ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 01/20/2015

ClinicalTrials.gov ID: NCT00448136

Study Identification

Unique Protocol ID:	ML20383
Brief Title:	A Study of Avastin (Bevacizumab) in Combination With Chemotherapy in Patients With Endocrine Tumors of the Gastrointestinal Tract.
Official Title:	An Open Label Study to Evaluate the Effect of Avastin in Association With Chemotherapy on Progression-free Survival in Patients With Progressive Advanced/Metastatic Well-differentiated Digestive Endocrine Tumors of the Gastrointestinal Tract
Secondary IDs:	

Study Status

Record Verification:	January 2015
Overall Status:	Completed
Study Start:	July 2007
Primary Completion:	November 2011 [Actual]
Study Completion:	November 2011 [Actual]

Sponsor/Collaborators

Sponsor:	Hoffmann-La Roche
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	No

IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 06 11 69 Board Name: Ile-de-France VIII, Boulogne Billancourt Board Affiliation: Unknown Phone: +33 149095814 Email: cppidf8@orange.fr
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	France: AFSSAPS (Agence francaise de securite sanitaire des produits de sante)

Study Description

Brief Summary:	This 2 arm study will assess the efficacy and safety of two systemic treatments including Avastin in patients with previously-untreated progressive locally advanced/metastatic well-differentiated digestive endocrine tumors. Patients with duodeno-pancreatic tumors (arm 1) will be treated with 5FU/streptozotocin iv (5FU 400mg/m2/d D1 to D5;streptozotocin 500mg/m2/d/ iv D1 to D5;D1=D42) every 6 weeks, plus Avastin 7.5mg/kg iv every 3 weeks. Patients with gastrointestinal tract tumors (arm 2) will be treated with Xeloda 1000mg/m2 po bid D1 to D14 plus Avastin 7.5mg/kg iv D1=D21 every 3 weeks. The patients will be treated with chemotherapy for a minimum of 6 months, unless there is tumor progression and/or unacceptable toxicity. The anticipated time on study treatment is until disease progression or unacceptable toxicity, and the target sample size is <100 individuals.
Detailed Description:	

Conditions

Conditions:	Neoplasms
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Parallel Assignment
Number of Arms:	2
Masking:	Open Label

Allocation:	Non-Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	83 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 1	Drug: bevacizumab [Avastin] 7.5mg/kg iv on day 1 every 3 weeks Drug: 5 FU 400mg/m2/day iv on days 1-5 every 6 weeks Drug: Streptozotocin 500mg/m2/day iv on days 1-5 every 6 weeks
Experimental: 2	Drug: bevacizumab [Avastin] 7.5mg/kg iv on day 1 every 3 weeks Drug: Xeloda 1000mg/m2 po bid on days 1-14 every 3 weeks

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	
Gender:	Both
Accepts Healthy Volunteers?:	No
Criteria:	Inclusion Criteria:

- adult patients, >=18 years of age;
- well-differentiated gastrointestinal tract endocrine tumors, or duodeno-pancreatic endocrine tumors;
- no previous anti-cancer therapy, other than surgery;
- progressive metastatic disease;
- >=1 measurable lesion.

Exclusion Criteria:

- abnormal cardiac function, with history of ischemic heart disease in past 6 months and/or abnormal 12 lead ECG;
- patients with known bleeding disorders;
- unstable systemic disease;

- chronic daily treatment with high-dose aspirin, NSAIDs or corticosteroids;
- previous history of malignancy (other than successfully treated basal and squamous cell cancer of the skin, and/or in situ cancer of the cervix).

Contacts/Locations

Study Officials: Clinical Trials
Study Director
Hoffmann-La Roche

Locations: France
Strasbourg, France, 67091

Paris, France, 75908

Reims, France, 51092

Villejuif, France, 94805

Caen, France, 14033

Angers, France, 49933

Rouen, France, 76031

Clichy, France, 92118

Montpellier, France, 34298

Poitiers, France, 86021

Marseille, France, 13285

Nice, France, 06189

Bordeaux, France, 33075

Marseille, France, 13273

Nantes, France, 44093

Toulouse, France, 31059

Paris, France, 75651

Boulogne Billancourt, France, 92104

Creteil, France, 94010

Dijon, France, 21079

Lille, France, 59020

Paris, France, 75571

Saint Brieuc, France, 22015

Lyon, France, 69437

Paris, France, 75970

Chambray Les Tours, France, 37171

Marseille, France, 13385

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Reporting Groups

	Description
Bevacizumab + 5-fluorouracil (5-FU) + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 milligrams per kilogram (mg/kg) intravenously (IV) on Days 1 and 22; 5-FU 400 mg per square meter per day (mg/m^2/day) IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.

	Description
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, orally (PO), twice daily (BID) on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Overall Study

	Bevacizumab + 5-fluorouracil (5-FU) + Streptozocin	Bevacizumab + Capecitabine
Started	34	49
Completed	30	41
Not Completed	4	8
Death	3	8
Investigator's decision (progression)	1	0

Baseline Characteristics

Analysis Population Description

Intent-to-treat (ITT) population: all participants who received at least 1 dose of treatment.

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Baseline Measures

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine	Total
Number of Participants	34	49	83
Age, Continuous [units: years] Mean (Standard Deviation)	55.93 (10.63)	61.64 (9.20)	59.29 (10.15)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine	Total
Gender, Male/Female [units: participants]			
Female	12	23	35
Male	22	26	48

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Progression-Free Survival (PFS) - Percentage of Participants With an Event
Measure Description	PFS is defined as the interval between the date of start of treatment and the date of evaluation by the investigator of progressive disease or death from any cause. The progression was assessed according to Response Evaluation Criteria In Solid Tumors (RECIST) using medical imaging during the treatment period and by the investigators (confirmed by medical imaging) during the follow-up period. Data for participants who were lost to follow-up were censored at the date of last evaluation without progression. Data for participants who completed the study without an event of disease progression or death were censored at the date of the last visit or follow-up without progression.
Time Frame	Screening, every 3 months during treatment, every 6 months during follow-up to 2 years
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	34	49
Progression-Free Survival (PFS) - Percentage of Participants With an Event [units: percentage of participants]	52.9	53.1

2. Primary Outcome Measure:

Measure Title	PFS - Time to Event
Measure Description	PFS is defined as the interval between the date of start of treatment and the date of evaluation by the investigator of progressive disease or death from any cause. The progression was assessed according to RECIST using medical imaging during the treatment period and by the investigators (confirmed by medical imaging) during the follow-up period. Data for participants who were lost to follow-up were censored at the date of last evaluation without progression. Data for participants who completed the study without an event of disease progression or death were censored at the date of the last visit or follow-up without progression. Median PFS was estimated using the Kaplan-Meier method.
Time Frame	Screening, every 3 months during treatment, every 6 months during follow-up to 2 years
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	34	49
PFS - Time to Event [units: months] Median (95% Confidence Interval)	23.7 (13.1 to NA) [1]	23.4 (13.2 to NA) [1]

[1] The upper limit for the median PFS was not estimated because it was longer than the latest censoring time, and therefore was not achieved.

3. Primary Outcome Measure:

Measure Title	PFS - Percentage of Participants Estimated to be Progression Free at 12 and 24 Months
Measure Description	PFS is defined as the interval between the date of start of treatment and the date of evaluation by the investigator of progressive disease or death from any cause. The progression was assessed according to RECIST using medical imaging during the treatment period and by the investigators (confirmed by medical imaging) during the follow-up period. Data for participants who were lost to follow-up were censored at the date of last evaluation without progression. Data for participants who completed the study without an event of disease progression or death were censored at the date of the last visit or follow-up without progression.
Time Frame	Screening, every 3 months during treatment, every 6 months during follow-up to 2 years
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	34	49
PFS - Percentage of Participants Estimated to be Progression Free at 12 and 24 Months [units: percentage of participants]		
12 months	76	65
24 months	50	48

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants With a Response by Best Overall Response

Measure Description	Best overall response defined as best response recorded during the study as defined according to RECIST; performed by the investigator and by centralized review. Complete response (CR): complete disappearance of all target lesions and non-target disease. All lesions, both target and non-target, must have decreased to normal (short axis, less than [<]10 millimeters [mm]). No new lesions. Partial response (PR): greater than or equal to (≥)30 percent (%) decrease under baseline of the sum of diameters of all target lesions. The short axis was used in the sum for target nodes, while the longest diameter (LD) was used in the sum for all other target lesions. No unequivocal progression of non-target disease. No new lesions. Stable disease (SD): not qualifying for CR, PR, or Progressive Disease (PD). PD: 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 or the appearance of 1 or more new lesions.
Time Frame	Screening, every 3 months during treatment, every 6 months during follow-up to 2 years
Safety Issue?	No

Analysis Population Description

ITT population. Data were missing from centralized review for 1 participant.

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	34	49
Percentage of Participants With a Response by Best Overall Response [units: percentage of participants] Number (95% Confidence Interval)		
PR (Investigator)	55.9 (39.2 to 72.6)	18.4 (7.5 to 29.2)
PR (Centralized review)	51.5 (34.5 to 68.6)	12.5 (3.1 to 21.9)
SD (Investigator)	44.1 (27.4 to 60.8)	69.4 (56.5 to 82.3)
SD (Centralized review)	48.5 (31.4 to 65.5)	81.3 (70.2 to 92.3)
PD (Investigator)	0 (0 to 0)	8.2 (0.5 to 15.8)
PD (Centralized review)	0 (0 to 0)	0 (0 to 0)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Not evaluable (Investigator)	0 (0 to 0)	4.1 (0.0 to 9.6)
Not evaluable (Centralized review)	0 (0 to 0)	6.3 (0.0 to 13.1)

5. Secondary Outcome Measure:

Measure Title	Duration of Overall Response (OR) - Percentage of Participants With an Event
Measure Description	Determined only for those participants with an overall response (CR or PR) and was defined as the time interval between the response (CR or PR) and the date of progression or death from any cause. Data for participants who were lost to follow-up were censored at the date of last evaluation without progression. Data for participants who completed the study without an event of progression or death were censored at the data of last visit or follow-up without progression.
Time Frame	Screening, every 3 months during treatment, every 6 months during follow-up to 2 years
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 + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	19	9
Duration of Overall Response (OR) - Percentage of Participants With an Event [units: percentage of participants]	42.1	22.2

6. Secondary Outcome Measure:

Measure Title	Duration of OR - Time to Event
Measure Description	Determined only for those participants with an overall response (CR or PR) and was defined as the time interval between the response (CR or PR) and the date of progression or death from any cause. Data for participants who were lost to follow-up were censored at the date of last evaluation without progression. Data for participants who completed the study without an event of progression or death were censored at the data of last visit or follow-up without progression. Median duration of OR was estimated using the Kaplan-Meier method.
Time Frame	Screening, every 3 months during treatment, every 6 months during follow-up to 2 years
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 + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	19	9
Duration of OR - Time to Event [units: months] Median (95% Confidence Interval)	NA (11.2 to NA) [1]	NA (3.2 to NA) [2]

[1] Median duration and upper limit of the 95% confidence interval (CI) could not be calculated due to an insufficient number of events.

[2] Median duration and upper limit of the 95% CI could not be calculated due to an insufficient number of events.

7. Secondary Outcome Measure:

Measure Title	Duration of OR - Percentage of Participants With Sustained Response at 12 and 24 Months

Measure Description	Duration of OR was determined only for those participants with an overall response of CR or PR and was defined as the time interval between the response (CR or PR) and the date of progression or death from any cause. Data for participants who were lost to follow-up were censored at the date of last evaluation without progression. Data for participants who completed the study without an event of progression or death were censored at the data of last visit or follow-up without progression.
Time Frame	Screening, every 3 months during treatment, every 6 months during follow-up to 2 years
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	19	9
Duration of OR - Percentage of Participants With Sustained Response at 12 and 24 Months [units: percentage of participants]		
12 months	74	70
24 months	55	NA [1]

[1] Not evaluable as data from all participants were censored, or participants had experienced events of progression or death before the 24-month timepoint.

8. Secondary Outcome Measure:

Measure Title	Duration of Overall Disease Control (ODC) - Percentage of Participants With an Event

Measure Description	Determined only for those participants with overall disease control (CR, PR or SD per RECIST) and was defined as the time interval between the first occurrence of disease control (CR, PR or SD) and the date of progression or death from any cause. Data for participants who were lost to follow-up were censored at the date of last evaluation without progression. Data for participants who completed the study without an event of progression or death were censored at the data of last visit or follow-up without progression.
Time Frame	Screening, every 3 months during treatment, every 6 months during follow-up to 2 years
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	34	43
Duration of Overall Disease Control (ODC) - Percentage of Participants With an Event [units: percentage of participants]	52.9	46.5

9. Secondary Outcome Measure:

Measure Title	Duration of ODC - Time to Event
Measure Description	Determined only for those participants with overall control disease (CR, PR, or SD per RECIST) and was defined as the time interval between the first occurrence of disease control (CR, PR or SD) and the date of progression or death from any cause. Data for participants who were lost to follow-up were censored at the date of last evaluation without progression. Data for participants who completed the study without an event of progression or death were censored at the data of last visit or follow-up without progression. Median time to event was estimated using the Kaplan-Meier method.
Time Frame	Screening, every 3 months during treatment, every 6 months during follow-up to 2 years

Safety Issue?	No

Analysis Population Description

ITT population; only participants with a response (CR, PR, or SD) were included in the analysis.

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	34	43
Duration of ODC - Time to Event [units: months] Median (95% Confidence Interval)	22.3 (11.9 to NA) [1]	23.4 (15.1 to NA) [1]

[1] The upper limit of the 95% CI was not estimated because it was longer than the latest censoring time, and therefore was not achieved.

10. Secondary Outcome Measure:

Measure Title	Duration of ODC - Percentage of Participants Maintaining Disease Control at 12 and 24 Months
Measure Description	Duration of ODC was determined only for those participants with overall control disease (CR, PR, or SD per RECIST) and was defined as the time interval between the first occurrence of disease control (CR, PR, or SD) and the date of progression or death from any cause. Data for participants who were lost to follow-up were censored at the date of last evaluation without progression. Data for participants who completed the study without an event of progression or death were censored at the data of last visit or follow-up without progression.
Time Frame	Screening, every 3 months during treatment, every 6 months during follow-up to 2 years
Safety Issue?	No

Analysis Population Description

ITT population; only participants with a response (CR, PR, or SD) were included in the analysis.

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	34	43
Duration of ODC - Percentage of Participants Maintaining Disease Control at 12 and 24 Months [units: percentage of participants]		
12 months	68	72
24 months	42	NA [1]

[1] Not evaluable as data from all participants were censored, or participants had experienced events of progression or death before the 24-month timepoint.

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 first treatment administration to death from any cause. Data for participants who were lost to follow-up were censored at the date of last evaluation. Data for participants who were alive at the end of the study were censored at the date of last visit.
Time Frame	Screening, Day 1 of every cycle during treatment, every 6 months during follow-up to 2 years
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	34	49
Overall Survival (OS) - Percentage of Participants With an Event [units: percentage of participants]	14.7	16.3

12. Secondary Outcome Measure:

Measure Title	OS - Time to Event
Measure Description	OS was defined as the time from the first treatment administration to death from any cause. Data for participants who were lost to follow-up were censored at the date of last evaluation. Data for participants who were alive at the end of the study were censored at the date of last visit. Median OS was estimated using the Kaplan-Meier method.
Time Frame	Screening, Day 1 of every cycle during treatment, every 6 months during follow-up to 2 years
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	34	49
OS - Time to Event [units: months] Median (95% Confidence Interval)	NA (27 to NA) [1]	NA (NA to NA) [2]

[1] The median (and upper 95% CI) OS was not estimated because it was longer than the latest censoring time, and therefore was not achieved.

[2] The median OS was not estimated because it was longer than the latest censoring time, and therefore was not achieved.

13. Secondary Outcome Measure:

Measure Title	OS - Percentage of Participants Surviving at 12 and 24 Months
Measure Description	OS was defined as the time from the first treatment administration to death from any cause. Data for participants who were lost to follow-up were censored at the date of last evaluation. Data for participants who were alive at the end of the study were censored at the date of last visit.
Time Frame	Screening, Day 1 of every cycle during treatment, every 6 months during follow-up to 2 years
Safety Issue?	No

Analysis Population Description

ITT population.

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	34	49

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
OS - Percentage of Participants Surviving at 12 and 24 Months [units: percentage of participants]		
12 months	94	88
24 months	88	85

14. Secondary Outcome Measure:

Measure Title	Global Health Status as Assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - C30 (EORTC QLQ-C30)
Measure Description	EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status, symptom scales (fatigue, pain, nausea/vomiting) and single items (dyspnoea, appetite loss, insomnia, constipation/ diarrhea and financial difficulties). Most questions used 4-point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale [1 'very poor' to 7 'Excellent']). Scores were averaged and transformed to 0-100 scale; higher score=better level of functioning or greater degree of symptoms.
Time Frame	Screening, every 3 months during treatment
Safety Issue?	No

Analysis Population Description

ITT population; only participants who completed the questionnaire at baseline and who had at least 1 post-baseline assessment were included in the analysis. Number (n) equals (=) the number of participants assessed for the specified parameter at a given visit.

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	29	40

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Global Health Status as Assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - C30 (EORTC QLQ-C30) [units: units on a scale] Mean (Standard Deviation)		
Baseline (n=29,40)	65.23 (23.89)	65.42 (20.02)
3 months (n=20,32)	65.83 (19.48)	57.03 (22.41)
6 months (n=20,24)	60.00 (21.90)	66.32 (21.35)
12 months (n=13,14)	66.03 (17.83)	72.62 (19.46)
End of treatment (n=13,23)	64.74 (23.36)	57.97 (28.48)

15. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Change From Baseline in Global Health Status by EORTC QLQ-C30 Improvement Category
Measure Description	EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status, symptom scales (fatigue, pain, nausea/vomiting) and single items (dyspnoea, appetite loss, insomnia, constipation/ diarrhea and financial difficulties). Most questions used 4-point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale [1 'very poor' to 7 'Excellent']). Scores averaged, transformed to 0-100 scale; higher score=better level of functioning or greater degree of symptoms. Changes from baseline were categorized as follows: Very much worsening (less than [<]-20); Moderate worsening (greater than or equal to [≥]-20 to <-10); Little worsening (≥-10 to <-5); No change (≥-5 to less than or equal to [≤]5); Little improvement (>5 to ≤10); Moderate improvement (>10 to ≤20); and Very much improved (>20).
Time Frame	Screening, every 3 months during treatment
Safety Issue?	No

Analysis Population Description

ITT population; only participants who completed the questionnaire at baseline and who had at least 1 post-baseline assessment were included in the analysis. n=number of participants assessed for the specified parameter at a given visit.

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	20	29
Percentage of Participants With Change From Baseline in Global Health Status by EORTC QLQ-C30 Improvement Category [units: percentage of participants]		
3 months, Very much worsening (n=20,29)	10.0	17.2
3 months, Moderate worsening (n=20,29)	10.0	24.1
3 months, Little worsening (n=20,29)	10.0	17.2
3 months, No change (n=20,29)	40.0	24.1
3 months, Little improving (n=20,29)	5.0	3.4
3 months, Moderate Improving (n=20,29)	15.0	3.4
3 months, Very much improving (n=20,29)	10.0	10.3
6 months, Very much worsening (n=20,22)	15.0	22.7
6 months, Moderate worsening (n=20,22)	10.0	18.2
6 months, Little worsening (n=20,22)	5.0	0
6 months, No change (n=20,22)	35.0	31.8
6 months, Little improving (n=20,22)	10.0	13.6
6 months, Moderate Improving (n=20,22)	15.0	0
6 months, Very much improving (n=20,22)	10.0	13.6
12 months, Very much worsening (n=12,13)	8.3	0
12 months, Moderate worsening (n=12,13)	8.3	15.4

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
12 months - Little worsening (n=12,13)	33.3	15.4
12 months, No change (n=12,13)	25.0	38.5
12 months, Little improving (n=12,13)	8.3	7.7
12 months, Moderate Improving (n=12,13)	16.7	15.4
12 months, Very much improving (n=12,13)	0	7.7
End of treatment, Very much worsening (n=13,20)	15.4	15.0
End of treatment, Moderate worsening (n=13,20)	30.8	5.0
End of treatment, Little worsening (n=13,20)	0	10.0
End of treatment, No change (n=13,20)	15.4	45.0
End of treatment, Little improving (n=13,20)	15.4	10.0
End of treatment, Moderate Improving (n=13,20)	15.4	5.0
End of treatment, Very much improving (n=13,20)	7.7	10.0

16. Secondary Outcome Measure:

Measure Title	EORTC QLQ-C30 Functional and Symptom Scale Scores
Measure Description	EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status, symptom scales (fatigue, pain, nausea/vomiting) and single items (dyspnoea, appetite loss, insomnia, constipation/ diarrhea and financial difficulties). Most questions used 4-point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale [1 'very poor' to 7 'Excellent']). Scores averaged, transformed to 0-100 scale; for functional scores, a higher score represents a better level of functioning. For symptom scale scores a higher level represents a more severe level of symptoms.
Time Frame	Screening, every 3 months during treatment
Safety Issue?	No

Analysis Population Description

ITT population; only participants who completed the questionnaire at baseline and who had at least 1 post-baseline assessment were included in the analysis. n=number of participants assessed for the specified parameter at a given visit.

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.
Bevacizumab + Capecitabine	Cycles 1-9 (21-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 1000 mg/m^2, tablets, PO, BID on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Measured Values

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Number of Participants Analyzed	30	43
EORTC QLQ-C30 Functional and Symptom Scale Scores [units: units on a scale] Mean (Standard Deviation)		
Physical functioning, Baseline (n=30,43)	90.44 (13.30)	87.71 (14.88)
Physical functioning, 3 months (n=22,33)	89.32 (12.77)	75.35 (24.07)
Physical functioning, 6 months (n=21,24)	81.98 (19.75)	82.50 (18.21)
Physical functioning, End of Treatment (n=13,24)	82.82 (20.21)	79.44 (19.85)
Role functioning, Baseline (n=30,43)	82.22 (27.31)	83.33 (25.46)
Role functioning, 3 months (n=22,33)	85.61 (21.39)	62.12 (33.66)
Role functioning, 6 months (n=21,24)	75.40 (29.16)	70.83 (28.34)
Role functioning, End of Treatment (n=13,24)	78.21 (32.90)	72.92 (29.00)
Emotional functioning, Baseline (n=30,42)	71.94 (28.32)	71.89 (20.50)
Emotional functioning, 3 months (n=21,33)	81.48 (20.53)	76.01 (24.27)
Emotional functioning, 6 months (n=21,24)	72.62 (28.28)	76.04 (26.27)
Emotional functioning, End of Treatment (n=13,24)	77.56 (23.17)	73.61 (24.04)
Cognitive functioning, Baseline (n=30,42)	86.67 (18.26)	87.30 (16.38)
Cognitive functioning, 3 months (n=22,33)	89.39 (15.04)	83.84 (21.03)
Cognitive functioning, 6 months (n=21,24)	83.33 (21.08)	82.64 (18.04)
Cognitive functioning, End of Treatment (n=13,24)	83.33 (22.57)	81.94 (25.97)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Social functioning, Baseline (n=30,41)	86.11 (21.48)	87.40 (20.34)
Social functioning, 3 months (n=22,33)	89.39 (17.48)	75.76 (27.35)
Social functioning, 6 months (n=21,24)	81.75 (26.30)	83.33 (21.42)
Social functioning, End of Treatment (n=13,24)	84.62 (24.96)	81.94 (21.93)
Fatigue, Baseline (n=30,42)	26.30 (23.61)	27.25 (21.70)
Fatigue, 3 months (n=21,33)	27.78 (23.70)	43.10 (31.76)
Fatigue, 6 months (n=20,24)	36.67 (29.09)	37.96 (23.61)
Fatigue, End of Treatment (n=13,24)	34.19 (28.85)	34.49 (32.93)
Nausea and vomiting, Baseline (n=30,42)	6.67 (14.91)	2.78 (7.29)
Nausea and vomiting, 3 months (n=22,33)	10.61 (14.13)	9.60 (16.15)
Nausea and vomiting, 6 months (n=21,24)	8.73 (17.97)	7.64 (12.98)
Nausea and vomiting, End of Treatment (n=13,24)	10.26 (19.88)	6.25 (14.59)
Pain, Baseline (n=30,43)	14.44 (19.44)	21.71 (27.83)
Pain, 3 months (n=22,33)	12.88 (18.50)	18.18 (25.47)
Pain, 6 months (n=21,24)	23.02 (31.83)	17.36 (19.95)
Pain, End of Treatment (n=13,24)	20.51 (28.18)	26.39 (32.94)
Dyspnea, Baseline (n=30,43)	16.67 (25.89)	16.28 (25.59)
Dyspnea, 3 months (n=21,33)	12.70 (19.65)	30.30 (32.66)
Dyspnea, 6 months (n=21,23)	19.05 (24.88)	23.19 (29.19)
Dyspnea, End of Treatment (n=13,24)	20.51 (28.99)	23.61 (30.26)
Insomnia, Baseline (n=30,43)	24.44 (27.59)	24.03 (24.48)
Insomnia, 3 months (n=21,33)	20.63 (22.30)	27.27 (30.57)
Insomnia, 6 months (n=21,24)	33.33 (34.96)	29.17 (30.00)
Insomnia, End of Treatment (n=13,24)	23.08 (25.04)	30.56 (33.93)
Appetite loss, Baseline (n=29,42)	12.64 (16.46)	8.73 (20.90)
Appetite loss, 3 months (n=22,33)	7.58 (14.30)	20.20 (24.92)
Appetite loss, 6 months (n=21,24)	15.87 (27.12)	25.00 (26.47)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
Appetite loss, End of Treatment (n=13,24)	12.82 (28.99)	25.00 (32.97)
Constipation, Baseline (n=27,40)	4.94 (15.20)	10.00 (21.62)
Constipation, 3 months (n=21,33)	15.87 (27.12)	7.07 (18.18)
Constipation, 6 months (n=21,23)	17.46 (27.12)	11.59 (21.58)
Constipation, End of Treatment (n=13,24)	12.82 (21.68)	13.89 (25.85)
Diarrhea, Baseline (n=30,41)	13.33 (24.13)	37.40 (31.79)
Diarrhea, 3 months (n=22,32)	9.09 (21.04)	45.83 (34.65)
Diarrhea, 6 months (n=21,23)	6.35 (17.06)	43.48 (30.87)
Diarrhea, End of Treatment (n=12,22)	2.78 (9.62)	28.79 (31.36)
Financial difficulties, Baseline (n=30,413)	14.44 (25.80)	8.13 (17.92)
Financial difficulties, 3 months (n=22,33)	9.09 (15.19)	6.06 (15.49)
Financial difficulties, 6 months (n=21,23)	15.87 (24.99)	2.90 (9.60)
Financial difficulties, End of treatment (n=13,24)	17.95 (25.88)	4.17 (14.95)

Reported Adverse Events

Time Frame	Adverse events (AEs) were collected from the date of first dose of study medication until 28 days after the last dose of study medication. Related serious AEs and AEs of special interest (AESIs) were recorded during follow-up.
Additional Description	All participants who received at least 1 dose of study treatment were included in the safety population. A separate analysis of nonserious AEs was not performed, therefore the AEs presented in the other nonserious AE table include all AEs reported during the study, not just nonserious events.

Reporting Groups

	Description
Bevacizumab + 5-FU + Streptozocin	Cycles 1-5 (42-day cycles): Participants received bevacizumab 7.5 mg/kg IV on Days 1 and 22; 5-FU 400 mg/m^2/day IV on Days 1 through 5; and streptozocin 500 mg/m^2/day IV on Days 1 through 5. Days 5-21 and 23-42 were rest periods. This 42-day cycle was repeated at least 4 times.

	Description
Bevacizumab + Capecitabine	Cycles 1-9 (21-Day cycle): Participants received bevacizumab 7.5 mg/kg IV on Day 1; capecitabine 2000 mg/m^2 tablets PO in a divided dose every 12 hours within 30 minutes following a meal, on Days 1 through 14. Days 15-21 were a rest period. This 21-day cycle was repeated at least 8 times.

Serious Adverse Events

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Total	11/34 (32.35%)	13/49 (26.53%)
Blood and lymphatic system disorders		
Febrile neutropenia [A] *	0/34 (0%)	1/49 (2.04%)
Cardiac disorders		
Cardiac failure [A] *	0/34 (0%)	1/49 (2.04%)
Gastrointestinal disorders		
Abdominal pain [A] *	0/34 (0%)	2/49 (4.08%)
Abdominal pain upper [A] *	2/34 (5.88%)	0/49 (0%)
Diarrhea [A] *	0/34 (0%)	1/49 (2.04%)
Gastrointestinal hemorrhage [A] *	2/34 (5.88%)	0/49 (0%)
Gastrointestinal perforation [A] *	0/34 (0%)	1/49 (2.04%)
Intestinal obstruction [A] *	0/34 (0%)	2/49 (4.08%)
General disorders		
General physical health deterioration [A] *	0/34 (0%)	2/49 (4.08%)
Hemorrhage [A] *	1/34 (2.94%)	1/49 (2.04%)
Influenza like illness [A] *	1/34 (2.94%)	0/49 (0%)
Pyrexia [A] *	3/34 (8.82%)	0/49 (0%)
Hepatobiliary disorders		
Jaundice [A] *	1/34 (2.94%)	0/49 (0%)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Immune system disorders		
Anaphylactic shock [A] *	0/34 (0%)	1/49 (2.04%)
Infections and infestations		
Peritonitis [A] *	0/34 (0%)	1/49 (2.04%)
Post-procedural sepsis [A] *	1/34 (2.94%)	0/49 (0%)
Respiratory tract infection [A] *	0/34 (0%)	1/49 (2.04%)
Injury, poisoning and procedural complications		
Chest injury [A] *	0/34 (0%)	1/49 (2.04%)
Wound [A] *	0/34 (0%)	1/49 (2.04%)
Metabolism and nutrition disorders		
Decreased appetite [A] *	0/34 (0%)	1/49 (2.04%)
Hypoglycaemia [A] *	2/34 (5.88%)	0/49 (0%)
Nervous system disorders		
Cerebral infarction [A] *	0/34 (0%)	1/49 (2.04%)
Cerebral ischaemia [A] *	0/34 (0%)	1/49 (2.04%)
Cerebrovascular accident [A] *	1/34 (2.94%)	0/49 (0%)
Hemorrhagic stroke [A] *	0/34 (0%)	1/49 (2.04%)
Respiratory, thoracic and mediastinal disorders		
Pleural effusion [A] *	1/34 (2.94%)	0/49 (0%)
Pulmonary embolism [A] *	1/34 (2.94%)	0/49 (0%)
Vascular disorders		
Thrombotic microangiopathy [A] *	1/34 (2.94%)	0/49 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (12.0)

Other Adverse Events

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

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Total	34/34 (100%)	49/49 (100%)
Blood and lymphatic system disorders		
Anaemia [A] *	4/34 (11.76%)	7/49 (14.29%)
Febrile neutropenia [A] *	0/34 (0%)	1/49 (2.04%)
Leukopenia [A] *	1/34 (2.94%)	5/49 (10.2%)
Lymphopenia [A] *	2/34 (5.88%)	4/49 (8.16%)
Neutropenia [A] *	2/34 (5.88%)	8/49 (16.33%)
Thrombocytopenia [A] *	3/34 (8.82%)	6/49 (12.24%)
Cardiac disorders		
Aortic valve incompetence [A] *	0/34 (0%)	1/49 (2.04%)
Cardiac disorder [A] *	0/34 (0%)	1/49 (2.04%)
Cardiac flutter [A] *	0/34 (0%)	1/49 (2.04%)
Cardiomyopathy [A] *	0/34 (0%)	1/49 (2.04%)
Non-obstructive cardiomyopathy [A] *	0/34 (0%)	1/49 (2.04%)
Palpitations [A] *	0/34 (0%)	1/49 (2.04%)
Sinus bradycardia [A] *	0/34 (0%)	1/49 (2.04%)
Tachycardia [A] *	1/34 (2.94%)	1/49 (2.04%)
Ventricular extrasystoles [A] *	0/34 (0%)	1/49 (2.04%)
Ear and labyrinth disorders		
Hypoacusis [A] *	1/34 (2.94%)	1/49 (2.04%)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Tinnitus [A] *	0/34 (0%)	2/49 (4.08%)
Vertigo positional [A] *	1/34 (2.94%)	0/49 (0%)
Eye disorders		
Conjunctivitis allergic [A] *	1/34 (2.94%)	0/49 (0%)
Dry eye [A] *	0/34 (0%)	1/49 (2.04%)
Eyelid oedema [A] *	0/34 (0%)	1/49 (2.04%)
Vision blurred [A] *	0/34 (0%)	1/49 (2.04%)
Visual acuity reduced [A] *	2/34 (5.88%)	0/49 (0%)
Visual impairment [A] *	1/34 (2.94%)	1/49 (2.04%)
Gastrointestinal disorders		
Abdominal discomfort [A] *	0/34 (0%)	2/49 (4.08%)
Abdominal distension [A] *	1/34 (2.94%)	1/49 (2.04%)
Abdominal pain [A] *	13/34 (38.24%)	12/49 (24.49%)
Abdominal pain lower [A] *	1/34 (2.94%)	1/49 (2.04%)
Abdominal pain upper [A] *	11/34 (32.35%)	11/49 (22.45%)
Abdominal rigidity [A] *	0/34 (0%)	1/49 (2.04%)
Anal fissure [A] *	1/34 (2.94%)	2/49 (4.08%)
Anorectal discomfort [A] *	0/34 (0%)	2/49 (4.08%)
Aphthous stomatitis [A] *	3/34 (8.82%)	4/49 (8.16%)
Constipation [A] *	19/34 (55.88%)	9/49 (18.37%)
Diarrhoea [A] *	12/34 (35.29%)	32/49 (65.31%)
Dry mouth [A] *	4/34 (11.76%)	4/49 (8.16%)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Dyspepsia [A] *	2/34 (5.88%)	3/49 (6.12%)
Dysphagia [A] *	0/34 (0%)	2/49 (4.08%)
Faeces discoloured [A] *	0/34 (0%)	1/49 (2.04%)
Flatulence [A] *	2/34 (5.88%)	2/49 (4.08%)
Gastritis [A] *	1/34 (2.94%)	0/49 (0%)
Gastrointestinal motility disorder [A] *	0/34 (0%)	1/49 (2.04%)
Gastrooesophageal reflux disease [A] *	5/34 (14.71%)	2/49 (4.08%)
Gingival bleeding [A] *	1/34 (2.94%)	1/49 (2.04%)
Haemorrhoids [A] *	4/34 (11.76%)	5/49 (10.2%)
Intestinal obstruction [A] *	0/34 (0%)	3/49 (6.12%)
Lip swelling [A] *	0/34 (0%)	1/49 (2.04%)
Loose tooth [A] *	1/34 (2.94%)	1/49 (2.04%)
Nausea [A] *	24/34 (70.59%)	24/49 (48.98%)
Proctalgia [A] *	0/34 (0%)	3/49 (6.12%)
Proctitis [A] *	0/34 (0%)	1/49 (2.04%)
Salivary hypersecretion [A] *	1/34 (2.94%)	0/49 (0%)
Steatorrhoea [A] *	1/34 (2.94%)	0/49 (0%)
Stomatitis [A] *	3/34 (8.82%)	3/49 (6.12%)
Tongue discolouration [A] *	0/34 (0%)	1/49 (2.04%)
Tongue haematoma [A] *	1/34 (2.94%)	0/49 (0%)
Toothache [A] *	0/34 (0%)	3/49 (6.12%)
Varices oesophageal [A] *	0/34 (0%)	1/49 (2.04%)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Vomiting [A] *	11/34 (32.35%)	7/49 (14.29%)
General disorders		
Asthenia [A] *	23/34 (67.65%)	28/49 (57.14%)
Catheter site haematoma [A] *	1/34 (2.94%)	0/49 (0%)
Catheter site pain [A] *	1/34 (2.94%)	0/49 (0%)
Chest pain [A] *	1/34 (2.94%)	2/49 (4.08%)
Chills [A] *	3/34 (8.82%)	0/49 (0%)
Drug intolerance [A] *	0/34 (0%)	1/49 (2.04%)
Face oedema [A] *	0/34 (0%)	1/49 (2.04%)
Fatigue [A] *	4/34 (11.76%)	5/49 (10.2%)
General physical health deterioration [A] *	0/34 (0%)	3/49 (6.12%)
Implant site inflammation [A] *	0/34 (0%)	1/49 (2.04%)
Influenza like illness [A] *	3/34 (8.82%)	0/49 (0%)
Injection site pain [A] *	0/34 (0%)	1/49 (2.04%)
Malaise [A] *	0/34 (0%)	2/49 (4.08%)
Mucosal dryness [A] *	0/34 (0%)	1/49 (2.04%)
Mucosal inflammation [A] *	14/34 (41.18%)	17/49 (34.69%)
Oedema [A] *	2/34 (5.88%)	0/49 (0%)
Oedema peripheral [A] *	4/34 (11.76%)	9/49 (18.37%)
Pain [A] *	1/34 (2.94%)	0/49 (0%)
Pyrexia [A] *	8/34 (23.53%)	4/49 (8.16%)
Xerosis [A] *	1/34 (2.94%)	3/49 (6.12%)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Hepatobiliary disorders		
Biliary colic [A] *	0/34 (0%)	1/49 (2.04%)
Cholestasis [A] *	0/34 (0%)	1/49 (2.04%)
Cytolytic hepatitis [A] *	2/34 (5.88%)	0/49 (0%)
Hepatic pain [A] *	0/34 (0%)	1/49 (2.04%)
Jaundice [A] *	1/34 (2.94%)	0/49 (0%)
Portal hypertension [A] *	2/34 (5.88%)	1/49 (2.04%)
Immune system disorders		
Anaphylactic shock [A] *	0/34 (0%)	1/49 (2.04%)
Infections and infestations		
Bronchitis [A] *	3/34 (8.82%)	3/49 (6.12%)
Candidiasis [A] *	0/34 (0%)	1/49 (2.04%)
Cholecystitis infective [A] *	1/34 (2.94%)	0/49 (0%)
Chronic sinusitis [A] *	0/34 (0%)	1/49 (2.04%)
Cystitis [A] *	1/34 (2.94%)	2/49 (4.08%)
Erysipelas [A] *	0/34 (0%)	1/49 (2.04%)
Folliculitis [A] *	0/34 (0%)	1/49 (2.04%)
Fungal infection [A] *	0/34 (0%)	1/49 (2.04%)
Gastroenteritis [A] *	2/34 (5.88%)	4/49 (8.16%)
Gastroenteritis escherichia coli [A] *	0/34 (0%)	1/49 (2.04%)
Gastroenteritis viral [A] *	0/34 (0%)	1/49 (2.04%)
Herpes simplex [A] *	1/34 (2.94%)	2/49 (4.08%)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Herpes zoster ophthalmic [A] *	0/34 (0%)	1/49 (2.04%)
Hordeolum [A] *	1/34 (2.94%)	0/49 (0%)
Infected cyst [A] *	1/34 (2.94%)	0/49 (0%)
Infection [A] *	1/34 (2.94%)	2/49 (4.08%)
Injection site infection [A] *	1/34 (2.94%)	1/49 (2.04%)
Laryngitis [A] *	0/34 (0%)	1/49 (2.04%)
Nasopharyngitis [A] *	4/34 (11.76%)	4/49 (8.16%)
Oral candidiasis [A] *	0/34 (0%)	1/49 (2.04%)
Oral herpes [A] *	2/34 (5.88%)	1/49 (2.04%)
Pharyngitis [A] *	2/34 (5.88%)	4/49 (8.16%)
Post procedural sepsis [A] *	1/34 (2.94%)	0/49 (0%)
Respiratory tract infection [A] *	0/34 (0%)	1/49 (2.04%)
Rhinitis [A] *	0/34 (0%)	2/49 (4.08%)
Sinusitis [A] *	2/34 (5.88%)	2/49 (4.08%)
Staphylococcal infection [A] *	0/34 (0%)	1/49 (2.04%)
Tonsillitis [A] *	3/34 (8.82%)	1/49 (2.04%)
Tooth abscess [A] *	1/34 (2.94%)	2/49 (4.08%)
Tooth infection [A] *	0/34 (0%)	2/49 (4.08%)
Tracheobronchitis [A] *	1/34 (2.94%)	0/49 (0%)
Urinary tract infection [A] *	2/34 (5.88%)	4/49 (8.16%)
Injury, poisoning and procedural complications		
Ankle fracture [A] *	1/34 (2.94%)	0/49 (0%)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Bite [A] *	0/34 (0%)	1/49 (2.04%)
Burn of internal organs [A] *	0/34 (0%)	1/49 (2.04%)
Chest injury [A] *	0/34 (0%)	1/49 (2.04%)
Contusion [A] *	1/34 (2.94%)	0/49 (0%)
Fall [A] *	0/34 (0%)	1/49 (2.04%)
Fibula fracture [A] *	0/34 (0%)	1/49 (2.04%)
Frostbite [A] *	1/34 (2.94%)	0/49 (0%)
Iatrogenic injury [A] *	0/34 (0%)	1/49 (2.04%)
Limb injury [A] *	1/34 (2.94%)	0/49 (0%)
Multiple fractures [A] *	0/34 (0%)	1/49 (2.04%)
Muscle strain [A] *	0/34 (0%)	1/49 (2.04%)
Radiation mucositis [A] *	1/34 (2.94%)	0/49 (0%)
Rib fracture [A] *	1/34 (2.94%)	1/49 (2.04%)
Wound [A] *	0/34 (0%)	2/49 (4.08%)
Investigations		
Activated partial thromboplastin time prolonged [A] *	1/34 (2.94%)	0/49 (0%)
Alanine aminotransferase abnormal [A] *	1/34 (2.94%)	0/49 (0%)
Alanine aminotransferase increased [A] *	1/34 (2.94%)	0/49 (0%)
Aspartate aminotransferase increased [A] *	1/34 (2.94%)	0/49 (0%)
Blood bilirubin abnormal [A] *	0/34 (0%)	2/49 (4.08%)
Blood creatinine decreased [A] *	1/34 (2.94%)	0/49 (0%)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Blood creatinine increased [A] *	1/34 (2.94%)	0/49 (0%)
Cardiac murmur [A] *	0/34 (0%)	1/49 (2.04%)
Creatinine renal clearance decreased [A] *	1/34 (2.94%)	0/49 (0%)
Gamma-glutamyltransferase abnormal [A] *	1/34 (2.94%)	0/49 (0%)
Gamma-glutamyltransferase increased [A] *	1/34 (2.94%)	0/49 (0%)
Haemoglobin [A] *	0/34 (0%)	1/49 (2.04%)
Lipase increased [A] *	1/34 (2.94%)	0/49 (0%)
Weight decreased [A] *	4/34 (11.76%)	5/49 (10.2%)
Metabolism and nutrition disorders		
Anorexia [A] *	2/34 (5.88%)	2/49 (4.08%)
Decreased appetite [A] *	5/34 (14.71%)	6/49 (12.24%)
Dehydration [A] *	0/34 (0%)	1/49 (2.04%)
Diabetes mellitus inadequate control [A] *	1/34 (2.94%)	0/49 (0%)
Food intolerance [A] *	0/34 (0%)	1/49 (2.04%)
Gout [A] *	1/34 (2.94%)	2/49 (4.08%)
Hyperglycaemia [A] *	3/34 (8.82%)	4/49 (8.16%)
Hyperkalaemia [A] *	0/34 (0%)	1/49 (2.04%)
Hypertriglyceridaemia [A] *	0/34 (0%)	1/49 (2.04%)
Hypocalcaemia [A] *	0/34 (0%)	3/49 (6.12%)
Hypoglycaemia [A] *	3/34 (8.82%)	0/49 (0%)
Hypoglycaemic unconsciousness [A] *	1/34 (2.94%)	0/49 (0%)
Hypokalaemia [A] *	0/34 (0%)	4/49 (8.16%)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Hyposideraemia [A] *	1/34 (2.94%)	0/49 (0%)
Iron deficiency [A] *	0/34 (0%)	1/49 (2.04%)
Malnutrition [A] *	1/34 (2.94%)	0/49 (0%)
Vitamin D deficiency [A] *	2/34 (5.88%)	0/49 (0%)
Vitamin K deficiency [A] *	0/34 (0%)	1/49 (2.04%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] *	8/34 (23.53%)	6/49 (12.24%)
Back pain [A] *	6/34 (17.65%)	4/49 (8.16%)
Bone pain [A] *	0/34 (0%)	2/49 (4.08%)
Flank pain [A] *	1/34 (2.94%)	2/49 (4.08%)
Haemarthrosis [A] *	1/34 (2.94%)	0/49 (0%)
Muscle fatigue [A] *	0/34 (0%)	1/49 (2.04%)
Muscle spasms [A] *	0/34 (0%)	1/49 (2.04%)
Musculoskeletal chest pain [A] *	0/34 (0%)	1/49 (2.04%)
Musculoskeletal pain [A] *	3/34 (8.82%)	3/49 (6.12%)
Myalgia [A] *	4/34 (11.76%)	0/49 (0%)
Neck pain [A] *	2/34 (5.88%)	4/49 (8.16%)
Osteoarthritis [A] *	1/34 (2.94%)	0/49 (0%)
Pain in extremity [A] *	2/34 (5.88%)	2/49 (4.08%)
Pain in jaw [A] *	1/34 (2.94%)	0/49 (0%)
Rheumatoid arthritis [A] *	0/34 (0%)	1/49 (2.04%)
Tendon disorder [A] *	1/34 (2.94%)	1/49 (2.04%)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Neoplasm progression [A] *	1/34 (2.94%)	0/49 (0%)
Pyogenic granuloma [A] *	0/34 (0%)	1/49 (2.04%)
Skin papilloma [A] *	1/34 (2.94%)	0/49 (0%)
Nervous system disorders		
Ageusia [A] *	0/34 (0%)	1/49 (2.04%)
Amnesia [A] *	1/34 (2.94%)	0/49 (0%)
Balance disorder [A] *	0/34 (0%)	1/49 (2.04%)
Burning sensation [A] *	1/34 (2.94%)	0/49 (0%)
Dizziness [A] *	3/34 (8.82%)	4/49 (8.16%)
Dysaesthesia [A] *	1/34 (2.94%)	1/49 (2.04%)
Dysgeusia [A] *	0/34 (0%)	4/49 (8.16%)
Epilepsy [A] *	1/34 (2.94%)	0/49 (0%)
Headache [A] *	13/34 (38.24%)	14/49 (28.57%)
Hypokinesia [A] *	1/34 (2.94%)	0/49 (0%)
Loss of consciousness [A] *	1/34 (2.94%)	0/49 (0%)
Migraine [A] *	0/34 (0%)	2/49 (4.08%)
Neuropathy peripheral [A] *	1/34 (2.94%)	1/49 (2.04%)
Paraesthesia [A] *	4/34 (11.76%)	4/49 (8.16%)
Parkinson's disease [A] *	0/34 (0%)	1/49 (2.04%)
Presyncope [A] *	0/34 (0%)	1/49 (2.04%)
Sciatica [A] *	1/34 (2.94%)	1/49 (2.04%)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Sensory disturbance [A] *	1/34 (2.94%)	0/49 (0%)
Transient ischaemic attack [A] *	1/34 (2.94%)	0/49 (0%)
Tremor [A] *	0/34 (0%)	1/49 (2.04%)
Psychiatric disorders		
Anxiety [A] *	6/34 (17.65%)	6/49 (12.24%)
Confusional state [A] *	0/34 (0%)	3/49 (6.12%)
Depression [A] *	1/34 (2.94%)	3/49 (6.12%)
Insomnia [A] *	4/34 (11.76%)	5/49 (10.2%)
Sleep disorder [A] *	0/34 (0%)	2/49 (4.08%)
Stress [A] *	0/34 (0%)	1/49 (2.04%)
Renal and urinary disorders		
Albuminuria [A] *	0/34 (0%)	1/49 (2.04%)
Dysuria [A] *	1/34 (2.94%)	1/49 (2.04%)
Glycosuria [A] *	0/34 (0%)	3/49 (6.12%)
Leukocyturia [A] *	0/34 (0%)	1/49 (2.04%)
Polyuria [A] *	0/34 (0%)	1/49 (2.04%)
Renal failure [A] *	2/34 (5.88%)	0/49 (0%)
Urinary incontinence [A] *	0/34 (0%)	1/49 (2.04%)
Reproductive system and breast disorders		
Epididymitis [A] *	0/34 (0%)	1/49 (2.04%)
Erosive balanitis [A] *	0/34 (0%)	1/49 (2.04%)
Metrorrhagia [A] *	0/34 (0%)	1/49 (2.04%)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Testicular pain [A] *	0/34 (0%)	1/49 (2.04%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] *	3/34 (8.82%)	5/49 (10.2%)
Dysphonia [A] *	1/34 (2.94%)	2/49 (4.08%)
Dyspnoea [A] *	2/34 (5.88%)	2/49 (4.08%)
Dyspnoea extertional [A] *	1/34 (2.94%)	2/49 (4.08%)
Nasal dryness [A] *	1/34 (2.94%)	0/49 (0%)
Pleural effusion [A] *	1/34 (2.94%)	1/49 (2.04%)
Pneumonia aspiration [A] *	0/34 (0%)	1/49 (2.04%)
Rhinorrhoea [A] *	2/34 (5.88%)	2/49 (4.08%)
Sleep apnoea syndrome [A] *	0/34 (0%)	1/49 (2.04%)
Skin and subcutaneous tissue disorders		
Acne [A] *	1/34 (2.94%)	1/49 (2.04%)
Alopecia [A] *	2/34 (5.88%)	1/49 (2.04%)
Angioedema [A] *	1/34 (2.94%)	1/49 (2.04%)
Dermatitis [A] *	0/34 (0%)	1/49 (2.04%)
Dry skin [A] *	3/34 (8.82%)	8/49 (16.33%)
Dyshidrosis [A] *	0/34 (0%)	1/49 (2.04%)
Erythema [A] *	3/34 (8.82%)	4/49 (8.16%)
Hyperkeratosis palmaris and plantaris [A] *	1/34 (2.94%)	1/49 (2.04%)
Nail discomfort [A] *	0/34 (0%)	1/49 (2.04%)
Nail disorder [A] *	0/34 (0%)	1/49 (2.04%)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Nail toxicity [A] *	0/34 (0%)	1/49 (2.04%)
Night sweats [A] *	0/34 (0%)	1/49 (2.04%)
Onychoclasis [A] *	0/34 (0%)	1/49 (2.04%)
Palmar-plantar erythrodysaesthesia syndrome [A] *	6/34 (17.65%)	31/49 (63.27%)
Petechiae [A] *	0/34 (0%)	2/49 (4.08%)
Photosensitivity reaction [A] *	0/34 (0%)	1/49 (2.04%)
Pigmentation disorder [A] *	0/34 (0%)	2/49 (4.08%)
Pruritus [A] *	5/34 (14.71%)	7/49 (14.29%)
Purpura [A] *	0/34 (0%)	1/49 (2.04%)
Rash [A] *	3/34 (8.82%)	1/49 (2.04%)
Skin chapped [A] *	0/34 (0%)	1/49 (2.04%)
Skin discolouration [A] *	1/34 (2.94%)	0/49 (0%)
Skin fissures [A] *	0/34 (0%)	1/49 (2.04%)
Skin hyperpigmentation [A] *	0/34 (0%)	2/49 (4.08%)
Skin lesion [A] *	1/34 (2.94%)	1/49 (2.04%)
Skin reaction [A] *	1/34 (2.94%)	0/49 (0%)
Skin toxicity [A] *	0/34 (0%)	1/49 (2.04%)
Spider naevus [A] *	0/34 (0%)	1/49 (2.04%)
Urticaria [A] *	1/34 (2.94%)	1/49 (2.04%)
Vascular disorders		
Flushing [A] *	2/34 (5.88%)	9/49 (18.37%)

	Bevacizumab + 5-FU + Streptozocin	Bevacizumab + Capecitabine
	Affected/At Risk (%)	Affected/At Risk (%)
Haematoma [A] *	0/34 (0%)	1/49 (2.04%)
Hot flush [A] *	3/34 (8.82%)	1/49 (2.04%)
Hypotension [A] *	0/34 (0%)	2/49 (4.08%)
Varicose vein [A] *	1/34 (2.94%)	0/49 (0%)
Vein discolouration [A] *	0/34 (0%)	1/49 (2.04%)
Venous insufficiency [A] *	0/34 (0%)	1/49 (2.04%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (12.0)

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 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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