ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 09/23/2014

A Study of Avastin (Bevacizumab) in Combination With Carboplatin-Based Chemotherapy in Patients With Advanced or Recurrent Non-Squamous Non-Small Cell Lung Cancer.

This study has been completed.

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT00700180

Purpose

This study will explore the correlation of biomarkers with response rate, and the overall efficacy and safety, of Avastin in combination with carboplatin-based chemotherapy in patients with advanced or recurrent non-squamous non-small cell lung cancer. Patients will be randomized to one of 2 groups, to receive either Avastin 7.5mg/kg iv on day 1 of each 3 week cycle, or Avastin 15mg/kg iv on day 1 of each 3 week cycle; all patients will also receive treatment with carboplatin and either gemcitabine or paclitaxel for a maximum of 6 cycles. The anticipated time on study treatment is until disease progression, and the target sample size is 100-500 individuals.

Condition	Intervention	Phase
Non-Small Cell Lung Cancer	Drug: bevacizumab [Avastin] Drug: Carboplatin-based chemotherapy	Phase 2

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Open Label, Randomized, Safety/Efficacy Study
Official Title: A Randomized, Open-label Study to Explore the Correlation of Biomarkers With Response Rate in Chemo-naive Patients With Advanced or Recurrent Non-squamous Non-small Cell Lung Cancer Who Receive Treatment With Avastin in Addition to Carboplatin-based Chemotherapy

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Percentage of Participants With a Best Overall Response of Complete Response (CR) or Partial Response (PR) by Dichotomized Baseline Plasma Marker Level [Time Frame: Baseline, Day 21 of Cycles 2, 4, and 6 (Bv + chemo), Day 21 of Cycles 7, 8, 9, and 10 (Bv), Day 21 of every other cycle (Bv), and at disease progression.] [Designated as safety issue: No]

  Overall response was analyzed and correlated within dichotomized (low- and high-level) baseline plasma biomarker (basic fibroblast growth factor [bFGF], E-selection, intracellular adhesion molecule [ICAM], placental growth factor [PlGF], vascular endothelial growth factor A [VEGF A], vascular endothelial growth factor receptor [VEGFR]-1, and VEGFR-2) subgroups: low-level equals (=) less than or equal to (≤) median baseline level, high-level=greater than (>) median baseline level. Per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.0 CR defined as disappearance of all target lesions, non-target lesions, and normalization of tumor marker level. PR defined as greater than or equal to (≥)30 percent (%) decrease under baseline of the sum of the longest diameter (LD) of all target lesions. No unequivocal progression of non-target disease; no new lesions. Complete and partial responses must have been confirmed no less than 4 weeks after criteria for response were first met

Secondary Outcome Measures:

- Progression-Free Survival - Percentage of Participants With an Event [Time Frame: Baseline, Day 1, weekly to disease progression] [Designated as safety issue: No]

  PFS was defined as the time between randomization and progressive disease (PD) according to RECIST criteria, or death due to any cause. PD was defined as at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started. Disease progression was evaluated according to the RECIST using computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, X-ray, bone scans, or clinical examination. Participants without an event were censored at the date of last follow up for progression. Participants with no post baseline follow-up for progression were censored at the day of randomization.
- Progression-Free Survival - Time to Event [Time Frame: Baseline, Day 1, weekly to disease progression] [Designated as safety issue: No]

  PFS was defined as the time between randomization and disease progression or death due to any cause. Participants without an event were censored at the date of last follow up for progression. Participants with no post baseline follow-up for progression were censored at the day of randomization. Disease progression was evaluated according to the RECIST using CT scans, MRI scans, X-ray, bone scans, or clinical examination. Median PFS was estimated using the Kaplan-Meier method.
- Percentage of Participants With Objective Response [Time Frame: Baseline, Day 21 of Cycles 2, 4, and 6, Day 21 of Cycles 7, 8, 9, and 10, Day 21 of every other cycle, and at disease progression] [Designated as safety issue: No]

  Percentage of participants with CR or PR according to RECIST criteria. Per RECIST v1.0: CR defined as disappearance of all target lesions, non-target lesions, and normalization of tumor marker level. PR was defined as ≥30% decrease under baseline of the sum of the LD of all target lesions. No unequivocal progression of non-target disease. No new lesions. Complete and partial responses were confirmed no less than 4 weeks after the criteria for response were first met.
- Percentage of Participants With Measurable Disease at Baseline Who Achieved CR, PR, or Stable Disease (SD) for at Least 6 Weeks [Time Frame: Baseline, Day 21 of Cycles 2, 4, and 6, Day 21 of Cycles 7, 8, 9, and 10, Day 21 of every other cycle, and at disease progression] [Designated as safety issue: No]

  Percentage of participants with measurable disease at baseline who on assessment achieved CR, PR, or SD according to RECIST. Per RECIST v1.0: CR defined as disappearance of all target lesions, non-target lesions, and normalization of tumor marker level. PR was defined as ≥30% decrease under baseline of the sum of the LD of all target lesions. No unequivocal progression of non-target disease. No new lesions. SD defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum LD since start of treatment. Complete and partial responses must have been confirmed no less than 4 weeks after the criteria for response were first met. For participants with SD, follow-up assessments must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.
- Duration of Response - Percentage of Participants With an Event [Time Frame: Baseline, Day 21 of Cycles 2, 4, and 6, Day 21 of Cycles 7, 8, 9, and 10, Day 21 of every other cycle, and at disease progression] [Designated as safety issue: No]

Duration of response is defined as time in months from the first documentation of objective tumor response (CR or PR) to objective tumor progression or death due to any cause. Participants without an event (documented progression or death) were censored at the date of last follow-up for progression. Duration of response was only calculated for participants who had a confirmed objective tumor response (CR or PR).

- Duration of Response - Time to Event [Time Frame: Baseline, Day 21 of Cycles 2, 4, and 6 (Bv + chemo), Day 21 of Cycles 7, 8, 9, and 10 (Bv), Day 21 of every other cycle (Bv), and at disease progression.] [Designated as safety issue: No]
  The median time, in months, from the first documentation of objective tumor response (CR or PR) to objective tumor progression or death due to any cause. Participants without an event (documented progression or death) were censored at the date of last follow-up for progression. Duration of response was only calculated for participants who had a confirmed objective tumor response (CR or PR). Median Duration of Response was estimated using the Kaplan-Meier method.
- Overall Survival - Percentage of Participants With an Event [Time Frame: Baseline, weekly to 28 days after last dose of study treatment, every 8 weeks thereafter to death due to any cause] [Designated as safety issue: No]
  Overall survival was defined as the time between randomization and death due to any cause. Participants without an event were censored at the last time they were known to be alive. Overall Survival was estimated using the Kaplan-Meier method.
- Overall Survival - Time to Event [Time Frame: Baseline, weekly to death due to any cause, or to end of study] [Designated as safety issue: No]
  Overall survival was defined as the time between randomization and death due to any cause. Participants without an event were censored at the last time they were known to be alive. Overall Survival was estimated using the Kaplan-Meier method.

Enrollment: 303
Study Start Date: September 2008
Primary Completion Date: September 2012
Study Completion Date: September 2012

Arms	Assigned Interventions
Experimental: 1	Drug: bevacizumab [Avastin] 7.5mg/kg iv on day 1 of each 3 week cycle Drug: Carboplatin-based chemotherapy As prescribed
Experimental: 2	Drug: bevacizumab [Avastin] 15mg/kg iv on day 1 of each 3 week cycle Drug: Carboplatin-based chemotherapy As prescribed

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;

- locally advanced metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC);
- >=1 measurable tumor lesion;
- ECOG performance status 0-1.

Exclusion Criteria:

- prior chemotherapy or treatment with another systemic anti-cancer agent;
- evidence of CNS metastases;
- history of grade 2 or higher hemoptysis;
- evidence of tumor invading or abutting major blood vessels;
- malignancies other than NSCLC within 5 years prior to randomization, other than adequately treated cancer in situ of cervix, basal or squamous cell skin cancer, localized prostate cancer or DCIS;
- clinically significant cardiovascular disease;
- current or recent use of aspirin (>325mg/day) or full dose anticoagulants or thrombolytic agents for therapeutic purposes.

Contacts and Locations

Locations

Australia, New South Wales
St. Leonards, New South Wales, Australia, 2065
Australia, South Australia
Adelaide, South Australia, Australia, 5041
Adelaide, South Australia, Australia, 5065
Australia, Victoria
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Belgium
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Hungary

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Krasnodar, Russian Federation, 350086
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Moscow, Russian Federation, 105229
Saint-Petersburg, Russian Federation, 197758
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Spain

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Valencia, Valencia, Spain, 46010
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Taichung, Taiwan, 404
Taichung, Taiwan, 402
Taichung, Taiwan, 407
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United Kingdom

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Investigators

Study Director:	Clinical Trials	Hoffmann-La Roche

More Information

Responsible Party:	Hoffmann-La Roche
Study ID Numbers:	BO21015 2008-000662-23
Health Authority:	Denmark: Danish Medicines Agency

Study Results

Participant Flow

Reporting Groups

	Description
Bevacizumab 7.5 Milligrams (mg) Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 7.5 mg per kilogram (mg/kg) intravenously (IV) on Day 1; either carboplatin at a dose required to achieve an area under the concentration-time curve (AUC) of 6 mg per milliliter (mg/mL) IV and paclitaxel 200 mg per square meter (mg/m^2) IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 7.5 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

	Description
Bevacizumab 15 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 15 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 15 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

Overall Study

	Bevacizumab 7.5 Milligrams (mg) Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
Started	154	149
Completed	0 [1]	0 [1]
Not Completed	154	149
Death	99	114
Alive on treatment	5	3
Alive in follow-up	46	27
Lost to Follow-up	4	5

[1] Clinical cutoff date: July 11, 2011

Baseline Characteristics

Analysis Population Description

Intent-to-treat (ITT) population. The ITT population included all participants randomized into the study.

Reporting Groups

	Description
Bevacizumab 7.5 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 7.5 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.
Bevacizumab 15 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 15 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 15 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

Baseline Measures

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy	Total
Number of Participants	154	149	303
Age, Continuous [units: years] Mean (Standard Deviation)	59.7 (10.13)	58.8 (11.20)	59.2 (10.66)
Gender, Male/Female [units: participants]			
Female	56	55	111
Male	98	94	192

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants With a Best Overall Response of Complete Response (CR) or Partial Response (PR) by Dichotomized Baseline Plasma Marker Level

Measure Description	Overall response was analyzed and correlated within dichotomized (low- and high-level) baseline plasma biomarker (basic fibroblast growth factor [bFGF], E-selection, intracellular adhesion molecule [ICAM], placental growth factor [PlGF], vascular endothelial growth factor A [VEGF A], vascular endothelial growth factor receptor [VEGFR]-1, and VEGFR-2) subgroups: low-level equals (=) less than or equal to (≤) median baseline level, high-level=greater than (>) median baseline level. Per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.0 CR defined as disappearance of all target lesions, non-target lesions, and normalization of tumor marker level. PR defined as greater than or equal to (≥)30 percent (%) decrease under baseline of the sum of the longest diameter (LD) of all target lesions. No unequivocal progression of non-target disease; no new lesions. Complete and partial responses must have been confirmed no less than 4 weeks after criteria for response were first met
Time Frame	Baseline, Day 21 of Cycles 2, 4, and 6 (Bv + chemo), Day 21 of Cycles 7, 8, 9, and 10 (Bv), Day 21 of every other cycle (Bv), and at disease progression.
Safety Issue?	No

Analysis Population Description

Biomarker Evaluable Protein Plasma (BEP) Population: Participants in the ITT population who started at least 1 dose of bevacizumab and had a non-missing baseline biomarker level determined for at least 1 biomarker. n (number) equals (=) number of participants assessed for the specified biomarker.

Reporting Groups

	Description
Bevacizumab 7.5 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 7.5 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.
Bevacizumab 15 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 15 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 15 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

Measured Values

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
Number of Participants Analyzed	82	75

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
Percentage of Participants With a Best Overall Response of Complete Response (CR) or Partial Response (PR) by Dichotomized Baseline Plasma Marker Level [units: percentage of participants]		
bFGF low level (n=77,65)	42.86	47.69
bFGF high level (n=66,75)	34.85	49.33
E-selectin low level (n=73,69)	36.99	42.03
E-selectin high level (n=70,71)	41.43	54.93
ICAM low level (n=70,72)	38.57	50.00
ICAM high level (n=29,32	39.73	47.06
PlGF low level (n=82, 64)	37.80	51.56
PlGF high level (n=27,29)	33.33	51.72
VEGF A low level (n=73,67)	42.47	44.78
VEGF A high level (n=67,73)	35.82	53.42
VEGFR-1 low level (n=72,70)	37.50	60.00
VEGFR-1 high level (n=71,70)	40.85	37.14
VEGFR-2 low level (n=74,69)	32.43	46.38
VEGFR-2 high level (n=69,71)	46.38	50.70

Statistical Analysis 1 for Percentage of Participants With a Best Overall Response of Complete Response (CR) or Partial Response (PR) by Dichotomized Baseline Plasma Marker Level

Statistical Analysis Overview	Comparison Groups	Bevacizumab 7.5 mg Plus Chemotherapy
	Comments	bFGF (high versus low)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8127

	Comments	Multiple logistic regression model with treatment, biomarker level (dichotomized) and baseline prognostic factors as covariates.
	Method	Regression, Logistic
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.07
	Confidence Interval	(2-Sided) 95% 0.63 to 1.80
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Percentage of Participants With a Best Overall Response of Complete Response (CR) or Partial Response (PR) by Dichotomized Baseline Plasma Marker Level

Statistical Analysis Overview	Comparison Groups	Bevacizumab 7.5 mg Plus Chemotherapy
	Comments	E-selectin (high versus low)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0285
	Comments	Multiple logistic regression model with treatment, biomarker level (dichotomized) and baseline prognostic factors as covariates.
	Method	Regression, Logistic
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.81
	Confidence Interval	(2-Sided) 95% 1.06 to 3.08
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Percentage of Participants With a Best Overall Response of Complete Response (CR) or Partial Response (PR) by Dichotomized Baseline Plasma Marker Level

Statistical Analysis Overview	Comparison Groups	Bevacizumab 7.5 mg Plus Chemotherapy
	Comments	ICAM (high versus low)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7478
	Comments	Multiple logistic regression model with treatment, biomarker level (dichotomized) and baseline prognostic factors as covariates.
	Method	Regression, Logistic
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.09
	Confidence Interval	(2-Sided) 95% 0.64 to 1.85
	Estimation Comments	[Not specified]

Statistical Analysis 4 for Percentage of Participants With a Best Overall Response of Complete Response (CR) or Partial Response (PR) by Dichotomized Baseline Plasma Marker Level

Statistical Analysis Overview	Comparison Groups	Bevacizumab 7.5 mg Plus Chemotherapy
	Comments	PlGF (high versus low)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.6761
	Comments	Multiple logistic regression model with treatment, biomarker level (dichotomized) and baseline prognostic factors as covariates.
	Method	Regression, Logistic
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.16
	Confidence Interval	(2-Sided) 95% 0.58 to 2.33
	Estimation Comments	[Not specified]

Statistical Analysis 5 for Percentage of Participants With a Best Overall Response of Complete Response (CR) or Partial Response (PR) by Dichotomized Baseline Plasma Marker Level

Statistical Analysis Overview	Comparison Groups	Bevacizumab 7.5 mg Plus Chemotherapy
	Comments	VEGF A (high versus low)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.4601
	Comments	Multiple logistic regression model with treatment, biomarker level (dichotomized) and baseline prognostic factors as covariates.
	Method	Regression, Logistic
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.22
	Confidence Interval	(2-Sided) 95% 0.72 to 2.09
	Estimation Comments	[Not specified]

Statistical Analysis 6 for Percentage of Participants With a Best Overall Response of Complete Response (CR) or Partial Response (PR) by Dichotomized Baseline Plasma Marker Level

Statistical Analysis Overview	Comparison Groups	Bevacizumab 7.5 mg Plus Chemotherapy
	Comments	VEGFR-1 (high versus low)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3193
	Comments	Multiple logistic regression model with treatment, biomarker level (dichotomized) and baseline prognostic factors as covariates.
	Method	Regression, Logistic
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	0.77
	Confidence Interval	(2-Sided) 95% 0.46 to 1.29
	Estimation Comments	[Not specified]

Statistical Analysis 7 for Percentage of Participants With a Best Overall Response of Complete Response (CR) or Partial Response (PR) by Dichotomized Baseline Plasma Marker Level

Statistical Analysis Overview	Comparison Groups	Bevacizumab 7.5 mg Plus Chemotherapy
	Comments	VEGFR-2 (high versus low)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1758
	Comments	Multiple logistic regression model with treatment, biomarker level (dichotomized) and baseline prognostic factors as covariates.
	Method	Regression, Logistic
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.44
	Confidence Interval	(2-Sided) 95% 0.85 to 2.45
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Progression-Free Survival - Percentage of Participants With an Event

Measure Description	PFS was defined as the time between randomization and progressive disease (PD) according to RECIST criteria, or death due to any cause. PD was defined as at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started. Disease progression was evaluated according to the RECIST using computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, X-ray, bone scans, or clinical examination. Participants without an event were censored at the date of last follow up for progression. Participants with no post baseline follow-up for progression were censored at the day of randomization.
Time Frame	Baseline, Day 1, weekly to disease progression
Safety Issue?	No

Analysis Population Description

ITT population.

Reporting Groups

	Description
Bevacizumab 7.5 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 7.5 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.
Bevacizumab 15 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 15 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 15 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

Measured Values

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
Number of Participants Analyzed	154	149
Progression-Free Survival - Percentage of Participants With an Event [units: percentage of participants]	83.1	85.9

3. Secondary Outcome Measure:

Measure Title	Progression-Free Survival - Time to Event
Measure Description	PFS was defined as the time between randomization and disease progression or death due to any cause. Participants without an event were censored at the date of last follow up for progression. Participants with no post baseline follow-up for progression were censored at the day of randomization. Disease progression was evaluated according to the RECIST using CT scans, MRI scans, X-ray, bone scans, or clinical examination. Median PFS was estimated using the Kaplan-Meier method.
Time Frame	Baseline, Day 1, weekly to disease progression
Safety Issue?	No

Analysis Population Description

ITT Population.

Reporting Groups

	Description
Bevacizumab 7.5 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 7.5 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.
Bevacizumab 15 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 15 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 15 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

Measured Values

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
Number of Participants Analyzed	154	149
Progression-Free Survival - Time to Event	6.8 (5.9 to 7.4)	6.7 (5.9 to 7.2)

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
[units: months] Median (95% Confidence Interval)		

Statistical Analysis 1 for Progression-Free Survival - Time to Event

Statistical Analysis Overview	Comparison Groups	Bevacizumab 7.5 mg Plus Chemotherapy, Bevacizumab 15 mg Plus Chemotherapy
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.9454
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.01
	Confidence Interval	(2-Sided) 95% 0.78 to 1.31
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Objective Response
Measure Description	Percentage of participants with CR or PR according to RECIST criteria. Per RECIST v1.0: CR defined as disappearance of all target lesions, non-target lesions, and normalization of tumor marker level. PR was defined as ≥30% decrease under baseline of the sum of the LD of all target lesions. No unequivocal progression of non-target disease. No new lesions. Complete and partial responses were confirmed no less than 4 weeks after the criteria for response were first met.
Time Frame	Baseline, Day 21 of Cycles 2, 4, and 6, Day 21 of Cycles 7, 8, 9, and 10, Day 21 of every other cycle, and at disease progression
Safety Issue?	No

Analysis Population Description

ITT Population. Data for 12 participants (3 at 7.5 mg and 9 at 15 mg) were excluded for reasons including but not limited to: no study treatment (ST), no postbaseline tumor assessment (TA), non-protocol defined antineoplastic therapy before first TA, first TA >70 days after last dose of last ST, last TA less than (<) 42 days from start of therapy.

Reporting Groups

	Description
Bevacizumab 7.5 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 7.5 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.
Bevacizumab 15 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 15 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 15 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

Measured Values

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
Number of Participants Analyzed	154	149
Percentage of Participants With Objective Response [units: percentage of participants] Number (95% Confidence Interval)	37.1 (29.4 to 45.3)	46.4 (38.0 to 55.0)

Statistical Analysis 1 for Percentage of Participants With Objective Response

Statistical Analysis Overview	Comparison Groups	Bevacizumab 7.5 mg Plus Chemotherapy, Bevacizumab 15 mg Plus Chemotherapy
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1737
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Difference in Responses Rates]
	Estimated Value	9.34
	Confidence Interval	(2-Sided) 95% -2.4 to 21.0
	Estimation Comments	Approximate 95% Confidence Interval (CI) for difference of two rates using Hauck-Anderson method.

5. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Measurable Disease at Baseline Who Achieved CR, PR, or Stable Disease (SD) for at Least 6 Weeks
Measure Description	Percentage of participants with measurable disease at baseline who on assessment achieved CR, PR, or SD according to RECIST. Per RECIST v1.0: CR defined as disappearance of all target lesions, non-target lesions, and normalization of tumor marker level. PR was defined as ≥30% decrease under baseline of the sum of the LD of all target lesions. No unequivocal progression of non-target disease. No new lesions. SD defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum LD since start of treatment. Complete and partial responses must have been confirmed no less than 4 weeks after the criteria for response were first met. For participants with SD, follow-up assessments must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.
Time Frame	Baseline, Day 21 of Cycles 2, 4, and 6, Day 21 of Cycles 7, 8, 9, and 10, Day 21 of every other cycle, and at disease progression
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Bevacizumab 7.5 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 7.5 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.
Bevacizumab 15 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 15 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 15 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

Measured Values

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
Number of Participants Analyzed	151	140
Percentage of Participants With Measurable Disease at Baseline Who Achieved CR, PR, or Stable Disease (SD) for at Least 6 Weeks [units: percentage of participants] Number (95% Confidence Interval)	76.8 (69.3 to 83.3)	78.6 (70.8 to 85.1)

Statistical Analysis 1 for Percentage of Participants With Measurable Disease at Baseline Who Achieved CR, PR, or Stable Disease (SD) for at Least 6 Weeks

Statistical Analysis Overview	Comparison Groups	Bevacizumab 7.5 mg Plus Chemotherapy, Bevacizumab 15 mg Plus Chemotherapy
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.6148
	Comments	[Not specified]
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	1.75
	Confidence Interval	(2-Sided) 95% -8.2 to 11.7
	Estimation Comments	Approximate 95% CI for difference of two rates using Hauck-Anderson method

6. Secondary Outcome Measure:

Measure Title	Duration of Response - Percentage of Participants With an Event
Measure Description	Duration of response is defined as time in months from the first documentation of objective tumor response (CR or PR) to objective tumor progression or death due to any cause. Participants without an event (documented progression or death) were censored at the date of last follow-up for progression. Duration of response was only calculated for participants who had a confirmed objective tumor response (CR or PR).
Time Frame	Baseline, Day 21 of Cycles 2, 4, and 6, Day 21 of Cycles 7, 8, 9, and 10, Day 21 of every other cycle, and at disease progression
Safety Issue?	No

Analysis Population Description

ITT population; only participants with an objective tumor response (CR or PR) were included in the analysis.

Reporting Groups

	Description
Bevacizumab 7.5 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 7.5 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

	Description
Bevacizumab 15 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 15 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 15 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

Measured Values

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
Number of Participants Analyzed	56	65
Duration of Response - Percentage of Participants With an Event [units: percentage of participants]	80.4	78.5

7. Secondary Outcome Measure:

Measure Title	Duration of Response - Time to Event
Measure Description	The median time, in months, from the first documentation of objective tumor response (CR or PR) to objective tumor progression or death due to any cause. Participants without an event (documented progression or death) were censored at the date of last follow-up for progression. Duration of response was only calculated for participants who had a confirmed objective tumor response (CR or PR). Median Duration of Response was estimated using the Kaplan-Meier method.
Time Frame	Baseline, Day 21 of Cycles 2, 4, and 6 (Bv + chemo), Day 21 of Cycles 7, 8, 9, and 10 (Bv), Day 21 of every other cycle (Bv), and at disease progression.
Safety Issue?	No

Analysis Population Description

ITT population: only participants with an objective tumor response (CR or PR) were included in the analysis.

Reporting Groups

	Description
Bevacizumab 7.5 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 7.5 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.
Bevacizumab 15 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 15 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 15 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

Measured Values

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
Number of Participants Analyzed	56	65
Duration of Response - Time to Event [units: months] Median (95% Confidence Interval)	5.8 (5.2 to 7.0)	5.6 (4.6 to 7.1)

Statistical Analysis 1 for Duration of Response - Time to Event

Statistical Analysis Overview	Comparison Groups	Bevacizumab 7.5 mg Plus Chemotherapy, Bevacizumab 15 mg Plus Chemotherapy
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7587
	Comments	[Not specified]

	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.07
	Confidence Interval	(2-Sided) 95% 0.68 to 1.69
	Estimation Comments	[Not specified]

8. Secondary Outcome Measure:

Measure Title	Overall Survival - Percentage of Participants With an Event
Measure Description	Overall survival was defined as the time between randomization and death due to any cause. Participants without an event were censored at the last time they were known to be alive. Overall Survival was estimated using the Kaplan-Meier method.
Time Frame	Baseline, weekly to 28 days after last dose of study treatment, every 8 weeks thereafter to death due to any cause
Safety Issue?	No

Analysis Population Description

ITT population.

Reporting Groups

	Description
Bevacizumab 7.5 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 7.5 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

	Description
Bevacizumab 15 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 15 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 15 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

Measured Values

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
Number of Participants Analyzed	154	149
Overall Survival - Percentage of Participants With an Event [units: percentage of participants]	64.3	76.5

9. Secondary Outcome Measure:

Measure Title	Overall Survival - Time to Event
Measure Description	Overall survival was defined as the time between randomization and death due to any cause. Participants without an event were censored at the last time they were known to be alive. Overall Survival was estimated using the Kaplan-Meier method.
Time Frame	Baseline, weekly to death due to any cause, or to end of study
Safety Issue?	No

Analysis Population Description

ITT Population.

Reporting Groups

	Description
Bevacizumab 7.5 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 7.5 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.
Bevacizumab 15 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 15 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 15 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

Measured Values

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
Number of Participants Analyzed	154	149
Overall Survival - Time to Event [units: months] Median (95% Confidence Interval)	13.4 (10.5 to 18.1)	13.7 (11.4 to 17.0)

Statistical Analysis 1 for Overall Survival - Time to Event

Statistical Analysis Overview	Comparison Groups	Bevacizumab 7.5 mg Plus Chemotherapy, Bevacizumab 15 mg Plus Chemotherapy
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3120
	Comments	[Not specified]

	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.16
	Confidence Interval	(2-Sided) 95% 0.87 to 1.53
	Estimation Comments	[Not specified]

Reported Adverse Events

Time Frame	Adverse events were assessed from first study treatment until 28 days after last study treatment (LST). In addition, surgical procedures, major injuries and adverse events of special interest for bevacizumab were assessed to at least 6 months after LST.
Additional Description	[Not specified]

Reporting Groups

	Description
Bevacizumab 7.5 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 7.5 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.
Bevacizumab 15 mg Plus Chemotherapy	Cycles 1-6 (3-week cycles): Participants received bevacizumab 15 mg/kg IV on Day 1; either carboplatin at a dose required to achieve an AUC of 6 mg/mL IV and paclitaxel 200 mg/m^2 IV on Day 1, or carboplatin at AUC 5 mg/mL IV on Day 1 and gemcitabine 1200 mg/m^2 IV on Days 1 and 8. The choice of chemotherapy doublet, either carboplatin/paclitaxel or carboplatin/gemcitabine, was left to the discretion of the investigator. The cycle was repeated until disease progression or for a maximum of 6 cycles. Cycle 7 and beyond (3-week cycles): If the first 6 cycles were tolerated with no disease progression, participants then received bevacizumab 15 mg/kg IV on Day 1. This cycle was repeated every 3 weeks until disease progression.

Serious Adverse Events

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Total	53/151 (35.1%)	57/143 (39.86%)
Blood and lymphatic system disorders		
Anaemia [A] *	10/151 (6.62%)	8/143 (5.59%)
Bone Marrow Failure [A] *	0/151 (0%)	1/143 (0.7%)
Febrile Neutropenia [A] *	2/151 (1.32%)	1/143 (0.7%)
Granulocytopenia [A] *	3/151 (1.99%)	1/143 (0.7%)
Leukopenia [A] *	2/151 (1.32%)	1/143 (0.7%)
Neutropenia [A] *	13/151 (8.61%)	7/143 (4.9%)
Pancytopenia [A] *	0/151 (0%)	1/143 (0.7%)
Thrombocytopenia [A] *	12/151 (7.95%)	13/143 (9.09%)
Cardiac disorders		
Angina Pectoris [A] *	1/151 (0.66%)	0/143 (0%)
Cardiac Failure [A] *	0/151 (0%)	2/143 (1.4%)
Left Ventricular Failure [A] *	1/151 (0.66%)	0/143 (0%)
Myocardial Infarction [A] *	2/151 (1.32%)	0/143 (0%)
Palapitations [A] *	1/151 (0.66%)	0/143 (0%)
Tachycardia Paroxysmal [A] *	1/151 (0.66%)	0/143 (0%)
Gastrointestinal disorders		
Constipation [A] *	0/151 (0%)	1/143 (0.7%)
Diarrhoea [A] *	0/151 (0%)	1/143 (0.7%)
Gastric Ulcer [A] *	1/151 (0.66%)	0/143 (0%)
Intestinal Perforation [A] *	0/151 (0%)	1/143 (0.7%)

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Melaena [A] *	1/151 (0.66%)	0/143 (0%)
Nausea [A] *	0/151 (0%)	1/143 (0.7%)
Rectal Haemorrhage [A] *	1/151 (0.66%)	0/143 (0%)
Vomiting [A] *	0/151 (0%)	1/143 (0.7%)
General disorders		
Asthenia [A] *	0/151 (0%)	1/143 (0.7%)
Chest Pain [A] *	1/151 (0.66%)	0/143 (0%)
Death [A] *	1/151 (0.66%)	1/143 (0.7%)
Fatigue [A] *	0/151 (0%)	1/143 (0.7%)
Pyrexia [A] *	1/151 (0.66%)	5/143 (3.5%)
Immune system disorders		
Hypersensitivity [A] *	0/151 (0%)	1/143 (0.7%)
Infections and infestations		
Appendicitis [A] *	1/151 (0.66%)	0/143 (0%)
Bronchopneumonia [A] *	0/151 (0%)	1/143 (0.7%)
Infection [A] *	0/151 (0%)	1/143 (0.7%)
Localised Infection [A] *	0/151 (0%)	1/143 (0.7%)
Lung Infection [A] *	1/151 (0.66%)	0/143 (0%)
Neutropenic Sepsis [A] *	0/151 (0%)	1/143 (0.7%)
Pneumonia [A] *	5/151 (3.31%)	7/143 (4.9%)
Pneumonia Legionella [A] *	0/151 (0%)	1/143 (0.7%)
Pseudomonal Sepsis [A] *	1/151 (0.66%)	0/143 (0%)

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Pulmonary Tuberculosis [A] *	0/151 (0%)	1/143 (0.7%)
Pyothorax [A] *	1/151 (0.66%)	1/143 (0.7%)
Sepsis [A] *	0/151 (0%)	2/143 (1.4%)
Injury, poisoning and procedural complications		
Femur Fracture [A] *	0/151 (0%)	1/143 (0.7%)
Intestinal Anastomosis Complication [A] *	0/151 (0%)	1/143 (0.7%)
Rib Fracture [A] *	0/151 (0%)	1/143 (0.7%)
Wound Dehiscence [A] *	0/151 (0%)	1/143 (0.7%)
Investigations		
Renal Scan Abnormal [A] *	1/151 (0.66%)	0/143 (0%)
Metabolism and nutrition disorders		
Fluid Retension [A] *	0/151 (0%)	1/143 (0.7%)
Hypercalcaemia [A] *	0/151 (0%)	1/143 (0.7%)
Hyperglycaemia [A] *	0/151 (0%)	1/143 (0.7%)
Hyponatraemia [A] *	1/151 (0.66%)	0/143 (0%)
Musculoskeletal and connective tissue disorders		
Musculoskeletal Pain [A] *	0/151 (0%)	1/143 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Breast Cancer [A] *	0/151 (0%)	1/143 (0.7%)
Cancer Pain [A] *	1/151 (0.66%)	0/143 (0%)
Neoplasm [A] *	0/151 (0%)	1/143 (0.7%)
Nervous system disorders		
Cerebral Infarction [A] *	1/151 (0.66%)	1/143 (0.7%)

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Cerebrovascular Accident [A] *	1/151 (0.66%)	1/143 (0.7%)
Embolic Stroke [A] *	0/151 (0%)	1/143 (0.7%)
Ischaemic Stoke [A] *	0/151 (0%)	1/143 (0.7%)
Neuropathy Peripheral [A] *	1/151 (0.66%)	1/143 (0.7%)
Syncope [A] *	1/151 (0.66%)	0/143 (0%)
Renal and urinary disorders		
Renal Failure [A] *	1/151 (0.66%)	0/143 (0%)
Urinary Tract Obstruction [A] *	1/151 (0.66%)	0/143 (0%)
Respiratory, thoracic and mediastinal disorders		
Bronchitis Chronic [A] *	1/151 (0.66%)	0/143 (0%)
Chronic Obstructive Pulmonary Disease [A] *	1/151 (0.66%)	1/143 (0.7%)
Dyspnoea [A] *	2/151 (1.32%)	3/143 (2.1%)
Epistaxis [A] *	3/151 (1.99%)	1/143 (0.7%)
Haemoptysis [A] *	1/151 (0.66%)	0/143 (0%)
Pleural Effusion [A] *	1/151 (0.66%)	0/143 (0%)
Pneumothorax [A] *	0/151 (0%)	2/143 (1.4%)
Pulmonary Artery Thrombosis [A] *	0/151 (0%)	1/143 (0.7%)
Pulmonary Embolism [A] *	1/151 (0.66%)	6/143 (4.2%)
Pulmonary Haemorrhage [A] *	1/151 (0.66%)	0/143 (0%)
Respiratory Failure [A] *	1/151 (0.66%)	0/143 (0%)
Vascular disorders		
Arterial Thrombosis [A] *	0/151 (0%)	1/143 (0.7%)

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Deep Vein Thrombosis [A] *	1/151 (0.66%)	1/143 (0.7%)
Hypertensive Crisis [A] *	1/151 (0.66%)	1/143 (0.7%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 14.0

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

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Total	137/151 (90.73%)	132/143 (92.31%)
Blood and lymphatic system disorders		
Anaemia [A] *	54/151 (35.76%)	39/143 (27.27%)
Leukopenia [A] *	28/151 (18.54%)	16/143 (11.19%)
Neutropenia [A] *	72/151 (47.68%)	57/143 (39.86%)
Thrombocytopenia [A] *	62/151 (41.06%)	41/143 (28.67%)
Gastrointestinal disorders		
Abdominal pain upper [A] *	10/151 (6.62%)	5/143 (3.5%)
Constipation [A] *	27/151 (17.88%)	20/143 (13.99%)
Diarrhoea [A] *	19/151 (12.58%)	16/143 (11.19%)
Mouth ulceration [A] *	12/151 (7.95%)	5/143 (3.5%)
Nausea [A] *	52/151 (34.44%)	38/143 (26.57%)
Stomatitis [A] *	9/151 (5.96%)	9/143 (6.29%)
Vomiting [A] *	18/151 (11.92%)	22/143 (15.38%)
General disorders		
Asthenia [A] *	13/151 (8.61%)	10/143 (6.99%)

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Chest pain [A] *	19/151 (12.58%)	9/143 (6.29%)
Fatigue [A] *	47/151 (31.13%)	41/143 (28.67%)
Mucosal inflammation [A] *	10/151 (6.62%)	9/143 (6.29%)
Pyrexia [A] *	17/151 (11.26%)	7/143 (4.9%)
Infections and infestations		
Nasopharyngitis [A] *	14/151 (9.27%)	13/143 (9.09%)
Urinary tract infection [A] *	8/151 (5.3%)	8/143 (5.59%)
Investigations		
Alanine aminotransferase increased [A] *	9/151 (5.96%)	4/143 (2.8%)
Weight decreased [A] *	14/151 (9.27%)	13/143 (9.09%)
Metabolism and nutrition disorders		
Decreased appetite [A] *	16/151 (10.6%)	26/143 (18.18%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] *	21/151 (13.91%)	15/143 (10.49%)
Back pain [A] *	13/151 (8.61%)	13/143 (9.09%)
Musculoskeletal pain [A] *	15/151 (9.93%)	6/143 (4.2%)
Pain in extremity [A] *	11/151 (7.28%)	7/143 (4.9%)
Nervous system disorders		
Dizziness [A] *	17/151 (11.26%)	16/143 (11.19%)
Dysgeusia [A] *	10/151 (6.62%)	8/143 (5.59%)
Headache [A] *	16/151 (10.6%)	12/143 (8.39%)
Neuropathy peripheral [A] *	19/151 (12.58%)	10/143 (6.99%)
Polyneuropathy [A] *	5/151 (3.31%)	8/143 (5.59%)

	Bevacizumab 7.5 mg Plus Chemotherapy	Bevacizumab 15 mg Plus Chemotherapy
	Affected/At Risk (%)	Affected/At Risk (%)
Psychiatric disorders		
Insomnia [A] *	12/151 (7.95%)	9/143 (6.29%)
Renal and urinary disorders		
Proteinuria [A] *	12/151 (7.95%)	17/143 (11.89%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] *	25/151 (16.56%)	18/143 (12.59%)
Dysphonia [A] *	10/151 (6.62%)	4/143 (2.8%)
Dyspnoea [A] *	12/151 (7.95%)	22/143 (15.38%)
Epistaxis [A] *	33/151 (21.85%)	37/143 (25.87%)
Haemoptysis [A] *	9/151 (5.96%)	8/143 (5.59%)
Oropharyngeal pain [A] *	9/151 (5.96%)	12/143 (8.39%)
Rhinorrhoea [A] *	11/151 (7.28%)	12/143 (8.39%)
Skin and subcutaneous tissue disorders		
Alopecia [A] *	35/151 (23.18%)	30/143 (20.98%)
Pruritus [A] *	9/151 (5.96%)	6/143 (4.2%)
Rash [A] *	15/151 (9.93%)	11/143 (7.69%)
Vascular disorders		
Hypertension [A] *	27/151 (17.88%)	30/143 (20.98%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 14.0

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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