ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 05/23/2014

A Study of Avastin (Bevacizumab) in Combination With Fotemustine in Patients With Metastatic Melanoma

This study has been completed.

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by:	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT01069627

Purpose

This study will investigate the efficacy and safety of bevacizumab + fotemustine in patients with stage IV melanoma, previously untreated with chemo- or immunotherapy for metastatic disease. Patients will receive Avastin (15mg/kg intravenously[IV]) on Day 1 of every 3 week cycle, in combination with fotemustine (100mg/m² IV) on Days 1, 8 and 15, followed by 4 weeks rest, followed by 100mg/m² IV every 3 weeks for 4-6 cycles. The anticipated time on study treatment is until disease progression, and the target sample size is <100 individuals.

Condition	Intervention	Phase
Malignant Melanoma	Drug: bevacizumab [Avastin] Drug: fotemustine	Phase 2

Study Type: Interventional
Study Design: Treatment, Single Group Assignment, Open Label, Non-Randomized, Safety/Efficacy Study
Official Title: An Open-label Study to Assess the Anti-tumor Activity of Avastin in Combination With Fotemustine as First-line Therapy in Patients With Metastatic Melanoma

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Percentage of Participants With Complete Response (CR) or Partial Response (PR) [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]

The percentage of participants with an objective response, defined as achieving CR or PR, as evaluated by the Response Evaluation Criteria In Solid Tumors (RECIST) criteria. CR: disappearance of all clinical and radiological evidence of tumor (both target and non-target), PR: at least a 30 percent (%) decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD.

- Percentage of Participants With Clinical Benefit of CR, PR, or Stable Disease (SD) [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]

  The percentage of participants with an objective response of CR, PR, or SD, as evaluated by RECIST criteria. CR: disappearance of all clinical and radiological evidence of tumor (both target and non-target), PR: at least a 30% decrease in the sum of the LD of target lesions taking as reference the baseline sum LD. SD: steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for pregressive disease (PD). The clinical benefit was finally assessed by computing absolute frequencies and percentages participants with best overall tumor response equal to CR, PR, or SD.

Secondary Outcome Measures:

- Time to Progression (TTP) - Percentage of Participants With an Event [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]

  TTP was defined as the time in days from the date of first study treatment until the date of tumor progression or death. Failure events were defined as occurrence of death or progression of disease. Data for participants who were alive without tumor progression at the end of the study were censured at the end of the observation period.

- TTP - Time to Event [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]

  TTP was defined as the time in days from the of first study treatment until the date of tumor progression or death. Failure events were defined as occurrence of death or progression of disease. Data for participants who were alive without tumor progression at the end of the study were censored at the end of the observation period. Median TTP was estimated using the Kaplan-Meier method.

- Duration of CR - Percentage of Participants With an Event [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]

  Evaluated only for participants whose best overall response was CR. The start date was the date of first documented CR and the end date was defined as the date of first documented progression of disease, or death. Participants who did not experience progression of disease were censored at last tumor assessment date or at maximum follow-up.

- Duration of CR - Time to Event [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]

  The start date was the date of first documented CR and the end date was defined as the date of first documented progression of disease, or death. Participants who did not experience progression of disease were censored at last tumor assessment date or at maximum follow-up. Median duration of CR was estimated using the Kaplan-Meier method.

- Duration of Overall Response of CR or PR - Percentage of Participants With an Event [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]

  The start date was the date of first documented CR or PR and the end date was defined as the date of first documented progression of disease, or death. Participants who did not experience progression of disease were censored at last tumor assessment date or at maximum follow-up.

- Duration of Overall Response of CR or PR - Time to Event [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]

  The start date was the date of first documented CR or PR and the end date was defined as the date of first documented progression of disease. Participants who did not experience progression of disease were censored at last tumor assessment date or at maximum follow-up. Median duration of CR or PR was estimated using the Kaplan-Meier method.

- Duration of Stable Disease - Percentage of Participants With an Event [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]

Stable disease was defined as achieving CR, PR, or SD. The start date was the date of first documented CR, PR, or SD and the end date was defined as the date of first documented progression of disease, or death. Participants who did not experience progression of disease were censored at last tumor assessment date or at maximum follow-up.

- Duration of Stable Disease - Time to Event [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]
  Stable disease was defined as achieving CR, PR, or SD. The start date was the date of first documented CR, PR, or SD and the end date was defined as the date of first documented progression of disease, or death. Participants who did not experience progression of disease were censored at last tumor assessment date or at maximum follow-up. Median duration of CR, PR, or SD was estimated using the Kaplan-Meier method.
- Overall Survival (OS) - Percentage of Participants With an Event [Time Frame: Baseline, every 3 weeks to end-of-treatment, every 3 months during follow-up, to death or end-of-study (maximum of 36 months)] [Designated as safety issue: No]
  OS was defined as the time from the starting day of the therapy up to death or the last date the participant was known to be alive.
- OS - Time to Event [Time Frame: Baseline, every 3 weeks to end-of-treatment, every 3 months during follow-up, to death or end-of-study (maximum of 36 months)] [Designated as safety issue: No]
  The time from the starting day of the therapy up to death or the last date the participant was known to be alive. Median OS was estimated using the Kaplan-Meier method.
- Time to Treatment Failure (TTF) - Percentage of Participants With an Event [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]
  The time from date of start of treatment to the earliest among date of progression, date of death due to any cause, or date of discontinuation due to reason other than 'Protocol Violation' or 'Administrative Problem'. For the participants who did not experience treatment failure, TTF was censored at last adequate tumour assessment.
- TTF - Time to Event [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]
  The time from date of start of treatment to the earliest among date of progression, date of death due to any cause, or date of discontinuation due to reason other than 'Protocol Violation' or 'Administrative Problem'. For the participants who did not experience treatment failure, TTF was censored at last adequate tumour assessment. Median TTF was estimated using the Kaplan-Meier method.
- Time to CR - Percentage of Participants With an Event [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]
  The time between date of start of treatment until first documented CR. This analysis included all responders. Participants who did not achieve a confirmed CR were censored at last adequate tumour assessment date or at maximum follow-up.
- Time to CR - Time To Event [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]
  The time between date of start of treatment until first documented CR. This analysis included all responders. Participants who did not achieve a confirmed CR were censored at last adequate tumour assessment date or at maximum follow-up. Mean time to CR was estimated using the Kaplan-Meier method.
- Time to Overall Response of CR or PR - Percentage of Participants With an Event [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]
  The time between date of start of treatment until first documented response of CR or PR. This analysis included all responders. Participants who did not achieve a confirmed CR or PR were censored at last adequate tumour assessment date or at maximum follow-up.
- Time to Overall Response of CR or PR - Time to Event [Time Frame: Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months] [Designated as safety issue: No]
  The time between date of start of treatment until first documented response of CR or PR. This analysis included all responders. Participants who did not achieve a confirmed CR or PR were censored at last adequate tumor assessment date or at maximum follow-up. Mean time to CR or PR was estimated using the Kaplan-Meier method.

Enrollment: 20

Primary Completion Date: April 2010
Study Completion Date: April 2010

Arms	Assigned Interventions
Experimental: 1	Drug: bevacizumab [Avastin] 15 mg/kg intravenously on day 1 of every 3 week cycle Drug: fotemustine 100 mg/m² intravenously on Days 1, 8, and 15, followed by 4 weeks of rest, then every 21 days up to 4 to 6 cycles

Eligibility

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

Criteria

Inclusion Criteria:

- cutaneous malignant melanoma;
- advanced, inoperable stage IV melanoma;
- measurable and/or evaluable sites of metastases.

Exclusion Criteria:

- prior chemotherapy and/or IFN/IL2 based immunotherapy for metastatic disease;
- prior malignancies within past 5 years, with the exception of cured non-melanoma skin cancer, or in situ cancer of cervix;
- clinically significant cardiovascular disease;
- ongoing treatment with aspirin (>325mg/day) or other medications known to predispose to gastrointestinal ulceration.

Contacts and Locations

Locations

Italy

Firenze, Italy, 50100
Genova, Italy, 16132
Milano, Italy, 20133
Torino, Italy, 10126

Investigators

Study Chair:	Clinical Trials	Hoffmann-La Roche

More Information

Responsible Party: Hoffmann-La Roche (Disclosures Group)
Study ID Numbers: ML19309
Health Authority: Italy: Ministero della Salute

Study Results

Participant Flow

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 milligrams/kilogram (mg/kg) intravenously (IV) on Day 1 and fotemustine 100 mg per square meter (mg/m^2) IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Overall Study

	Bevacizumab + Fotemustine
Started	20
Completed	0
Not Completed	20
Disease progression	7
Adverse Event	12
Protocol Violation	1

Baseline Characteristics

Analysis Population Description

Safety Population: all participants who signed the informed consent form, were assigned a study patient number, and took at least one dose of each drug of study combination.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Baseline Measures

	Bevacizumab + Fotemustine
Number of Participants	20
Age, Continuous [units: years] Mean (Standard Deviation)	51 (15)
Gender, Male/Female [units: participants]	
Female	8
Male	12

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants With Complete Response (CR) or Partial Response (PR)

Measure Description	The percentage of participants with an objective response, defined as achieving CR or PR, as evaluated by the Response Evaluation Criteria In Solid Tumors (RECIST) criteria. CR: disappearance of all clinical and radiological evidence of tumor (both target and non-target), PR: at least a 30 percent (%) decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who signed the informed consent form and were assigned a study patient number; data for 1 participant were not assessable as the participant was discontinued from the study due to a protocol violation.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	20
Percentage of Participants With Complete Response (CR) or Partial Response (PR) [units: percentage of participants] Number (95% Confidence Interval)	15 (3 to 38)

2. Primary Outcome Measure:

Measure Title	Percentage of Participants With Clinical Benefit of CR, PR, or Stable Disease (SD)

Measure Description	The percentage of participants with an objective response of CR, PR, or SD, as evaluated by RECIST criteria. CR: disappearance of all clinical and radiological evidence of tumor (both target and non-target), PR: at least a 30% decrease in the sum of the LD of target lesions taking as reference the baseline sum LD. SD: steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for pregressive disease (PD). The clinical benefit was finally assessed by computing absolute frequencies and percentages participants with best overall tumor response equal to CR, PR, or SD.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT population; data for 1 participant were not assessable as the participant was discontinued from the study due to a protocol violation.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	20
Percentage of Participants With Clinical Benefit of CR, PR, or Stable Disease (SD) [units: percentage of participants] Number (95% Confidence Interval)	65 (41 to 85)

3. Secondary Outcome Measure:

Measure Title	Time to Progression (TTP) - Percentage of Participants With an Event

Measure Description	TTP was defined as the time in days from the date of first study treatment until the date of tumor progression or death. Failure events were defined as occurrence of death or progression of disease. Data for participants who were alive without tumor progression at the end of the study were censured at the end of the observation period.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT population; data for 1 participant were not assessable as the participant was discontinued from the study due to a protocol violation.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	19
Time to Progression (TTP) - Percentage of Participants With an Event [units: percentage of participants]	73.68

4. Secondary Outcome Measure:

Measure Title	TTP - Time to Event
Measure Description	TTP was defined as the time in days from the of first study treatment until the date of tumor progression or death. Failure events were defined as occurrence of death or progression of disease. Data for participants who were alive without tumor progression at the end of the study were censored at the end of the observation period. Median TTP was estimated using the Kaplan-Meier method.

Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT population; data for 1 participant were not assessable as the participant was discontinued from the study due to a protocol violation.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	19
TTP - Time to Event [units: days] Median (95% Confidence Interval)	249.00 (122.00 to 726.00)

5. Secondary Outcome Measure:

Measure Title	Duration of CR - Percentage of Participants With an Event
Measure Description	Evaluated only for participants whose best overall response was CR. The start date was the date of first documented CR and the end date was defined as the date of first documented progression of disease, or death. Participants who did not experience progression of disease were censored at last tumor assessment date or at maximum follow-up.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT population; only participants with a best overall response of CR were included in the analysis.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	1
Duration of CR - Percentage of Participants With an Event [units: percentage of participants]	0

6. Secondary Outcome Measure:

Measure Title	Duration of CR - Time to Event
Measure Description	The start date was the date of first documented CR and the end date was defined as the date of first documented progression of disease, or death. Participants who did not experience progression of disease were censored at last tumor assessment date or at maximum follow-up. Median duration of CR was estimated using the Kaplan-Meier method.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT population; only participants with a CR were included in the analysis

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	1
Duration of CR - Time to Event [units: days] Median (95% Confidence Interval)	NA (NA to NA) [1]

[1] Complete response was achieved by a single participant who reached confirmed CR during the study period. This participant did not have worsening of his status during the observation period, no failures were observed relative to this endpoint.

7. Secondary Outcome Measure:

Measure Title	Duration of Overall Response of CR or PR - Percentage of Participants With an Event
Measure Description	The start date was the date of first documented CR or PR and the end date was defined as the date of first documented progression of disease, or death. Participants who did not experience progression of disease were censored at last tumor assessment date or at maximum follow-up.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT population; only participants with a best overall response of CR or PR were included in the analysis.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	3
Duration of Overall Response of CR or PR - Percentage of Participants With an Event [units: percentage of participants]	66.67

8. Secondary Outcome Measure:

Measure Title	Duration of Overall Response of CR or PR - Time to Event
Measure Description	The start date was the date of first documented CR or PR and the end date was defined as the date of first documented progression of disease. Participants who did not experience progression of disease were censored at last tumor assessment date or at maximum follow-up. Median duration of CR or PR was estimated using the Kaplan-Meier method.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT population; only participants with a best overall response of CR or PR were included in the analysis.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	3
Duration of Overall Response of CR or PR - Time to Event [units: days] Median (95% Confidence Interval)	324.00 (155.00 to NA) [1]

[1] Number of data points is too small to support the calculation of an upper limit for the 95% confidence interval.

9. Secondary Outcome Measure:

Measure Title	Duration of Stable Disease - Percentage of Participants With an Event
Measure Description	Stable disease was defined as achieving CR, PR, or SD. The start date was the date of first documented CR, PR, or SD and the end date was defined as the date of first documented progression of disease, or death. Participants who did not experience progression of disease were censored at last tumor assessment date or at maximum follow-up.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT population; only participants with a best overall response of CR, PR, or SD were included in the anlaysis.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	12
Duration of Stable Disease - Percentage of Participants With an Event [units: percentage of participants]	58.33

10. Secondary Outcome Measure:

Measure Title	Duration of Stable Disease - Time to Event
Measure Description	Stable disease was defined as achieving CR, PR, or SD. The start date was the date of first documented CR, PR, or SD and the end date was defined as the date of first documented progression of disease, or death. Participants who did not experience progression of disease were censored at last tumor assessment date or at maximum follow-up. Median duration of CR, PR, or SD was estimated using the Kaplan-Meier method.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT population; only participants with a best overall response of CR, PR, or SD were included in the analysis.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	12
Duration of Stable Disease - Time to Event [units: days] Median (95% Confidence Interval)	619.00 (249.00 to NA) [1]

[1] Number of data points is too small to support the calculation of an upper limit for the 95% confidence interval.

11. Secondary Outcome Measure:

Measure Title	Overall Survival (OS) - Percentage of Participants With an Event
Measure Description	OS was defined as the time from the starting day of the therapy up to death or the last date the participant was known to be alive.
Time Frame	Baseline, every 3 weeks to end-of-treatment, every 3 months during follow-up, to death or end-of-study (maximum of 36 months)
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	20
Overall Survival (OS) - Percentage of Participants With an Event [units: percentage of participants]	60

12. Secondary Outcome Measure:

Measure Title	OS - Time to Event
Measure Description	The time from the starting day of the therapy up to death or the last date the participant was known to be alive. Median OS was estimated using the Kaplan-Meier method.
Time Frame	Baseline, every 3 weeks to end-of-treatment, every 3 months during follow-up, to death or end-of-study (maximum of 36 months)
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	20
OS - Time to Event [units: days] Median (95% Confidence Interval)	615.00 (298.00 to 796.00)

13. Secondary Outcome Measure:

Measure Title	Time to Treatment Failure (TTF) - Percentage of Participants With an Event
Measure Description	The time from date of start of treatment to the earliest among date of progression, date of death due to any cause, or date of discontinuation due to reason other than ‘Protocol Violation’ or ‘Administrative Problem’. For the participants who did not experience treatment failure, TTF was censored at last adequate tumour assessment.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT Population; data for 1 participant were not assessable as the participant was discontinued from the study due to a protocol violation.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	19
Time to Treatment Failure (TTF) - Percentage of Participants With an Event [units: percentage of participants]	100

14. Secondary Outcome Measure:

Measure Title	TTF - Time to Event
Measure Description	The time from date of start of treatment to the earliest among date of progression, date of death due to any cause, or date of discontinuation due to reason other than ‘Protocol Violation’ or ‘Administrative Problem’. For the participants who did not experience treatment failure, TTF was censored at last adequate tumour assessment. Median TTF was estimated using the Kaplan-Meier method.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT population; data for 1 participant were not assessable as the participant was discontinued from the study due to a protocol violation.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	19
TTF - Time to Event [units: days] Median (95% Confidence Interval)	126.00 (43.00 to 158.00)

15. Secondary Outcome Measure:

Measure Title	Time to CR - Percentage of Participants With an Event
Measure Description	The time between date of start of treatment until first documented CR. This analysis included all responders. Participants who did not achieve a confirmed CR were censored at last adequate tumour assessment date or at maximum follow-up.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT Population; data for 1 participant were not assessable as the participant was discontinued from the study due to a protocol violation.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	19
Time to CR - Percentage of Participants With an Event [units: percentage of participants]	5.26

16. Secondary Outcome Measure:

Measure Title	Time to CR - Time To Event
Measure Description	The time between date of start of treatment until first documented CR. This analysis included all responders. Participants who did not achieve a confirmed CR were censored at last adequate tumour assessment date or at maximum follow-up. Mean time to CR was estimated using the Kaplan-Meier method.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT population; only participants with a CR were included in the analysis.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	1
Time to CR - Time To Event [units: days] Mean (Standard Deviation)	76.00 (NA) [1]

[1] Number of data points is too small to support the calculation of the standard deviation.

17. Secondary Outcome Measure:

Measure Title	Time to Overall Response of CR or PR - Percentage of Participants With an Event
Measure Description	The time between date of start of treatment until first documented response of CR or PR. This analysis included all responders. Participants who did not achieve a confirmed CR or PR were censored at last adequate tumour assessment date or at maximum follow-up.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT Population; data for 1 participant were not assessable as the participant was discontinued from the study due to a protocol violation.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	19
Time to Overall Response of CR or PR - Percentage of Participants With an Event [units: percentage of participants]	15.79

18. Secondary Outcome Measure:

Measure Title	Time to Overall Response of CR or PR - Time to Event
Measure Description	The time between date of start of treatment until first documented response of CR or PR. This analysis included all responders. Participants who did not achieve a confirmed CR or PR were censored at last adequate tumor assessment date or at maximum follow-up. Mean time to CR or PR was estimated using the Kaplan-Meier method.
Time Frame	Baseline, every 9 weeks during study treatment, and every 3 months during follow-up, up to 36 months
Safety Issue?	No

Analysis Population Description

ITT Population; only participants with a response of CR or PR were included in the analysis.

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Measured Values

	Bevacizumab + Fotemustine
Number of Participants Analyzed	3
Time to Overall Response of CR or PR - Time to Event [units: days] Mean (Standard Deviation)	116.50 (7.58)

Reported Adverse Events

Time Frame	From date of first administration of study drug to 28 days after last administration of study drug.
Additional Description	[Not specified]

Reporting Groups

	Description
Bevacizumab + Fotemustine	Cycle 1 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 and fotemustine 100 mg/m^2 IV on Days 1, 8, and 15 followed by 1 week off. Cycle 1 was not repeated. Cycle 2 (3-week cycle): Participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. Cycle 2 was not repeated. Cycles 3-8 (3-week cycles): Participants received bevacizumab 15 mg/kg IV and fotemustine 100 mg/m^2 IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks for 4 to 6 cycles. Cycles 9 and beyond (3-week cycles): If the previous 6 to 8 cycles were tolerated with no disease progression, then participants received bevacizumab 15 mg/kg IV on Day 1 followed by 2 weeks off. This cycle was repeated every 3 weeks until disease progression or unacceptable toxicity.

Serious Adverse Events

	Bevacizumab + Fotemustine
	Affected/At Risk (%)
Total	4/20 (20%)
Blood and lymphatic system disorders	
Thrombocytopenia [A] *	1/20 (5%)
Reproductive system and breast disorders	
Metrorrhagia [A] *	1/20 (5%)
Respiratory, thoracic and mediastinal disorders	
Dyspnoea [A] *	1/20 (5%)
Pleural effusion [A] *	1/20 (5%)
Pulmonary embolism [A] *	1/20 (5%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (11.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	Bevacizumab + Fotemustine
	Affected/At Risk (%)
Total	18/20 (90%)

	Bevacizumab + Fotemustine
	Affected/At Risk (%)
Blood and lymphatic system disorders	
Anaemia [A] *	1/20 (5%)
Febrile neutropenia [A] *	2/20 (10%)
Leukopenia [A] *	3/20 (15%)
Lymphadenopathy [A] *	1/20 (5%)
Neutropenia [A] *	13/20 (65%)
Thrombocytopenia [A] *	14/20 (70%)
Eye disorders	
Cataract [A] *	1/20 (5%)
Gastrointestinal disorders	
Abdominal pain [A] *	2/20 (10%)
Abdominal pain upper [A] *	1/20 (5%)
Constipation [A] *	1/20 (5%)
Diarrhoea [A] *	1/20 (5%)
Dyspepsia [A] *	2/20 (10%)
Dysphagia [A] *	1/20 (5%)
Gastric dilatation [A] *	1/20 (5%)
Gingival bleeding [A] *	1/20 (5%)
Haemorrhoids [A] *	1/20 (5%)
Mouth haemorrhage [A] *	1/20 (5%)
Nausea [A] *	3/20 (15%)
Oesophageal achalasia [A] *	1/20 (5%)

	Bevacizumab + Fotemustine
	Affected/At Risk (%)
Rectal haemorrhage [A] *	1/20 (5%)
Salivary gland mass [A] *	1/20 (5%)
Vomiting [A] *	1/20 (5%)
General disorders	
Asthenia [A] *	10/20 (50%)
Mucosal inflammation [A] *	1/20 (5%)
Oedema [A] *	1/20 (5%)
Oedema peripheral [A] *	2/20 (10%)
Pyrexia [A] *	3/20 (15%)
Immune system disorders	
Hypersensitivity [A] *	1/20 (5%)
Infections and infestations	
Cystitis [A] *	1/20 (5%)
Influenza [A] *	1/20 (5%)
Lymphangitis [A] *	1/20 (5%)
Nasopharyngitis [A] *	1/20 (5%)
Urinary tract infection [A] *	1/20 (5%)
Injury, poisoning and procedural complications	
Thermal burn [A] *	1/20 (5%)
Investigations	
Alanine aminotransferase [A] *	1/20 (5%)
Aspartate aminotransferase [A] *	1/20 (5%)
Haematocrit decreased [A] *	1/20 (5%)

	Bevacizumab + Fotemustine
	Affected/At Risk (%)
Red blood cell count decreased [A] *	1/20 (5%)
Metabolism and nutrition disorders	
Anorexia [A] *	3/20 (15%)
Hyperuricaemia [A] *	1/20 (5%)
Hypokalaemia [A] *	2/20 (10%)
Musculoskeletal and connective tissue disorders	
Back pain [A] *	1/20 (5%)
Musculoskeletal chest pain [A] *	1/20 (5%)
Musculoskeletal pain [A] *	1/20 (5%)
Pain in extremity [A] *	2/20 (10%)
Vertebral column mass [A] *	1/20 (5%)
Nervous system disorders	
Dizziness [A] *	1/20 (5%)
Headache [A] *	2/20 (10%)
Psychiatric disorders	
Depression [A] *	1/20 (5%)
Insomnia [A] *	1/20 (5%)
Renal and urinary disorders	
Haematuria [A] *	1/20 (5%)
Reproductive system and breast disorders	
Metrorrhagia [A] *	1/20 (5%)
Respiratory, thoracic and mediastinal disorders	
Cough [A] *	1/20 (5%)

	Bevacizumab + Fotemustine
	Affected/At Risk (%)
Dysphonia [A] *	1/20 (5%)
Dyspnoea [A] *	1/20 (5%)
Epistaxis [A] *	4/20 (20%)
Oropharyngeal pain [A] *	1/20 (5%)
Pleural effusion [A] *	1/20 (5%)
Pulmonary embolism [A] *	1/20 (5%)
Skin and subcutaneous tissue disorders	
Skin disorder [A] *	1/20 (5%)
Vascular disorders	
Hypertension [A] *	8/20 (40%)
Hypotension [A] *	1/20 (5%)
Thrombosis [A] *	1/20 (5%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (11.1)

Limitations and Caveats

Nonserious adverse events presented in this record include all adverse events reported during the study, not just nonserious events.

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 the Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

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