ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 07/24/2014

A Study of Avastin (Bevacizumab) Plus Xeloda (Capecitabine) in Patients With Locally Advanced Rectal Cancer.

This study has been completed.

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT01227707

Purpose

This open-label study will assess the efficacy and safety of Avastin (bevacizumab) plus Xeloda (capecitabine) in combination with standard technique radiotherapy of the pelvic region in the neo-adjuvant setting in patients with locally advanced primary rectal cancer. Patients will receive 4 courses of Avastin at a dose of 5 mg/kg intravenously (iv) every 2 weeks and for 38 days Xeloda at dose of 825 mg/kg twice daily orally, plus radiation therapy. After surgery, adjuvant treatment with 5-fluorouracil/leucovorin and, at the discretion of the investigator, with Avastin 5 mg/kg iv every 2 weeks for at least 6 months will be given.

Condition	Intervention	Phase
Colorectal Cancer	Drug: bevacizumab [Avastin] Drug: capecitabine [Xeloda] Radiation: Radiation therapy Procedure/Surgery: Mesorectal excision Drug: 5-fluorouracil Drug: leucovorin	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 Effect of Combination Treatment With Avastin and Xeloda, Plus Pre-operative Standard Radiotherapy, on Response Rate in Patients With Locally Advanced Rectal Cancer.

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Percentage of Participants With Pathological Complete Response (pCR) [Time Frame: 6 to 8 weeks following completion of neoadjuvant treatment] [Designated as safety issue: No]

  pCR was defined as the absence of viable tumor cells, as determined by standard histologic procedure, in the tumor specimen (including regional lymph nodes) obtained at surgery. In order to minimize evaluation bias, tumor specimens were analyzed by both a central and local pathologist. The number of participants with pathological tumor stage 0 (pT0) and regional lymph nodes stage 0 (pN0) at surgery was determined. pCR was defined as the number of participants with pT0 and pN0 at surgery divided by the total number of participants with pathological tumor stage data collected.

Secondary Outcome Measures:

- Percentage of Participants by Primary Tumor (T), Regional Lymph Nodes (N), and Distant Metastasis (M) Clinical Stage at Baseline and at the End of Neo-Adjuvant Treatment (NAT) [Time Frame: Baseline (BL) and end of neoadjuvant treatment (within 6 weeks after the completion of study treatment)] [Designated as safety issue: No]

  The frequencies of clinical tumor stage T (0, 1, 2, 3, 4, or X), regional lymph nodes stage N (0, 1, 2, 3, or 4), and distant metastasis clinical stage M (0, 1, or X) at baseline and at the end of NAT were assessed. The frequencies of pathological tumor stage T and regional lymph nodes stage N at surgery were evaluated. The clinical tumor and lymph node status was assessed by clinical examination, endosonography, and/or rectosigmoidoscopy, and pelvic and abdomen computerized tomography (CT) scan or magnetic resonance imaging (MRI). Response to treatment had to be assessed within 6 weeks after end of treatment by using the same techniques performed at baseline.
- Percentage of Participants Undergoing Sphincter-Saving Surgery by Type of Procedure [Time Frame: 6 to 8 weeks after completion of study treatment] [Designated as safety issue: No]
- Percentage of Participants With Complete Response (CR) at the End of Neoadjuvant Treatment [Time Frame: BL and within 6 weeks after the completion of study treatment] [Designated as safety issue: No]

  Percentage of participants with CR was evaluated as the proportion of participants with complete response for the target and non-target lesions, separately, at the end of NAT according to the Response Evaluation Criteria in Solid Tumors (RECIST). CR was defined as disappearance of all target lesions or all non-target lesions and normalization of tumor marker levels.
- Percentage of Participants With an Overall Response of CR at the End of Neoadjuvant Treatment [Time Frame: BL and within 6 weeks after the completion of study treatment] [Designated as safety issue: No]

  Percentage of participants with an overall response of CR was evaluated as the proportion of participants with CR for the target and non-target lesions plus absence of new lesions at the end of NAT according to RECIST. CR was defined as disappearance of all target lesions, all non-target lesions, and normalization of tumor marker levels.
- Percentage of Participants With New Lesions at the Primary Tumor Site at the End of Neoadjuvant Treatment [Time Frame: BL and within 6 weeks after the completion of study treatment] [Designated as safety issue: No]

  The percentage of participants with new lesions located at the primary tumor site were evaluated at the end of NAT.
- Percentage of Participants With Relapse During Follow-Up [Time Frame: BL, within 6 weeks after the completion of neoadjuvant treatment, every 2 weeks for 1 year following surgery, every 3 months thereafter until progression, up to 45 months] [Designated as safety issue: No]

  The percentage of participants with local and/or regional relapse during follow-up. New lesions located at rectum or at colon or at lymph node detected at the end of NAT were evaluated as local and/or regional relapse.
- Disease-Free Survival (DFS) - Percentage of Participants With an Event [Time Frame: BL, within 6 weeks after the completion of neoadjuvant treatment, every 2 weeks for 1 year following surgery, every 3 months thereafter until progression, up to 45 months] [Designated as safety issue: No]

  DFS was defined as the time from treatment start date to the date of first progression of disease or date of death due to any cause.
- DFS - Time to Event [Time Frame: BL, within 6 weeks after the completion of neoadjuvant treatment, every 2 weeks for 1 year following surgery, every 3 months thereafter until progression, up to 45 months] [Designated as safety issue: No]

  The time in months from date of start-of-treatment to the date of event defined as the first documented disease progression or death due to any cause. If a participant did not have an event, the time was censored at the date of last adequate tumor assessment. DFS was estimated using the Kaplan-Meier method.

- Overall Survival (OS) - Percentage of Participants With an Event [Time Frame: BL, within 6 weeks after the completion of neoadjuvant treatment, every 2 weeks for 1 year following surgery, every 3 months thereafter until death, up to 45 months] [Designated as safety issue: No]
  OS was defined as the time from the date of first day of treatment until death due to any cause or the last date the participant was known to be alive.
- OS - Time to Event [Time Frame: BL, within 6 weeks after the completion of neoadjuvant treatment, every 2 weeks for 1 year following surgery, every 3 months thereafter until death, up to 45 months] [Designated as safety issue: No]
  OS was defined as the time from the date of first day of treatment until death due to any cause or the last date the participant was known to be alive. OS was estimated using the Kaplan-Meier method.
- Time to Disease Progression (TTP) - Percentage of Participants With an Event [Time Frame: BL, within 6 weeks after the completion of neoadjuvant treatment, every 2 weeks for 1 year following surgery, every 3 months thereafter until death, up to 45 months] [Designated as safety issue: No]
  TTP was defined as the time from date of treatment start until first documented progression of disease or death due to underlying cancer.
- TTP - Time to Event [Time Frame: BL, within 6 weeks after the completion of neoadjuvant treatment, every 2 weeks for 1 year following surgery, every 3 months thereafter until death, up to 45 months] [Designated as safety issue: No]
  TTP was defined as the time from date of treatment start until first documented progression of disease or death due to underlying cancer. TTP was estimated using the Kaplan-Meier method.

Enrollment: 43
Study Start Date: November 2005
Primary Completion Date: August 2010
Study Completion Date: August 2010

Arms	Assigned Interventions
Experimental: Single Arm	Drug: bevacizumab [Avastin] 5 mg/kg intravenously every 2 weeks, 4 cycles Drug: capecitabine [Xeloda] 825 mg/m2 twice daily orally, 38 days Radiation: Radiation therapy Total dose of 45 Gy over 38 days Procedure/Surgery: Mesorectal excision 6-8 weeks after completion of neoadjuvant treatment Drug: bevacizumab [Avastin] Post-surgery adjuvant treatment at the discretion of the investigator: 5 mg/kg iv every 2 weeks for at least 6 months Drug: 5-fluorouracil Post-surgery adjuvant therapy: bolus of 400mg/m2 iv plus iv infusion of 600 mg/m2 on Days 1 and 2 of each 2-week cycle for 6 months Drug: leucovorin Post-surgery adjuvant treatment: 100 mg/m2 iv on Days 1 and 2 of each 2-week cycle for 6 months

Eligibility

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

Criteria

Inclusion Criteria:

- Adult patients, >=18 years of age
- Patients with confirmed rectal cancer who are subject to surgery and would benefit from pre-operative combined chemo-radiotherapy
- Measurable and/or evaluable lesions according to RECIST criteria
- EOCG performance status 0-1

Exclusion Criteria:

- Prior radiotherapy or chemotherapy for rectal cancer
- Untreated brain metastases or spinal cord compression or primary brain tumors
- Chronic daily treatment with high-dose aspirin (>325 mg/day) or other medications known to predispose to gastrointestinal ulceration
- Co-existing malignancies, or malignancies diagnosed within the last 5 years, with the exception of basal and squamous cell cancer, or cervical cancer in situ.

Contacts and Locations

Locations

Italy

Ancona, Italy, 60121
Bologna, Italy, 40139
Cuneo, Italy, 12100
Genova, Italy, 16132
Napoli, Italy, 80131
Paola, Italy, 87027
Pisa, Italy, 56100
Roma, Italy, 00135
Siena, Italy, 53100

Investigators

Study Chair:	Clinical Trials	Hoffmann-La Roche

More Information

Responsible Party:	Hoffmann-La Roche
Study ID Numbers:	ML18522
Health Authority:	Italy: Ministry of Health

Study Results

Participant Flow

Reporting Groups

	Description
Bevacizumab (Bv)+Capecitabine/Bv +Leucovorin+5-fluorouracil	Participants received bevacizumab 5 milligrams per kilogram (mg/kg) intravenously (IV) on Days -14, 1, 15, and 29 and capecitabine 825 milligrams per square meter (mg/m^2) orally (PO) twice daily (BID) from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gray (Gy) administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-fluorouracil (5-FU) 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Overall Study

	Bevacizumab (Bv)+Capecitabine/Bv+Leucovorin+5-fluorouracil
Started	43
Completed	19
Not Completed	24
Adverse Event	10
Progression of disease	3
Withdrawal by Subject	1
Patient non-compliance	3
Medical decision	6
Death	1

Baseline Characteristics

Analysis Population Description

Intent to treat (ITT) population: all participants who were included in the trial by signing the informed consent and were assigned to a study patient number.

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Baseline Measures

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Number of Participants	43
Age, Continuous [units: years] Mean (Standard Deviation)	61.49 (10.85)
Gender, Male/Female [units: participants]	
Female	18
Male	25

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants With Pathological Complete Response (pCR)
Measure Description	pCR was defined as the absence of viable tumor cells, as determined by standard histologic procedure, in the tumor specimen (including regional lymph nodes) obtained at surgery. In order to minimize evaluation bias, tumor specimens were analyzed by both a central and local pathologist. The number of participants with pathological tumor stage 0 (pT0) and regional lymph nodes stage 0 (pN0) at surgery was determined. pCR was defined as the number of participants with pT0 and pN0 at surgery divided by the total number of participants with pathological tumor stage data collected.
Time Frame	6 to 8 weeks following completion of neoadjuvant treatment
Safety Issue?	No

Analysis Population Description

ITT population; only participants who underwent surgery and had pathological tumor stage data were included in the analysis.

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Measured Values

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Number of Participants Analyzed	40
Percentage of Participants With Pathological Complete Response (pCR) [units: percentage of participants] Number (95% Confidence Interval)	10.00 (2.79 to 23.66)

Statistical Analysis 1 for Percentage of Participants With Pathological Complete Response (pCR)

Statistical Analysis Overview	Comparison Groups	Bv+Capecitabine/Bv+Leucovorin+5-FU
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	1.00
	Comments	[Not specified]
	Method	Other [one sample binomial test]
	Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Percentage of Participants by Primary Tumor (T), Regional Lymph Nodes (N), and Distant Metastasis (M) Clinical Stage at Baseline and at the End of Neo-Adjuvant Treatment (NAT)

Measure Description	The frequencies of clinical tumor stage T (0, 1, 2, 3, 4, or X), regional lymph nodes stage N (0, 1, 2, 3, or 4), and distant metastasis clinical stage M (0, 1, or X) at baseline and at the end of NAT were assessed. The frequencies of pathological tumor stage T and regional lymph nodes stage N at surgery were evaluated. The clinical tumor and lymph node status was assessed by clinical examination, endosonography, and/or rectosigmoidoscopy, and pelvic and abdomen computerized tomography (CT) scan or magnetic resonance imaging (MRI). Response to treatment had to be assessed within 6 weeks after end of treatment by using the same techniques performed at baseline.
Time Frame	Baseline (BL) and end of neoadjuvant treatment (within 6 weeks after the completion of study treatment)
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Measured Values

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Number of Participants Analyzed	43
Percentage of Participants by Primary Tumor (T), Regional Lymph Nodes (N), and Distant Metastasis (M) Clinical Stage at Baseline and at the End of Neo-Adjuvant Treatment (NAT) [units: percentage of participants]	
Baseline: T0, N0	0
End of NAT: T0, N0	4.65
Baseline: T1, N0	0
End of NAT: T1, N0	4.65
Baseline: T1, NX	0
End of NAT: T1, NX	2.33
Baseline: T2, N0	0

	Bv+Capecitabine/Bv+Leucovorin+5-FU
End of NAT: T2, N0	18.60
Baseline: T2, N1	9.30
End of NAT: T2, N1	9.30
Baseline: T2, NX	0
End of NAT: T2, NX	6.98
Baseline: T3, N0	32.56
End of NAT: T3, N0	18.60
Baseline: T3, N1	46.51
End of NAT: T3, N1	9.30
Baseline: T3, N2	0
End of NAT: T3, N2	2.33
Baseline: T3, NX	2.33
End of NAT: T3, NX	6.98
Baseline: T4, N0	0
End of NAT: T4, N0	4.65
Baseline: T4, N1	2.33
End of NAT: T4, N1	0
Baseline: T4, N2	2.33
End of NAT: T4, N2	0
Baseline: T4, N3	2.33
End of NAT: T4, N3	0
Baseline: TX, N0	0
End of NAT: TX, N0	2.33
Baseline: TX, N2	2.33
End of NAT: TX, N2	0
Baseline: M0	97.67
End of NAT: M0	81.40

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Baseline: M1	2.33
End of NAT: M1	2.33
Baseline: MX	0
End of NAT: MX	9.30

3. Secondary Outcome Measure:

Measure Title	Percentage of Participants Undergoing Sphincter-Saving Surgery by Type of Procedure
Measure Description	
Time Frame	6 to 8 weeks after completion of study treatment
Safety Issue?	No

Analysis Population Description

ITT population; only participants who underwent surgery were included in the analysis. n (number) equals (=) number of participants assessed for the specified parameter (colostomy)

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Measured Values

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Number of Participants Analyzed	40
Percentage of Participants Undergoing Sphincter-Saving Surgery by Type of Procedure [units: percentage of participants]	
Anterior resection	70.0

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Abdomen-peritoneal amputation (Miles)	22.5
Other	3.0
Colostomy, temporary (n=32)	47.50
Colostomy, definitive (n=32)	32.50
No colostomy	20.0

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Complete Response (CR) at the End of Neoadjuvant Treatment
Measure Description	Percentage of participants with CR was evaluated as the proportion of participants with complete response for the target and non-target lesions, separately, at the end of NAT according to the Response Evaluation Criteria in Solid Tumors (RECIST). CR was defined as disappearance of all target lesions or all non-target lesions and normalization of tumor marker levels.
Time Frame	BL and within 6 weeks after the completion of study treatment
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Measured Values

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Number of Participants Analyzed	43
Percentage of Participants With Complete Response (CR) at the End of Neoadjuvant Treatment	

	Bv+Capecitabine/Bv+Leucovorin+5-FU
[units: percentage of participants]	
CR of target lesion(s)	11.63
CR of non-target lesion(s)	18.60

5. Secondary Outcome Measure:

Measure Title	Percentage of Participants With an Overall Response of CR at the End of Neoadjuvant Treatment
Measure Description	Percentage of participants with an overall response of CR was evaluated as the proportion of participants with CR for the target and non-target lesions plus absence of new lesions at the end of NAT according to RECIST. CR was defined as disappearance of all target lesions, all non-target lesions, and normalization of tumor marker levels.
Time Frame	BL and within 6 weeks after the completion of study treatment
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Measured Values

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Number of Participants Analyzed	43
Percentage of Participants With an Overall Response of CR at the End of Neoadjuvant Treatment [units: percentage of participants]	9.30

6. Secondary Outcome Measure:

Measure Title	Percentage of Participants With New Lesions at the Primary Tumor Site at the End of Neoadjuvant Treatment
Measure Description	The percentage of participants with new lesions located at the primary tumor site were evaluated at the end of NAT.
Time Frame	BL and within 6 weeks after the completion of study treatment
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Measured Values

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Number of Participants Analyzed	43
Percentage of Participants With New Lesions at the Primary Tumor Site at the End of Neoadjuvant Treatment [units: percentage of participants]	4.65

7. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Relapse During Follow-Up
Measure Description	The percentage of participants with local and/or regional relapse during follow-up. New lesions located at rectum or at colon or at lymph node detected at the end of NAT were evaluated as local and/or regional relapse.
Time Frame	BL, within 6 weeks after the completion of neoadjuvant treatment, every 2 weeks for 1 year following surgery, every 3 months thereafter until progression, up to 45 months
Safety Issue?	No

Analysis Population Description
ITT population; only participants who underwent radical surgery were included in the analysis

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Measured Values

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Number of Participants Analyzed	38
Percentage of Participants With Relapse During Follow-Up [units: percentage of participants]	
No Relapse	84.21
1 Relapse	7.89
2 Relapses	7.89

8. Secondary Outcome Measure:

Measure Title	Disease-Free Survival (DFS) - Percentage of Participants With an Event
Measure Description	DFS was defined as the time from treatment start date to the date of first progression of disease or date of death due to any cause.
Time Frame	BL, within 6 weeks after the completion of neoadjuvant treatment, every 2 weeks for 1 year following surgery, every 3 months thereafter until progression, up to 45 months
Safety Issue?	No

Analysis Population Description
ITT population

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Measured Values

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Number of Participants Analyzed	43
Disease-Free Survival (DFS) - Percentage of Participants With an Event [units: percentage of participants]	30.23

9. Secondary Outcome Measure:

Measure Title	DFS - Time to Event
Measure Description	The time in months from date of start-of-treatment to the date of event defined as the first documented disease progression or death due to any cause. If a participant did not have an event, the time was censored at the date of last adequate tumor assessment. DFS was estimated using the Kaplan-Meier method.
Time Frame	BL, within 6 weeks after the completion of neoadjuvant treatment, every 2 weeks for 1 year following surgery, every 3 months thereafter until progression, up to 45 months
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Measured Values

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Number of Participants Analyzed	43
DFS - Time to Event [units: months] Mean (Standard Deviation)	27.43 (1.71)

10. Secondary Outcome Measure:

Measure Title	Overall Survival (OS) - Percentage of Participants With an Event
Measure Description	OS was defined as the time from the date of first day of treatment until death due to any cause or the last date the participant was known to be alive.
Time Frame	BL, within 6 weeks after the completion of neoadjuvant treatment, every 2 weeks for 1 year following surgery, every 3 months thereafter until death, up to 45 months
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Measured Values

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Number of Participants Analyzed	43
Overall Survival (OS) - Percentage of Participants With an Event [units: percentage of participants]	25.58

11. Secondary Outcome Measure:

Measure Title	OS - Time to Event
Measure Description	OS was defined as the time from the date of first day of treatment until death due to any cause or the last date the participant was known to be alive. OS was estimated using the Kaplan-Meier method.
Time Frame	BL, within 6 weeks after the completion of neoadjuvant treatment, every 2 weeks for 1 year following surgery, every 3 months thereafter until death, up to 45 months
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Measured Values

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Number of Participants Analyzed	43
OS - Time to Event [units: months] Mean (Standard Deviation)	32.14 (1.46)

12. Secondary Outcome Measure:

Measure Title	Time to Disease Progression (TTP) - Percentage of Participants With an Event
Measure Description	TTP was defined as the time from date of treatment start until first documented progression of disease or death due to underlying cancer.
Time Frame	BL, within 6 weeks after the completion of neoadjuvant treatment, every 2 weeks for 1 year following surgery, every 3 months thereafter until death, up to 45 months
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Measured Values

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Number of Participants Analyzed	43
Time to Disease Progression (TTP) - Percentage of Participants With an Event [units: percentage of participants]	27.91

13. Secondary Outcome Measure:

Measure Title	TTP - Time to Event
Measure Description	TTP was defined as the time from date of treatment start until first documented progression of disease or death due to underlying cancer. TTP was estimated using the Kaplan-Meier method.
Time Frame	BL, within 6 weeks after the completion of neoadjuvant treatment, every 2 weeks for 1 year following surgery, every 3 months thereafter until death, up to 45 months
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Measured Values

	Bv+Capecitabine/Bv+Leucovorin+5-FU
Number of Participants Analyzed	43
TTP - Time to Event [units: months] Mean (Standard Deviation)	27.68 (1.72)

Reported Adverse Events

Time Frame	Adverse events were collected from the date of first study-drug administration until 28 days after the last dose of study drug administration.
Additional Description	All enrolled participants who received at least 1 dose of study medication were included in the safety population. Nonserious adverse events presented in this record include all adverse events reported during the study, not just nonserious events.

Reporting Groups

	Description
Bv+Capecitabine/Bv+Leucovorin+5-FU	Participants received bevacizumab 5 mg/kg IV on Days -14, 1, 15, and 29 and capecitabine 825 mg/m^2 PO BID from Days 1 to 38. Participants also received radiation therapy given at a daily fraction of 1.8 Gy administered in 5 weekly fractions starting at Week 1 (through Week 6) for a maximum total dose of 45 Gy. Six to 8 weeks following all above treatments, participants received complete mesorectal excision surgery. After surgery, participants received bevacizumab 5 mg/kg IV on Day 1 and leucovorin 100 mg/m^2 IV (over 2 hours) followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV (over 22 hours) on Days 1 and 2 every 2 weeks for a maximum of 12 cycles.

Serious Adverse Events

	Bv+Capecitabine/Bv+Leucovorin+5-FU
	Affected/At Risk (%)
Total	8/42 (19.05%)
Cardiac disorders	
Cardiac ischemia [A] *	1/42 (2.38%)
Miocardic ischemia [A] *	1/42 (2.38%)
Gastrointestinal disorders	
Bowel perforation [A] *	1/42 (2.38%)
Diarrhoea [A] *	1/42 (2.38%)
Intestinal occlusion [A] *	1/42 (2.38%)
Injury, poisoning and procedural complications	
Anastomosis dehiscence [A] *	1/42 (2.38%)
Postoperative abscess [A] *	1/42 (2.38%)
Metabolism and nutrition disorders	
Ipokaliemia [A] *	1/42 (2.38%)

* 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%

	Bv+Capecitabine/Bv+Leucovorin+5-FU
	Affected/At Risk (%)
Total	39/42 (92.86%)
Blood and lymphatic system disorders	
Anemia [A] *	5/42 (11.9%)
Leukopenia [A] *	7/42 (16.67%)
Neutropenia [A] *	6/42 (14.29%)

	Bv+Capecitabine/Bv+Leucovorin+5-FU
	Affected/At Risk (%)
Gastrointestinal disorders	
Abdominal pain [A] *	6/42 (14.29%)
Constipation [A] *	4/42 (9.52%)
Diarrhea [A] *	19/42 (45.24%)
Hematochezia [A] *	8/42 (19.05%)
Nausea [A] *	9/42 (21.43%)
Proctalgia [A] *	10/42 (23.81%)
Proctitis [A] *	5/42 (11.9%)
Rectal hemorrhage [A] *	3/42 (7.14%)
Rectal tenesmus [A] *	7/42 (16.67%)
General disorders	
Asthenia [A] *	6/42 (14.29%)
Fatigue [A] *	4/42 (9.52%)
Pyrexia [A] *	3/42 (7.14%)
Infections and infestations	
Cystitis [A] *	4/42 (9.52%)
Metabolism and nutrition disorders	
Hypokalemia [A] *	3/42 (7.14%)
Renal and urinary disorders	
Dysuria [A] *	3/42 (7.14%)
Vascular disorders	
Hypertension [A] *	6/42 (14.29%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA 11.1

Limitations and Caveats

This study did not include a separate analysis of non-serious AEs therefore non-serious adverse events presented in this record include all adverse events reported during the study, not just non-serious 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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