
# events		
Eye disorders		
Periorbital oedema † [A]		
# participants affected/at risk	4/80 (5%)	0/80 (0%)
# events		
Vision blurred † [A]		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
# participants affected/at risk	7/80 (8.75%)	10/80 (12.5%)
# events		
Gastrointestinal disorders		
Abdominal distension †[A]		
# participants affected/at risk	7/80 (8.75%)	8/80 (10%)
# events		
Abdominal pain †[A]		
# participants affected/at risk	15/80 (18.75%)	14/80 (17.5%)
# events		
Abdominal pain upper †[A]		
# participants affected/at risk	9/80 (11.25%)	9/80 (11.25%)
# events		
Ascites †[A]		
# participants affected/at risk	6/80 (7.5%)	8/80 (10%)
# events		
Constipation †[A]		
# participants affected/at	23/80	20/80 (25%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
risk	(28.75%)	
# events		
Diarrhoea † [A]		
# participants affected/at risk	43/80 (53.75%)	22/80 (27.5%)
# events		
Dry mouth † [A]		
# participants affected/at risk	4/80 (5%)	5/80 (6.25%)
# events		
Dyspepsia † [A]		
# participants affected/at risk	8/80 (10%)	4/80 (5%)
# events		
Flatulence † [A]		
# participants affected/at risk	3/80 (3.75%)	7/80 (8.75%)
# events		
Gingival bleeding † [A]		
# participants affected/at risk	4/80 (5%)	0/80 (0%)
# events		
Haemorrhoids † [A]		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
# participants affected/at risk	4/80 (5%)	0/80 (0%)
# events		
Nausea †[A]		
# participants affected/at risk	43/80 (53.75%)	41/80 (51.25%)
# events		
Stomatitis †[A]		
# participants affected/at risk	29/80 (36.25%)	6/80 (7.5%)
# events		
Vomiting †[A]		
# participants affected/at risk	38/80 (47.5%)	36/80 (45%)
# events		
General disorders		
Asthenia †[A]		
# participants affected/at risk	9/80 (11.25%)	13/80 (16.25%)
# events		
Chills †[A]		
# participants affected/at risk	8/80 (10%)	9/80 (11.25%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
# events		
Fatigue † [A]		
# participants affected/at risk	30/80 (37.5%)	30/80 (37.5%)
# events		
Influenza like illness † [A]		
# participants affected/at risk	1/80 (1.25%)	7/80 (8.75%)
# events		
Mucosal inflammation † [A]		
# participants affected/at risk	9/80 (11.25%)	4/80 (5%)
# events		
Oedema peripheral † [A]		
# participants affected/at risk	30/80 (37.5%)	25/80 (31.25%)
# events		
Pain † [A]		
# participants affected/at risk	4/80 (5%)	3/80 (3.75%)
# events		
Pyrexia † [A]		
# participants affected/at	27/80	26/80 (32.5%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
risk	(33.75%)	
# events		
Infections and infestations		
Cellulitis † [A]		
# participants affected/at risk	1/80 (1.25%)	5/80 (6.25%)
# events		
Nasopharyngitis † [A]		
# participants affected/at risk	4/80 (5%)	3/80 (3.75%)
# events		
Paronychia † [A]		
# participants affected/at risk	9/80 (11.25%)	0/80 (0%)
# events		
Urinary tract infection † [A]		
# participants affected/at risk	2/80 (2.5%)	7/80 (8.75%)
# events		
Investigations		
Alanine aminotransferase increased † [A]		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
# participants affected/at risk	12/80 (15%)	16/80 (20%)
# events		
Aspartate aminotransferase increased † [A]		
# participants affected/at risk	11/80 (13.75%)	12/80 (15%)
# events		
Blood alkaline phosphatase increased † [A]		
# participants affected/at risk	3/80 (3.75%)	11/80 (13.75%)
# events		
Blood bilirubin increased † [A]		
# participants affected/at risk	1/80 (1.25%)	4/80 (5%)
# events		
Blood creatinine increased † [A]		
# participants affected/at risk	5/80 (6.25%)	0/80 (0%)
# events		
Ejection fraction decreased † [A]		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
# participants affected/at risk	7/80 (8.75%)	2/80 (2.5%)
# events		
Haemoglobin decreased † [A]		
# participants affected/at risk	5/80 (6.25%)	7/80 (8.75%)
# events		
Neutrophil count decreased † [A]		
# participants affected/at risk	9/80 (11.25%)	14/80 (17.5%)
# events		
Platelet count decreased † [A]		
# participants affected/at risk	22/80 (27.5%)	16/80 (20%)
# events		
Weight decreased † [A]		
# participants affected/at risk	9/80 (11.25%)	9/80 (11.25%)
# events		
White blood cell count decreased † [A]		
# participants affected/at risk	0/80 (0%)	8/80 (10%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
# events		
Metabolism and nutrition disorders		
Decreased appetite †[A]		
# participants affected/at risk	25/80 (31.25%)	25/80 (31.25%)
# events		
Dehydration †[A]		
# participants affected/at risk	5/80 (6.25%)	4/80 (5%)
# events		
Hyperglycaemia †[A]		
# participants affected/at risk	1/80 (1.25%)	5/80 (6.25%)
# events		
Hypoalbuminaemia †[A]		
# participants affected/at risk	9/80 (11.25%)	4/80 (5%)
# events		
Hypokalaemia †[A]		
# participants affected/at risk	7/80 (8.75%)	7/80 (8.75%)
# events		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
Musculoskeletal and connective tissue disorders		
Back pain †[A]		
# participants affected/at risk	5/80 (6.25%)	8/80 (10%)
# events		
Myalgia †[A]		
# participants affected/at risk	5/80 (6.25%)	3/80 (3.75%)
# events		
Pain in extremity †[A]		
# participants affected/at risk	2/80 (2.5%)	4/80 (5%)
# events		
Nervous system disorders		
Dizziness †[A]		
# participants affected/at risk	12/80 (15%)	11/80 (13.75%)
# events		
Dysgeusia †[A]		
# participants affected/at	7/80 (8.75%)	7/80 (8.75%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
risk		
# events		
Headache †[A]		
# participants affected/at risk	6/80 (7.5%)	10/80 (12.5%)
# events		
Tremor †[A]		
# participants affected/at risk	2/80 (2.5%)	6/80 (7.5%)
# events		
Psychiatric disorders		
Anxiety †[A]		
# participants affected/at risk	4/80 (5%)	5/80 (6.25%)
# events		
Depression †[A]		
# participants affected/at risk	5/80 (6.25%)	9/80 (11.25%)
# events		
Insomnia †[A]		
# participants affected/at risk	8/80 (10%)	3/80 (3.75%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
# events		
Renal and urinary disorders		
Dysuria † [A]		
# participants affected/at risk	4/80 (5%)	3/80 (3.75%)
# events		
Respiratory, thoracic and mediastinal disorders		
Cough † [A]		
# participants affected/at risk	9/80 (11.25%)	6/80 (7.5%)
# events		
Dyspnoea † [A]		
# participants affected/at risk	13/80 (16.25%)	12/80 (15%)
# events		
Dyspnoea exertional † [A]		
# participants affected/at risk	4/80 (5%)	2/80 (2.5%)
# events		
Epistaxis † [A]		

	Trametinib + Gemcitabine	Placebo + Gemcitabine
# participants affected/at risk	5/80 (6.25%)	2/80 (2.5%)
# events		
Oropharyngeal pain †[A]		
# participants affected/at risk	6/80 (7.5%)	2/80 (2.5%)
# events		
Skin and subcutaneous tissue disorders		
Acne †[A]		
# participants affected/at risk	6/80 (7.5%)	1/80 (1.25%)
# events		
Alopecia †[A]		
# participants affected/at risk	14/80 (17.5%)	10/80 (12.5%)
# events		
Dermatitis acneiform †[A]		
# participants affected/at risk	12/80 (15%)	4/80 (5%)
# events		
Pruritus †[A]		
# participants affected/at	4/80 (5%)	4/80 (5%)

	Trametinib + Gemcitabine	Placebo + Gemcitabine
risk		
# events		
Rash † [A]		
# participants affected/at risk	38/80 (47.5%)	20/80 (25%)
# events		
Vascular disorders		
Deep vein thrombosis † [A]		
# participants affected/at risk	6/80 (7.5%)	4/80 (5%)
# events		
Hypertension † [A]		
# participants affected/at risk	2/80 (2.5%)	6/80 (7.5%)
# events		
Hypotension † [A]		
# participants affected/at risk	4/80 (5%)	6/80 (7.5%)
# events		

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

GSK agreements may vary with individual investigators, but will not prohibit any investigator from publishing. GSK supports the publication of results from all centers of a multi-center trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

Limitations and Caveats:

Results Point of Contact:

Name/Official Title: GSK Response Center
Organization: GlaxoSmithKline
Phone: 866-435-7343
Email: