ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 07/23/2014

A Study of Avastin (Bevacizumab) Added to a Chemotherapeutic Regimen in Patients With Metastatic Pancreatic Cancer

This study has been completed.

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT01214720

Purpose

This study will evaluate efficacy, safety and tolerability of Avastin versus placebo added to a chemotherapeutic regimen in patients with metastatic pancreatic cancer. The anticipated time of study treatment is until confirmed evidence of disease progression, and the target sample size is 500+ individuals.

Condition	Intervention	Phase
Pancreatic Cancer	Drug: bevacizumab [Avastin]	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind, Randomized, Safety/Efficacy Study
Official Title: A Randomized, Double-blind Study of the Effect of Avastin Plus Gemcitabine and Erlotinib Compared With Placebo Plus Gemcitabine and Erlotinib on Overall Survival in Patients With Metastatic Pancreatic Cancer

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Duration of Overall Survival - Percentage of Participants With an Event [Time Frame: Randomization, Weeks 1-8 of Cycle 1, Weeks 1-3 of consecutive cycles, 28 days and 3 months after lst treatment, and every 3 months for up to 18 months from last participant randomized] [Designated as safety issue: No]

Duration of overall survival (OS) was defined as the time between date of randomization and date of death due to any cause. Participants without an event were censored at the date last known to be alive. Participants who were randomized but not exposed to study drug and had no further follow up were censored at the date of randomization.

- Duration of Overall Survival - Time to Event [Time Frame: Randomization, Weeks 1-8 of Cycle 1, Weeks 1-3 of consecutive cycles, 28 days and 3 months after lst treatment, and every 3 months for up to 18 months from last participant randomized] [Designated as safety issue: No]

  Duration of OS was defined as the time between date of randomization and date of death due to any cause. Participants without an event were censored at the date last known to be alive. Participants who were randomized but not exposed to study drug and had no further follow up were censored at the date of randomization. Median duration of survival was estimated using the Kaplan-Meier method.

Secondary Outcome Measures:

- Clinical Benefit Response (CBR) [Time Frame: Randomization, Weeks 1-8 of Cycle 1, Weeks 1-3 of consecutive cycles, 28 days and 3 months after lst treatment, and every 3 months for up to 18 months from last participant randomized] [Designated as safety issue: No]
- Progression-Free Survival (PFS) - Percentage of Participants With an Event [Time Frame: Screening, Weeks 8, 16, 24, 32, 40, and every 12 weeks thereafter or until confirmed evidence of disease progression] [Designated as safety issue: No]

  PFS was defined as the time between the date of randomization and the date of documented progressive disease (PD) defined according to modified Response Evaluation Criteria in Solid Tumors (RECIST) evaluation, or date of death due to any cause. PD was defined as at least a 20 percent (%) increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum (LD) recorded since the treatment started. Participants without an event were censored at the date of last follow up for progression, or date of last available tumor assessment if no further follow up assessment for progression was performed. Participants who were randomized but not exposed to study drug and had no further follow up were censored at the date of randomization.
- Progression-Free Survival (PFS) - Time to Event [Time Frame: Screening, Weeks 8, 16, 24, 32, 40, and every 12 weeks thereafter or until confirmed evidence of disease progression] [Designated as safety issue: No]

  PFS was defined as the time between the date of randomization and the date of documented PD (per RECIST), or date of death due to any cause. Data for participants without an event were censored at the date of last follow up for progression, or date of last available tumor assessment if no further follow up assessment for progression was performed. Participants who were randomized but not exposed to study drug and had no further follow up were censored at the date of randomization. Median PFS was estimated using the Kaplan-Meier method.
- Percentage of Participants With Complete Response (CR), Partial Response (PR), or Stable Disease (SD) at First Postbaseline Tumor Assessment [Time Frame: Baseline and Week 8] [Designated as safety issue: No]

  Percentage of participants with CR, PR, or SD according to modified RECIST evaluation at the first postbaseline tumor assessment. CR equaled (=) complete disappearance of all target lesions and non-target disease, with normalization of tumor marker level. PR is greater than or equal to (≥) a 30% decrease of the sum of the LD of all target lesions as referenced to the baseline sum LD of all target lesions. Persistence of one or more non-target lesions(s) and/or maintenance of tumor marker level above normal limits. SD=neither sufficient shrinkage of target lesions to qualify for PR nor sufficient increase to qualify for PD with persistence of one or more non-target lesions(s) and/or maintenance of tumor marker level above normal limits.
- Bevacizumab Concentration in the Presence of Gemcitabine and Erlotinib [Time Frame: Weeks 1, 3, 5, 7, and 9] [Designated as safety issue: No]

  Blood samples were collected from a subgroup of participants, in selected centers for the determination of bevacizumab serum concentration before the first bevacizumab/placebo exposure (Week 1) and at Weeks 3, 5, 7, and 9. Each time blood samples were collected just (preferably within 1 hour) before the start of the study treatment.

Enrollment: 607
Study Start Date: July 2005
Primary Completion Date: October 2008
Study Completion Date: October 2008

Arms	Assigned Interventions
Experimental: 1	Drug: bevacizumab [Avastin] Intervenous repeating dose

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- adult patients, >=18 years of age;
- metastatic pancreatic cancer (adenocarcinoma);
- good liver, kidney, and bone marrow function.

Exclusion Criteria:

- previous systemic treatment for metastatic pancreatic cancer;
- pregnant or lactating females;
- fertile men, or women of childbearing potential, not using adequate contraception;
- major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study treatment start;
- current or recent treatment (within 30 days prior to starting study treatment) with another investigational drug, or participation in another investigational study.

Contacts and Locations

Locations

Australia

Adelaide, Australia, 5011
Camperdown, Australia, 2050
Footscray, Australia, 3011
Heidelberg, Australia, 3084
Kurralta Park, Australia, 5037
Melbourne, Australia, 3128
Melbourne, Australia, 3002
St. Leonards, Australia, 2065
Sydney, Australia, 2031
Sydney, Australia, 2217

Austria

Graz, Austria, 8036
Innsbruck, Austria, 6020

Salzburg, Austria, 5020
Wien, Austria, 1090
Wien, Austria, 1090

Belgium
Antwerpen, Belgium, 2020
Bruxelles, Belgium, 1200
Bruxelles, Belgium, 1070
Leuven, Belgium, 3000
Wilrijk, Belgium, 2610

Canada, Alberta
Edmonton, Alberta, Canada, T6G 1Z2

Canada, British Columbia
Vancouver, British Columbia, Canada, V5Z 4E6

Canada, Ontario
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Toronto, Ontario, Canada, M5G 2M9

Canada, Quebec
Montreal, Quebec, Canada, H2W 1S6
Quebec City, Quebec, Canada, G1R 2J6

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Beijing, China, 100036
Shanghai, China, 200433

Czech Republic
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Hradec Kralove, Czech Republic, 500 05

Finland
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Bordeaux, France, 33000
Boulogne-billancourt, France, 92104
Clichy, France, 92118
Limoges, France, 87042
Marseille, France, 13273
Paris, France, 75674
Paris, France, 75679
Rouen, France, 76031
Saint Herblain, France, 44805
Strasbourg, France, 67091

Germany
Berlin, Germany, 13353
Bochum, Germany, 44892
Bonn, Germany, 53127
Halle, Germany, 06120

Hamburg, Germany, 20249
Heidelberg, Germany, 69120
Leipzig, Germany, 04103
Magdeburg, Germany, 39130
Mainz, Germany, 55101
Muenchen, Germany, 81377
Mönchengladbach, Germany, 41061
Trier, Germany, 54290

Israel

Kfar Saba, Israel, 44281
Petach Tikva, Israel, 49100
Rehovot, Israel, 76100
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Italy

Bergamo, Italy, 24128
Bologna, Italy, 40138
Brescia, Italy, 25124
Chieti, Italy, 66100
Genova, Italy, 16132
Napoli, Italy, 80131
Orbassano, Italy, 10043
Parma, Italy, 43100
San Giovanni Rotondo, Italy, 71013

Netherlands

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New Zealand

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Peru

Lima, Peru, 11
Lima, Peru, 18

Poland

Gliwice, Poland, 44-101
Lublin, Poland, 20-081
Szczecin, Poland, 71-730
Wroclaw, Poland, 53-413

Singapore

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Singapore, Singapore, 119228

South Africa

Cape Town, South Africa, 7506
Pretoria, South Africa, 0001

Spain

Alicante, Spain, 03010
Barcelona, Spain, 08041

Barcelona, Spain, 08035
Barcelona, Spain, 08907
Barcelona, Spain, 08036
Cordoba, Spain, 14004
Elche, Spain, 03203
Madrid, Spain, 28040
Santander, Spain, 39008
Valencia, Spain, 46009
Valencia, Spain, 46010

Sweden

Stockholm, Sweden, 11883

Taiwan

Kueishan, Taiwan, 333
Taipei, Taiwan, 00112

United Kingdom

Glasgow, United Kingdom, G11 6NT
Leicester, United Kingdom, LE1 5WW
London, United Kingdom, SW3 6JJ
Manchester, United Kingdom, M20 4BX
Northwood, United Kingdom, HA6 2RN
Sutton, United Kingdom, SM2 5PT
Truro, United Kingdom, TR1 3LJ

Investigators

Study Director:	Clinical Trials	Hoffmann-La Roche

More Information

Responsible Party:	Hoffmann-La Roche
Study ID Numbers:	BO17706
Health Authority:	France: Ministry of Health

Participant Flow

Reporting Groups

	Description
Bevacizumab + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received bevacizumab 5 milligrams per kilogram (mg/kg) intravenously (IV) on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg per square meter (mg/m^2) IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, orally (PO), once daily (QD) for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.
Placebo + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received placebo IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received placebo IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.

Overall Study

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
Started	306	301
Completed	221 [1]	233 [1]
Not Completed	85	68
Alive and still on treatment	34	18
Alive and in follow-up	45	48
Lost to Follow-up	6	2

[1] Indicates patients who had died at the time of the data cut-off

Baseline Characteristics

Analysis Population Description

Intent-to-Treat (ITT) Population: All 607 participants randomized to treatment.

Reporting Groups

	Description
Bevacizumab + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.
Placebo + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received placebo IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received placebo IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/ capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.

Baseline Measures

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib	Total
Number of Participants	306	301	607
Age, Continuous [units: years] Mean (Standard Deviation)	61.5 (10.36)	61.0 (10.03)	61.2 (10.19)
Gender, Male/Female [units: participants]			
Female	132	113	245
Male	174	188	362

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Duration of Overall Survival - Percentage of Participants With an Event

Measure Description	Duration of overall survival (OS) was defined as the time between date of randomization and date of death due to any cause. Participants without an event were censored at the date last known to be alive. Participants who were randomized but not exposed to study drug and had no further follow up were censored at the date of randomization.
Time Frame	Randomization, Weeks 1-8 of Cycle 1, Weeks 1-3 of consecutive cycles, 28 days and 3 months after lst treatment, and every 3 months for up to 18 months from last participant randomized
Safety Issue?	No

Analysis Population Description

ITT population.

Reporting Groups

	Description
Bevacizumab + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.
Placebo + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received placebo IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received placebo IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/ capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.

Measured Values

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
Number of Participants Analyzed	306	301
Duration of Overall Survival - Percentage of Participants With an Event [units: percentage of participants]	72.2	77.4

2. Primary Outcome Measure:

Measure Title	Duration of Overall Survival - Time to Event

Measure Description	Duration of OS was defined as the time between date of randomization and date of death due to any cause. Participants without an event were censored at the date last known to be alive. Participants who were randomized but not exposed to study drug and had no further follow up were censored at the date of randomization. Median duration of survival was estimated using the Kaplan-Meier method.
Time Frame	Randomization, Weeks 1-8 of Cycle 1, Weeks 1-3 of consecutive cycles, 28 days and 3 months after lst treatment, and every 3 months for up to 18 months from last participant randomized
Safety Issue?	No

Analysis Population Description

ITT Population.

Reporting Groups

	Description
Bevacizumab + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.
Placebo + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received placebo IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received placebo IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/ capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.

Measured Values

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
Number of Participants Analyzed	306	301
Duration of Overall Survival - Time to Event [units: months] Median (95% Confidence Interval)	7.1 (6.4 to 7.8)	6.0 (5.5 to 6.7)

Statistical Analysis 1 for Duration of Overall Survival - Time to Event

Statistical Analysis Overview	Comparison Groups	Bevacizumab + Gemcitabine + Erlotinib, Placebo + Gemcitabine + Erlotinib
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2087
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.89
	Confidence Interval	(2-Sided) 95% 0.74 to 1.07
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Clinical Benefit Response (CBR)
Measure Description	
Time Frame	Randomization, Weeks 1-8 of Cycle 1, Weeks 1-3 of consecutive cycles, 28 days and 3 months after lst treatment, and every 3 months for up to 18 months from last participant randomized
Safety Issue?	No

Analysis Population Description

The analysis of the CBR was dependent on the calculation of analgesic therapy (AT); this calculation relies on established conversion factors for different morphine derivatives (MD). Many MD utilized by participants do not have well-established conversion factors, yielding uninterpretable results. Therefore, CBR was not analyzed in this study.

Reporting Groups

	Description
Bevacizumab + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.
Placebo + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received placebo IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received placebo IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/ capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.

Measured Values

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

4. Secondary Outcome Measure:

Measure Title	Progression-Free Survival (PFS) - Percentage of Participants With an Event
Measure Description	PFS was defined as the time between the date of randomization and the date of documented progressive disease (PD) defined according to modified Response Evaluation Criteria in Solid Tumors (RECIST) evaluation, or date of death due to any cause. PD was defined as at least a 20 percent (%) increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum (LD) recorded since the treatment started. Participants without an event were censored at the date of last follow up for progression, or date of last available tumor assessment if no further follow up assessment for progression was performed. Participants who were randomized but not exposed to study drug and had no further follow up were censored at the date of randomization.
Time Frame	Screening, Weeks 8, 16, 24, 32, 40, and every 12 weeks thereafter or until confirmed evidence of disease progression
Safety Issue?	No

Analysis Population Description

ITT population.

Reporting Groups

	Description
Bevacizumab + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.
Placebo + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received placebo IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received placebo IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.

Measured Values

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
Number of Participants Analyzed	306	301
Progression-Free Survival (PFS) - Percentage of Participants With an Event [units: percentage of participants]	84.0	92.4

5. Secondary Outcome Measure:

Measure Title	Progression-Free Survival (PFS) - Time to Event
Measure Description	PFS was defined as the time between the date of randomization and the date of documented PD (per RECIST), or date of death due to any cause. Data for participants without an event were censored at the date of last follow up for progression, or date of last available tumor assessment if no further follow up assessment for progression was performed. Participants who were randomized but not exposed to study drug and had no further follow up were censored at the date of randomization. Median PFS was estimated using the Kaplan-Meier method.
Time Frame	Screening, Weeks 8, 16, 24, 32, 40, and every 12 weeks thereafter or until confirmed evidence of disease progression
Safety Issue?	No

Analysis Population Description
ITT Population

Reporting Groups

	Description
Bevacizumab + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.
Placebo + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received placebo IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received placebo IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/ capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.

Measured Values

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
Number of Participants Analyzed	306	301
Progression-Free Survival (PFS) - Time to Event [units: months] Median (95% Confidence Interval)	4.6 (3.9 to 5.4)	3.6 (3.4 to 3.7)

Statistical Analysis 1 for Progression-Free Survival (PFS) - Time to Event

Statistical Analysis Overview	Comparison Groups	Bevacizumab + Gemcitabine + Erlotinib, Placebo + Gemcitabine + Erlotinib
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0002
	Comments	[Not specified]

	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.73
	Confidence Interval	(2-Sided) 95% 0.61 to 0.86
	Estimation Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Complete Response (CR), Partial Response (PR), or Stable Disease (SD) at First Postbaseline Tumor Assessment
Measure Description	Percentage of participants with CR, PR, or SD according to modified RECIST evaluation at the first postbaseline tumor assessment. CR equaled (=) complete disappearance of all target lesions and non-target disease, with normalization of tumor marker level. PR is greater than or equal to (≥) a 30% decrease of the sum of the LD of all target lesions as referenced to the baseline sum LD of all target lesions. Persistence of one or more non-target lesions(s) and/or maintenance of tumor marker level above normal limits. SD=neither sufficient shrinkage of target lesions to qualify for PR nor sufficient increase to qualify for PD with persistence of one or more non-target lesions(s) and/or maintenance of tumor marker level above normal limits.
Time Frame	Baseline and Week 8
Safety Issue?	No

Analysis Population Description

ITT Population.

Reporting Groups

	Description
Bevacizumab + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.

	Description
Placebo + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received placebo IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received placebo IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/ capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.

Measured Values

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
Number of Participants Analyzed	306	301
Percentage of Participants With Complete Response (CR), Partial Response (PR), or Stable Disease (SD) at First Postbaseline Tumor Assessment [units: percentage of participants] Number (95% Confidence Interval)	62.1 (56.4 to 67.6)	58.5 (52.7 to 64.1)

Statistical Analysis 1 for Percentage of Participants With Complete Response (CR), Partial Response (PR), or Stable Disease (SD) at First Postbaseline Tumor Assessment

Statistical Analysis Overview	Comparison Groups	Bevacizumab + Gemcitabine + Erlotinib, Placebo + Gemcitabine + Erlotinib
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3621
	Comments	[Not specified]
	Method	Chi-squared
	Comments	Approximate 95% confidence interval (CI) for difference of two rates using Hauck-Anderson method.

Method of Estimation	Estimation Parameter	Other [Difference in Response Rates]
	Estimated Value	3.62
	Confidence Interval	(2-Sided) 95%

		-4.3 to 11.6
	Estimation Comments	[Not specified]

7. Secondary Outcome Measure:

Measure Title	Bevacizumab Concentration in the Presence of Gemcitabine and Erlotinib
Measure Description	Blood samples were collected from a subgroup of participants, in selected centers for the determination of bevacizumab serum concentration before the first bevacizumab/placebo exposure (Week 1) and at Weeks 3, 5, 7, and 9. Each time blood samples were collected just (preferably within 1 hour) before the start of the study treatment.
Time Frame	Weeks 1, 3, 5, 7, and 9
Safety Issue?	No

Analysis Population Description

ITT Population. Number (n) = number of participants assessed at a specific visit.

Reporting Groups

	Description
Bevacizumab + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.

Measured Values

	Bevacizumab + Gemcitabine + Erlotinib
Number of Participants Analyzed	78
Bevacizumab Concentration in the Presence of Gemcitabine and Erlotinib [units: micrograms/milliliter] Geometric Mean (Standard Deviation)	
Week 1 (n=4)	0.52 (14.98)
Week 3 (n=78)	27.09 (18.23)
Week 5 (n=73)	35.23 (24.88)
Week 7 (n=72)	41.19 (19.68)

	Bevacizumab + Gemcitabine + Erlotinib
Week 9 (n=61)	44.60 (22.57)

Reported Adverse Events

Time Frame	Adverse Events (AEs) were reported from Day 1 (or prior to Day 1 for serious AEs [SAEs] related to study specific procedures) until 28 days after last dose. Related nonserious SAEs occurring up to 6 months after last dose of study drug were reported.
Additional Description	Related SAEs: reported indefinitely; related AEs: followed to return to baseline/stabilizing or causal relationship changed. Unrelated, mild/moderate AEs: followed for 28 days after last dose. Severe, life-threatening/related AEs: followed to resolution, causal relationship changed or death.

Reporting Groups

	Description
Bevacizumab + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received bevacizumab 5 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.
Placebo + Gemcitabine + Erlotinib	Cycle 1 (8-week cycle): Participants received placebo IV on Days 1, 15, 29, and 43 (followed by 1 week off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, 15, 22, 29, 36, and 43 (followed by 1 week off); and erlotinib 100 mg tablets/capsules, PO, QD for 8 weeks. Cycles 2 and beyond (4-week cycle): Participants received placebo IV on Days 1 and 15 (followed by 2 weeks off); gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (followed by 1 week off); and erlotinib 100 mg tablets/ capsules PO QD. Participants continued on treatment until disease progression, unacceptable toxicity, or participant withdrawal.

Serious Adverse Events

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
	Affected/At Risk (%)	Affected/At Risk (%)
Total	139/297 (46.8%)	119/286 (41.61%)

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
	Affected/At Risk (%)	Affected/At Risk (%)
Blood and lymphatic system disorders		
Acquired haemophilia with anti FVIII, XI, or XIII [A] *	1/297 (0.34%)	0/286 (0%)
Anaemia [A] *	5/297 (1.68%)	3/286 (1.05%)
Febrile neutropenia [A] *	1/297 (0.34%)	2/286 (0.7%)
Haemolytic uraemic syndrome [A] *	2/297 (0.67%)	1/286 (0.35%)
Hypercoagulation [A] *	0/297 (0%)	1/286 (0.35%)
Neutropenia [A] *	2/297 (0.67%)	0/286 (0%)
Pancytopenia [A] *	1/297 (0.34%)	0/286 (0%)
Splenic infarction [A] *	0/297 (0%)	1/286 (0.35%)
Thrombocytopenia [A] *	1/297 (0.34%)	1/286 (0.35%)
Cardiac disorders		
Acute coronary syndrome [A] *	1/297 (0.34%)	0/286 (0%)
Angina pectoris [A] *	1/297 (0.34%)	0/286 (0%)
Cardiac failure [A] *	1/297 (0.34%)	1/286 (0.35%)
Left ventricular failure [A] *	0/297 (0%)	1/286 (0.35%)
Myocardial infarction [A] *	4/297 (1.35%)	1/286 (0.35%)
Myocardial ischaemia [A] *	1/297 (0.34%)	0/286 (0%)
Pericarditis [A] *	0/297 (0%)	1/286 (0.35%)
Gastrointestinal disorders		
Abdominal pain [A] *	5/297 (1.68%)	2/286 (0.7%)
Abdominal pain upper [A] *	1/297 (0.34%)	1/286 (0.35%)
Anal fistula [A] *	1/297 (0.34%)	0/286 (0%)

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
	Affected/At Risk (%)	Affected/At Risk (%)
Anal ulcer [A] *	1/297 (0.34%)	0/286 (0%)
Ascites [A] *	0/297 (0%)	1/286 (0.35%)
Constipation [A] *	1/297 (0.34%)	1/286 (0.35%)
Diarrhoea [A] *	2/297 (0.67%)	4/286 (1.4%)
Duodenal perforation [A] *	1/297 (0.34%)	0/286 (0%)
Duodenal ulcer haemorrhage [A] *	0/297 (0%)	1/286 (0.35%)
Dysphagia [A] *	0/297 (0%)	1/286 (0.35%)
Faeces discoloured [A] *	0/297 (0%)	1/286 (0.35%)
Gastric haemorrhage [A] *	2/297 (0.67%)	0/286 (0%)
Gastric perforation [A] *	0/297 (0%)	1/286 (0.35%)
Gastric ulcer haemorrhage [A] *	0/297 (0%)	1/286 (0.35%)
Gastric ulcer perforation [A] *	0/297 (0%)	1/286 (0.35%)
Gastrointestinal haemorrhage [A] *	3/297 (1.01%)	4/286 (1.4%)
Gastrointestinal perforation [A] *	1/297 (0.34%)	1/286 (0.35%)
Gastrointestinal ulcer haemorrhage [A] *	2/297 (0.67%)	0/286 (0%)
Haematemesis [A] *	2/297 (0.67%)	0/286 (0%)
Haematochezia [A] *	0/297 (0%)	1/286 (0.35%)
Ileus [A] *	1/297 (0.34%)	1/286 (0.35%)
Ileus paralytic [A] *	2/297 (0.67%)	0/286 (0%)
Intestinal infarction [A] *	0/297 (0%)	1/286 (0.35%)
Intestinal mass [A] *	1/297 (0.34%)	0/286 (0%)
Intestinal obstruction [A] *	3/297 (1.01%)	3/286 (1.05%)

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
	Affected/At Risk (%)	Affected/At Risk (%)
Intestinal perforation [A] *	1/297 (0.34%)	0/286 (0%)
Intra-abdominal haematoma [A] *	1/297 (0.34%)	0/286 (0%)
Malabsorption [A] *	0/297 (0%)	1/286 (0.35%)
Melaena [A] *	1/297 (0.34%)	0/286 (0%)
Nausea [A] *	3/297 (1.01%)	4/286 (1.4%)
Pancreatitis acute [A] *	1/297 (0.34%)	0/286 (0%)
Peptic ulcer haemorrhage [A] *	0/297 (0%)	1/286 (0.35%)
Peritoneal haemorrhage [A] *	1/297 (0.34%)	0/286 (0%)
Peritonitis [A] *	2/297 (0.67%)	0/286 (0%)
Rectal haemorrhage [A] *	1/297 (0.34%)	2/286 (0.7%)
Sigmoiditis [A] *	1/297 (0.34%)	0/286 (0%)
Small intestinal haemorrhage [A] *	0/297 (0%)	2/286 (0.7%)
Subileus [A] *	0/297 (0%)	1/286 (0.35%)
Upper gastrointestinal haemorrhage [A] *	4/297 (1.35%)	2/286 (0.7%)
Vomiting [A] *	8/297 (2.69%)	4/286 (1.4%)
General disorders		
Asthenia [A] *	1/297 (0.34%)	2/286 (0.7%)
Death [A] *	0/297 (0%)	1/286 (0.35%)
Fatigue [A] *	1/297 (0.34%)	0/286 (0%)
General physical health deterioration [A] *	1/297 (0.34%)	3/286 (1.05%)
Oedema [A] *	1/297 (0.34%)	0/286 (0%)
Oedema peripheral [A] *	0/297 (0%)	2/286 (0.7%)

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
	Affected/At Risk (%)	Affected/At Risk (%)
Pyrexia [A] *	16/297 (5.39%)	11/286 (3.85%)
Sudden death [A] *	1/297 (0.34%)	0/286 (0%)
Hepatobiliary disorders		
Biliary dilatation [A] *	1/297 (0.34%)	0/286 (0%)
Cholangitis [A] *	4/297 (1.35%)	4/286 (1.4%)
Cholangitis acute [A] *	0/297 (0%)	1/286 (0.35%)
Cholestasis [A] *	1/297 (0.34%)	0/286 (0%)
Gallbladder perforation [A] *	0/297 (0%)	1/286 (0.35%)
Hepatic function abnormal [A] *	2/297 (0.67%)	1/286 (0.35%)
Hyperbilirubinaemia [A] *	1/297 (0.34%)	0/286 (0%)
Jaundice [A] *	3/297 (1.01%)	0/286 (0%)
Jaundice cholestatic [A] *	1/297 (0.34%)	0/286 (0%)
Infections and infestations		
Abdominal abscess [A] *	2/297 (0.67%)	1/286 (0.35%)
Abscess [A] *	1/297 (0.34%)	0/286 (0%)
Bacterial infection [A] *	1/297 (0.34%)	0/286 (0%)
Bacterial sepsis [A] *	2/297 (0.67%)	0/286 (0%)
Biliary sepsis [A] *	0/297 (0%)	1/286 (0.35%)
Biliary tract infection [A] *	0/297 (0%)	2/286 (0.7%)
Bronchitis [A] *	0/297 (0%)	3/286 (1.05%)
Cellulitis [A] *	1/297 (0.34%)	0/286 (0%)
Central line infection [A] *	0/297 (0%)	2/286 (0.7%)

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
	Affected/At Risk (%)	Affected/At Risk (%)
Disseminated cytomegaloviral infection [A] *	0/297 (0%)	1/286 (0.35%)
Diverticulitis [A] *	1/297 (0.34%)	0/286 (0%)
Escherichia sepsis [A] *	2/297 (0.67%)	0/286 (0%)
Gastroenteritis [A] *	1/297 (0.34%)	0/286 (0%)
Infected insect bite [A] *	0/297 (0%)	1/286 (0.35%)
Infection [A] *	1/297 (0.34%)	0/286 (0%)
Laryngitis [A] *	1/297 (0.34%)	0/286 (0%)
Lower respiratory tract infection [A] *	0/297 (0%)	2/286 (0.7%)
Osteomyelitis [A] *	0/297 (0%)	1/286 (0.35%)
Perianal abcess [A] *	1/297 (0.34%)	0/286 (0%)
Peritonitis bacterial [A] *	0/297 (0%)	1/286 (0.35%)
Pilonidal cyst [A] *	1/297 (0.34%)	0/286 (0%)
Pneumocystis jiroveci pneumonia [A] *	0/297 (0%)	1/286 (0.35%)
Pneumonia [A] *	9/297 (3.03%)	2/286 (0.7%)
Pneumonia klebsiella [A] *	0/297 (0%)	1/286 (0.35%)
Renal cyst infection [A] *	0/297 (0%)	1/286 (0.35%)
Sepsis [A] *	8/297 (2.69%)	6/286 (2.1%)
Septic Shock [A] *	0/297 (0%)	3/286 (1.05%)
Subcutaneous abscess [A] *	2/297 (0.67%)	0/286 (0%)
Upper respiratory tract infection [A] *	0/297 (0%)	1/286 (0.35%)
Wound infection [A] *	1/297 (0.34%)	0/286 (0%)
Injury, poisoning and procedural complications		

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
	Affected/At Risk (%)	Affected/At Risk (%)
Femoral neck fracture [A] *	1/297 (0.34%)	0/286 (0%)
Head injury [A] *	0/297 (0%)	1/286 (0.35%)
Hepatic haematoma [A] *	0/297 (0%)	1/286 (0.35%)
Overdose [A] *	1/297 (0.34%)	1/286 (0.35%)
Stent occlusion [A] *	1/297 (0.34%)	1/286 (0.35%)
Thoracic vertebral fracture [A] *	1/297 (0.34%)	0/286 (0%)
Investigations		
Alanine aminotransferase increased [A] *	1/297 (0.34%)	0/286 (0%)
Aspartate aminotransferase increased [A] *	1/297 (0.34%)	0/286 (0%)
Blood creatinine increased [A] *	1/297 (0.34%)	0/286 (0%)
Blood potassium decreased [A] *	1/297 (0.34%)	0/286 (0%)
C-reactive protein increased [A] *	1/297 (0.34%)	0/286 (0%)
Haemoglobin decreased [A] *	0/297 (0%)	1/286 (0.35%)
Hepatic enzyme increased [A] *	1/297 (0.34%)	0/286 (0%)
Metabolism and nutrition disorders		
Anorexia [A] *	0/297 (0%)	3/286 (1.05%)
Cachexia [A] *	1/297 (0.34%)	0/286 (0%)
Dehydration [A] *	3/297 (1.01%)	3/286 (1.05%)
Diabetes mellitus [A] *	0/297 (0%)	2/286 (0.7%)
Diabetes mellitus inadequate control [A] *	2/297 (0.67%)	0/286 (0%)
Failure to thrive [A] *	1/297 (0.34%)	0/286 (0%)
Hyperglycaemia [A] *	2/297 (0.67%)	1/286 (0.35%)

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
	Affected/At Risk (%)	Affected/At Risk (%)
Hyperkalaemia [A] *	1/297 (0.34%)	0/286 (0%)
Type 1 diabetes mellitus [A] *	0/297 (0%)	1/286 (0.35%)
Musculoskeletal and connective tissue disorders		
Hypercreatinaemia [A] *	1/297 (0.34%)	0/286 (0%)
Pain in extremity [A] *	1/297 (0.34%)	0/286 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Endometrial cancer [A] *	1/297 (0.34%)	0/286 (0%)
Lymphangiosis carcinomatosa [A] *	0/297 (0%)	1/286 (0.35%)
Tumour haemorrhage [A] *	1/297 (0.34%)	0/286 (0%)
Nervous system disorders		
Cerebral artery embolism [A] *	1/297 (0.34%)	0/286 (0%)
Cerebral infarction [A] *	1/297 (0.34%)	1/286 (0.35%)
Cerebrovascular accident [A] *	2/297 (0.67%)	3/286 (1.05%)
Dizziness [A] *	0/297 (0%)	1/286 (0.35%)
Ischaemic stroke [A] *	0/297 (0%)	1/286 (0.35%)
Lacunar infarction [A] *	0/297 (0%)	1/286 (0.35%)
Neurological symptom [A] *	0/297 (0%)	1/286 (0.35%)
Syncope [A] *	1/297 (0.34%)	1/286 (0.35%)
Transient ischaemic attack [A] *	0/297 (0%)	1/286 (0.35%)
Psychiatric disorders		
Anxiety [A] *	0/297 (0%)	1/286 (0.35%)
Depression [A] *	1/297 (0.34%)	0/286 (0%)
Renal and urinary disorders		

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
	Affected/At Risk (%)	Affected/At Risk (%)
Anuria [A] *	0/297 (0%)	1/286 (0.35%)
Nephrolithiasis [A] *	0/297 (0%)	1/286 (0.35%)
Proteinuria [A] *	1/297 (0.34%)	0/286 (0%)
Renal colic [A] *	2/297 (0.67%)	0/286 (0%)
Renal failure [A] *	2/297 (0.67%)	0/286 (0%)
Renal failure acute [A] *	0/297 (0%)	1/286 (0.35%)
Renal impairment [A] *	2/297 (0.67%)	0/286 (0%)
Reproductive system and breast disorders		
Oedema genital [A] *	1/297 (0.34%)	0/286 (0%)
Vaginal haemorrhage [A] *	1/297 (0.34%)	0/286 (0%)
Respiratory, thoracic and mediastinal disorders		
Acute respiratory distress syndrome [A] *	1/297 (0.34%)	1/286 (0.35%)
Alveolitis [A] *	1/297 (0.34%)	0/286 (0%)
Chronic obstructive pulmonary disease [A] *	0/297 (0%)	1/286 (0.35%)
Dyspnoea [A] *	3/297 (1.01%)	3/286 (1.05%)
Epistaxis [A] *	2/297 (0.67%)	0/286 (0%)
Interstitial lung disease [A] *	2/297 (0.67%)	1/286 (0.35%)
Lung disorder [A] *	0/297 (0%)	1/286 (0.35%)
Pleural effusion [A] *	1/297 (0.34%)	2/286 (0.7%)
Pneumonitis [A] *	0/297 (0%)	1/286 (0.35%)
Pneumothorax [A] *	1/297 (0.34%)	0/286 (0%)
Pulmonary Haemorrhage [A] *	1/297 (0.34%)	0/286 (0%)

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
	Affected/At Risk (%)	Affected/At Risk (%)
Pulmonary embolism [A] *	9/297 (3.03%)	12/286 (4.2%)
Pulmonary oedema [A] *	0/297 (0%)	1/286 (0.35%)
Respiratory failure [A] *	2/297 (0.67%)	2/286 (0.7%)
Skin and subcutaneous tissue disorders		
Blister [A] *	1/297 (0.34%)	0/286 (0%)
Eczema [A] *	0/297 (0%)	1/286 (0.35%)
Rash [A] *	2/297 (0.67%)	0/286 (0%)
Surgical and medical procedures		
Ileectomy [A] *	1/297 (0.34%)	0/286 (0%)
Vascular disorders		
Aortic dissection [A] *	0/297 (0%)	1/286 (0.35%)
Cardiovascular insufficiency [A] *	0/297 (0%)	1/286 (0.35%)
Deep vein thrombosis [A] *	4/297 (1.35%)	5/286 (1.75%)
Haemorrhage [A] *	1/297 (0.34%)	0/286 (0%)
Hypertension [A] *	2/297 (0.67%)	0/286 (0%)
Jugular vein thrombosis [A] *	0/297 (0%)	1/286 (0.35%)
Subclavian vein thrombosis [A] *	1/297 (0.34%)	0/286 (0%)
Thrombosis [A] *	1/297 (0.34%)	2/286 (0.7%)
Vena cava thrombosis [A] *	1/297 (0.34%)	0/286 (0%)
Venous thrombosis [A] *	1/297 (0.34%)	0/286 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (10.1)

Other Adverse Events

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

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
	Affected/At Risk (%)	Affected/At Risk (%)
Total	290/297 (97.64%)	276/286 (96.5%)
Blood and lymphatic system disorders		
Anaemia [A] *	77/297 (25.93%)	96/286 (33.57%)
Leukopenia [A] *	16/297 (5.39%)	20/286 (6.99%)
Neutropenia [A] *	87/297 (29.29%)	75/286 (26.22%)
Thrombocytopenia [A] *	93/297 (31.31%)	76/286 (26.57%)
Gastrointestinal disorders		
Abdominal pain [A] *	46/297 (15.49%)	39/286 (13.64%)
Abdominal pain upper [A] *	33/297 (11.11%)	29/286 (10.14%)
Constipation [A] *	79/297 (26.6%)	65/286 (22.73%)
Diarrhoea [A] *	145/297 (48.82%)	144/286 (50.35%)
Dyspepsia [A] *	25/297 (8.42%)	20/286 (6.99%)
Flatulence [A] *	19/297 (6.4%)	10/286 (3.5%)
Nausea [A] *	135/297 (45.45%)	146/286 (51.05%)
Stomatitis [A] *	34/297 (11.45%)	19/286 (6.64%)
Vomiting [A] *	108/297 (36.36%)	118/286 (41.26%)
General disorders		
Asthenia [A] *	41/297 (13.8%)	44/286 (15.38%)
Chills [A] *	18/297 (6.06%)	15/286 (5.24%)
Fatigue [A] *	104/297 (35.02%)	97/286 (33.92%)
Mucosal inflammation [A] *	25/297 (8.42%)	29/286 (10.14%)

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
	Affected/At Risk (%)	Affected/At Risk (%)
Oedema peripheral [A] *	51/297 (17.17%)	49/286 (17.13%)
Pyrexia [A] *	94/297 (31.65%)	99/286 (34.62%)
Infections and infestations		
Urinary tract infection [A] *	29/297 (9.76%)	17/286 (5.94%)
Investigations		
Weight decreased [A] *	15/297 (5.05%)	21/286 (7.34%)
Metabolism and nutrition disorders		
Anorexia [A] *	64/297 (21.55%)	66/286 (23.08%)
Musculoskeletal and connective tissue disorders		
Back pain [A] *	21/297 (7.07%)	22/286 (7.69%)
Pain in extremity [A] *	20/297 (6.73%)	9/286 (3.15%)
Nervous system disorders		
Dizziness [A] *	20/297 (6.73%)	23/286 (8.04%)
Dysgeusia [A] *	35/297 (11.78%)	26/286 (9.09%)
Headache [A] *	39/297 (13.13%)	24/286 (8.39%)
Psychiatric disorders		
Anxiety [A] *	18/297 (6.06%)	10/286 (3.5%)
Depression [A] *	15/297 (5.05%)	18/286 (6.29%)
Insomnia [A] *	35/297 (11.78%)	25/286 (8.74%)
Renal and urinary disorders		
Proteinuria [A] *	15/297 (5.05%)	4/286 (1.4%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] *	24/297 (8.08%)	24/286 (8.39%)

	Bevacizumab + Gemcitabine + Erlotinib	Placebo + Gemcitabine + Erlotinib
	Affected/At Risk (%)	Affected/At Risk (%)
Dyspnoea [A] *	31/297 (10.44%)	26/286 (9.09%)
Epistaxis [A] *	89/297 (29.97%)	32/286 (11.19%)
Pharyngolaryngeal pain [A] *	16/297 (5.39%)	7/286 (2.45%)
Skin and subcutaneous tissue disorders		
Acne [A] *	30/297 (10.1%)	17/286 (5.94%)
Alopecia [A] *	40/297 (13.47%)	44/286 (15.38%)
Dermatitis acneiform [A] *	25/297 (8.42%)	19/286 (6.64%)
Dry skin [A] *	37/297 (12.46%)	23/286 (8.04%)
Pruritus [A] *	22/297 (7.41%)	18/286 (6.29%)
Rash [A] *	146/297 (49.16%)	126/286 (44.06%)
Vascular disorders		
Hypertension [A] *	58/297 (19.53%)	28/286 (9.79%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (10.1)

Limitations and Caveats

[Not specified]

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.

The Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

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