Clinical trial results:
Safety and Efficacy Study to Compare Capecitabine + Bevacizumab Versus Capecitabine, Concomitantly With Radiotherapy as Neoadjuvant Treatment for Patients With Localized and Resectable Rectal Cancer (AVAXEL)

Summary

EudraCT number	2009-010192-24
Trial protocol	ES
Global end of trial date	04 August 2016

Results information

Result version number	v1 (current)
This version publication date	16 July 2020
First version publication date	16 July 2020

Trial information

Trial identification

Sponsor protocol code	TTD-08-05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01043484
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TTD (Grupo de Tratamiento de los Tumores Digestivos)
Sponsor organisation address	C/ Téllez Nº 30 posterior 1º oficina 4.2 , MADRID, Spain, 28007
Public contact	TTD (Grupo de Tratamiento de los Tumores Digestivos), TTD (Grupo de Tratamiento de los Tumores Digestivos), +3491 3788275, ttd@ttdgroup.org
Scientific contact	TTD (Grupo de Tratamiento de los Tumores Digestivos), TTD (Grupo de Tratamiento de los Tumores Digestivos), +3491 3788275, ttd@ttdgroup.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 August 2016
Global end of trial reached?	Yes
Global end of trial date	04 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the efficacy of neoadjuvant treatment with BVZ administered biweekly concomitantly with capecitabine and external RT measured as rate of complete pathological responses (RC p), and compare it with the rate of RC p obtained with capecitabine and external RT

Protection of trial subjects:

In this trial safety and patient´s protection was an important objetive. Therefore, 3 intermediate safety analyzes were planned, after the first 6, 12 and 18 evaluable patients, in a dynamic way through direct feed back via e-mail or teleconference with researchers who had recruited these first patients without having to stop the recruitment or close the database in each of the 3 recruitment milestones. The possibility of two dose reductions of capecitabine depending on the toxicity observed was contemplated (725 and 625mg / m2) in the case that there were unacceptable toxicities in ≥ 33% of patients at the initial doses or that have been reduced doses in more than 50% of patients. The doses of RT and bevacizumab were maintained unchanged.
The security assessment was done on the safety population and was based mainly in the frequency and severity of adverse events abd serious adverse events.
The use of any medication that patients needed for their correct clinical control was allowed, according to the criteria of the researcher, with the exception of those detailed in the protocol as forbidden.
Data of all concomitant medication, as well as the diagnostic, therapeutic or surgical procedures performed during the study was required to be recorded in the eCRF.

Background therapy:

differentUntil very recently, 5-Fluorouracil (5-FU) was the only systemic treatment effective to treat colorectal cancer but in the last five years, the incorporation into the therapeutic arsenal of new cytotoxics (capecitabine, irinotecan and oxaliplatin) and monoclonal antibodies against different targets (Cetuximab and Bevacizumab) have opened up new possibilities that have improved substantially the therapeutic results. In addition, the multidisciplinary treatment of rectal cancer has achieved an improvement both in the local and systemic control based on the recognition that the high incidence of local recurrences is due to the lack of sterility of the surgical radial margin, which led to the development of the total mesorectal resection (RTM) as a technique that achieves a substantial decrease in local recurrences, which is considered, at the present time, the standard surgical treatment for the medium and low rectal cancer.
in addition, pelvic radiotherapy has also become an standard preoperative treatment in medium and low rectal cancer, based on its effect on the reduction of the tumor size and stage and the increase in the possibility of preservation of the anal sphincter in low tumors.

Evidence for comparator:

In this trial, the comparator arm will inlcude bevacizumab as neoadjuvant treatment in combination with capecitabine and radiotherapy. In this sense, a preliminary phase II study conducted at the MDACC with the combination of RT + capecitabine (900 mg / m2 / 12 hours on RT days) and bevacizumab 5 mg / kg in rectal cancer has shown promising safety and efficacy, with 29%
pCR in 17 patients.

Actual start date of recruitment	23 December 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 90
Worldwide total number of subjects	90
EEA total number of subjects	90

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	51
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Ninety patients were randomly assigned from December 2009 until March 2011 in 12 hospitals in Spain.

Pre-assignment

Screening details:

Patients >18y with locally advanced rectal adenocarcinoma, clinical stage II-III within <15 cm from the anal verge, and ECOG 0-1 were eligible. All patients were required to be candidates for definitive surgical resection and have adequate bone marrow and organ function and no previous chemotherapy or radiation for rectal cancer.

Period 1

Period 1 title	OVERALL TRIAL (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

No blinded trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	ARM A

Arm description:

5 weeks of radiotherapy 45 Gy/25 fractions with concurrent capecitabine 825 mg/m2 twice daily 5 days per week and bevacizumab 5 mg/kg once every 2 weeks as neoadjuvant treatment followed by surgery

Arm type	Experimental
Investigational medicinal product name	CAPECITABINE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

825 mg/m2 twice daily 5 days per week

Investigational medicinal product name	BEVACIUMAB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was given at the dose of 5 mg/kg once every 2 weeks (3 doses) as iv infusion.

Investigational medicinal product name	radiotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radionuclide generator
Routes of administration	Route of administration not applicable

Dosage and administration details:

Radiotherapy was given during5 weeks of radiotherapy 45 Gy/25 fractions

Arm title	ARM B

Arm description:

- Capecitabine: 825 mg/m2/12 h 5 days per week for 5 weeks.

- Radiation therapy: 45 Gy (1.8 Gy per session, 5 days per week for 5 weeks)

Arm type	Active comparator
Investigational medicinal product name	CAPECITABINE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

- Capecitabine from ROCHE (Xeloda®) in film-coated tablets of 150 mg and 500 mg per tablet, at the dose of 825 mg/m2/12 h 5 days per week for 5 weeks.

Investigational medicinal product name	radiotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radionuclide generator
Routes of administration	Route of administration not applicable

Dosage and administration details:

- Radiation therapy: 45 Gy (1.8 Gy per session, 5 days per week for 5 weeks)

Number of subjects in period 1	ARM A	ARM B
Started	44	46
Completed	41	43
Not completed	3	3
Adverse event, non-fatal	2	3
Non surgery	1	-

Baseline characteristics

Reporting groups

Reporting group title	ARM A

Reporting group description:

5 weeks of radiotherapy 45 Gy/25 fractions with concurrent capecitabine 825 mg/m2 twice daily 5 days per week and bevacizumab 5 mg/kg once every 2 weeks as neoadjuvant treatment followed by surgery

Reporting group title	ARM B

Reporting group description:

- Capecitabine: 825 mg/m2/12 h 5 days per week for 5 weeks.
- Radiation therapy: 45 Gy (1.8 Gy per session, 5 days per week for 5 weeks)

Reporting group values	ARM A	ARM B	Total
Number of subjects	44	46	90
Age categorical			
Subjects were between 37 and 78 years old.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	23	28	51
From 65-84 years	21	18	39
85 years and over	0	0	0
Age continuous			
Units: years			
log mean	62.80	61.17	
standard deviation	± 9.99	± 10.55	-
Gender categorical			
Units: Subjects			
Female	19	16	35
Male	25	30	55
ECOG			
Units: Subjects			
ECOG 0	22	30	52
ECOG 1	22	16	38
PRIMARY TUMOR LOCATION			
Units: Subjects			
UPPER THIRD	10	10	20
MIDDLE THIRD	14	19	33
LOWER THIRD	20	16	36
ND	0	1	1
TNM (T)			
Units: Subjects			

T3	33	38	71
T4	10	7	17
T2	1	1	2
TNM (N9 Units: Subjects			
N0	7	5	12
N1	18	27	45
N2	19	14	33
TNM (M) Units: Subjects			
M0	43	43	86
MX	1	3	4
HISTOLOGIC SUBTYPE Units: Subjects			
ADENOCARCINOMA NOS	38	44	82
MUCINOUS ADENOCARCINOMA	1	1	2
OTHER	5	1	6
HISTOLOGICAL GRADE Units: Subjects			
GX	13	17	30
G1	7	11	18
G2	20	16	36
G3	4	2	6
TIME FROM DIAGNOSIS Units: YEEARS			
log mean	1.13	1.07	
standard deviation	± 0.51	± 0.51	-
DISTANCE TO THE ANAL VERGE Units: CM			
log mean	6.74	6.75	
standard deviation	± 3.78	± 3.40	-

End points

End points reporting groups

Reporting group title	ARM A

Reporting group description:

5 weeks of radiotherapy 45 Gy/25 fractions with concurrent capecitabine 825 mg/m2 twice daily 5 days per week and bevacizumab 5 mg/kg once every 2 weeks as neoadjuvant treatment followed by surgery

Reporting group title	ARM B

Reporting group description:

- Capecitabine: 825 mg/m2/12 h 5 days per week for 5 weeks.
- Radiation therapy: 45 Gy (1.8 Gy per session, 5 days per week for 5 weeks)

Primary: PATHOLOGICAL COMPLETE RESPONSE-ITT POPULATION

End point title	PATHOLOGICAL COMPLETE RESPONSE-ITT POPULATION

End point description:

Defined as ypT y el ypN = T0 y N0, it meaans, absence of tumoral cells in the surgical sample.

End point type	Primary

End point timeframe:

OVERALL STUDY

End point values	ARM A	ARM B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	46		
Units: SUBJECTS				
Pathological complete response	7	5		
No pathological complete response	36	41		
Missing	1	0		

Statistical analyses

Statistical analysis title	PRIMARY OBJECTIVE: PATHOLOGICAL COMPLETE RESPONSE

Statistical analysis description:

ITT POPULATION

Comparison groups	ARM A v ARM B
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5424
Method	Fisher exact

Secondary: TUMORAL REGRESSION RATE- ITT POPULATION

End point title	TUMORAL REGRESSION RATE- ITT POPULATION

End point description:

Degree of tumor regression has 5 categories, DRT 1 is complete pathological response; DRT 5 is disease progression.

End point type	Secondary

End point timeframe:

OVERALL STUDY

End point values	ARM A	ARM B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	46		
Units: Subjects				
DTR 1	8	5		
DTR 2	8	15		
DTR 3	14	19		
DTR 4	12	6		
DTR 5	0	1		
ND	1	0		
Missing	1	0		

Statistical analyses

Statistical analysis title	Pathologic response
Comparison groups	ARM A v ARM B
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1458
Method	Fisher exact

Secondary: Local relapse-free survival

End point title	Local relapse-free survival

End point description:

Local relapse-free survival at 3 and 5 years was defined as the time between subject randomization and the first local relapse. Patients were censored if no local relapse was observed and the date of censorship used was the date of last contact.

End point type	Secondary

End point timeframe:

At 3 and 5 years after randomization

End point values	ARM A	ARM B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	46		
Units: Subjects				
Yes	0	1		
No	44	45		

Statistical analyses

Statistical analysis title	ITT population
Statistical analysis description:	
Local relapse-free survival at 3 and 5 years was the same value	
Comparison groups	ARM A v ARM B
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1
Method	Fisher exact

Secondary: Distant relapse free surival rate

End point title	Distant relapse free surival rate
End point description:	
Distant relapse-free survival at 3 and 5 years was defined as the time between randomization of a subject and the presence of the first distant relapse. A subject was censored if no relapse was observed and the date of censorship used was the date of last contact.	
End point type	Secondary
End point timeframe:	
At 3 and 5 years post-randomization.	

End point values	ARM A	ARM B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	46		
Units: Subjects				
Yes	11	10		
No	33	36		

Statistical analyses

Statistical analysis title	ITT population
Statistical analysis description:	
There were no significant differences at 3 and 5 years, therefore only the global results are posted	

Comparison groups	ARM A v ARM B
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7147
Method	Chi-squared

Secondary: Overal survival rate at 3 and 5 years

End point title	Overal survival rate at 3 and 5 years

End point description:

End point type	Secondary

End point timeframe:

At 3 and 5 years post-randomization.

End point values	ARM A	ARM B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	46		
Units: Subjects				
Dead	10	7		
Alive	34	39		

Statistical analyses

Statistical analysis title	ITT population
Comparison groups	ARM B v ARM A
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3629
Method	Chi-squared

Secondary: To determine the percentage of R0 resections-PP population

End point title	To determine the percentage of R0 resections-PP population

End point description:

R0 means complete resection

End point type	Secondary

End point timeframe:

After surgery

End point values	ARM A	ARM B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	43		
Units: Subjects				
R0	39	41		
R1	1	2		

Statistical analyses

Statistical analysis title	Percentage of R0 resections
Statistical analysis description: PP population	
Comparison groups	ARM A v ARM B
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1
Method	Fisher exact

Secondary: Rate of local relapse-PP population

End point title	Rate of local relapse-PP population
End point description:	
End point type	Secondary
End point timeframe: Rate of local relapse at 3 and 5 years	

End point values	ARM A	ARM B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	43		
Units: Subjects				
Yes	0	1		
No	40	42		

Statistical analyses

Statistical analysis title	Local relapse-free survival rate.
Statistical analysis description: PP population	
Comparison groups	ARM A v ARM B
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1
Method	Fisher exact

Secondary: Rate of distant relapse-PP population	
End point title	Rate of distant relapse-PP population
End point description:	
End point type	Secondary
End point timeframe: Rate of distant relapse at 3 and 5 years	

End point values	ARM A	ARM B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	43		
Units: Subjects				
yes	11	9		
No	29	34		

Statistical analyses

Statistical analysis title	Distant relapse-free survival rate.
Statistical analysis description: PP population	
Comparison groups	ARM A v ARM B
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.4844
Method	Chi-squared

Secondary: Rate of surgical complications-PP population	
End point title	Rate of surgical complications-PP population

End point description:

End point type	Secondary
End point timeframe: Post-operatory complications	

End point values	ARM A	ARM B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	43		
Units: subjects				
Yes	18	17		
No	22	26		

Statistical analyses

Statistical analysis title	Rate of surgical complications
Statistical analysis description: PP population	
Comparison groups	ARM A v ARM B
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6144
Method	Chi-squared

Secondary: Rate of sphincter preservation-PP population

End point title	Rate of sphincter preservation-PP population
End point description:	

End point type	Secondary
End point timeframe: Following CT-RT	

End point values	ARM A	ARM B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	43		
Units: Subjects				
Yes	25	28		
No	15	15		

Statistical analyses

Statistical analysis title	Rate of sphincter preservation
Statistical analysis description: PP population	
Comparison groups	ARM A v ARM B
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8043
Method	Chi-squared

Secondary: T downstaging	
End point title	T downstaging
End point description:	
End point type	Secondary
End point timeframe: Following treatment	

End point values	ARM A	ARM B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	43		
Units: subbjects				
Improved	23	17		
No changes	16	26		
Worsened	1	0		

Statistical analyses

Statistical analysis title	T downstaging
Comparison groups	ARM A v ARM B

Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0979
Method	Fisher exact

Secondary: N downstaging

End point title	N downstaging

End point description:

End point type	Secondary

End point timeframe:
Following treatment

End point values	ARM A	ARM B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	43		
Units: Subjects				
Improved	23	33		
No changes	13	8		
Worsened	4	1		
Non/evaluable	0	1		

Statistical analyses

Statistical analysis title	N downstaging
Comparison groups	ARM A v ARM B
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1127
Method	Fisher exact

Secondary: Improvement in ypT and ypN

End point title	Improvement in ypT and ypN

End point description:

End point type	Secondary

End point timeframe:
Following treatment

End point values	ARM A	ARM B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	43		
Units: Subjects				
Improvement in both	17	15		
Improvement in one	12	19		
No improvement	11	8		
Non/evaluable	0	1		

Statistical analyses

Statistical analysis title	Improvement in ypT and ypN
Comparison groups	ARM A v ARM B
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3635
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs manifested up to 28 days after the last dose of study medications. Serious and not serious AEs related to study treatment up to 6 months after the last dose of study treatment.• AEs related to the administration of RT and were manifested by the (cont)

Adverse event reporting additional description:

(cont)patients and/or that appeared in the control tests and were attributable to this procedure. • Possible surgical complications occurring either at the execution of the surgical resection of the tumor or those occurring within the first 30 days following the procedure.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Arm A
Reporting group description: -	
Reporting group title	Arm B

Reporting group description: -

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 44 (29.55%)	11 / 46 (23.91%)	
number of deaths (all causes)	10	7	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer of the larynx			
subjects affected / exposed	0 / 44 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomosis dehiscence			
subjects affected / exposed	4 / 44 (9.09%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Pre-sacral hematoma			

subjects affected / exposed	0 / 44 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 44 (2.27%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal fistula			
subjects affected / exposed	0 / 44 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	1 / 44 (2.27%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	0 / 44 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowel occlusion			
subjects affected / exposed	2 / 44 (4.55%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal hemorrhage			
subjects affected / exposed	1 / 44 (2.27%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

paralytic ileus			
subjects affected / exposed	0 / 44 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 44 (2.27%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Kidney failure			
subjects affected / exposed	0 / 44 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fistula			
subjects affected / exposed	1 / 44 (2.27%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	2 / 44 (4.55%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
subjects affected / exposed	0 / 44 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hemorrhagic intestinal diverticulitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	1 / 44 (2.27%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary infection			
subjects affected / exposed	0 / 44 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purulent exudate			
subjects affected / exposed	0 / 44 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	0 / 44 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 44 (97.73%)	44 / 46 (95.65%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 44 (6.82%)	3 / 46 (6.52%)	
occurrences (all)	3	3	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	27 / 44 (61.36%)	12 / 46 (26.09%)	
occurrences (all)	27	12	
Pain			
subjects affected / exposed	6 / 44 (13.64%)	3 / 46 (6.52%)	
occurrences (all)	6	3	
Pyrexia			
subjects affected / exposed	4 / 44 (9.09%)	4 / 46 (8.70%)	
occurrences (all)	4	4	
Inflammation of the mucosa			
subjects affected / exposed	4 / 44 (9.09%)	2 / 46 (4.35%)	
occurrences (all)	4	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 44 (13.64%)	6 / 46 (13.04%)	
occurrences (all)	6	6	
Neutropenia			
subjects affected / exposed	4 / 44 (9.09%)	2 / 46 (4.35%)	
occurrences (all)	4	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	17 / 44 (38.64%)	21 / 46 (45.65%)	
occurrences (all)	17	21	
Rectal tenesmus			
subjects affected / exposed	13 / 44 (29.55%)	15 / 46 (32.61%)	
occurrences (all)	13	15	
Rectal haemorrhage			
subjects affected / exposed	10 / 44 (22.73%)	13 / 46 (28.26%)	
occurrences (all)	11	13	
Proctalgia			
subjects affected / exposed	7 / 44 (15.91%)	10 / 46 (21.74%)	
occurrences (all)	7	10	
Nausea			
subjects affected / exposed	7 / 44 (15.91%)	5 / 46 (10.87%)	
occurrences (all)	7	5	
Abdominal pain			

subjects affected / exposed	7 / 44 (15.91%)	5 / 46 (10.87%)	
occurrences (all)	7	5	
Vomiting			
subjects affected / exposed	7 / 44 (15.91%)	4 / 46 (8.70%)	
occurrences (all)	7	4	
Anorectal discomfort			
subjects affected / exposed	5 / 44 (11.36%)	5 / 46 (10.87%)	
occurrences (all)	5	5	
Proctitis			
subjects affected / exposed	3 / 44 (6.82%)	3 / 46 (6.52%)	
occurrences (all)	3	3	
Constipation			
subjects affected / exposed	3 / 44 (6.82%)	2 / 46 (4.35%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	6 / 44 (13.64%)	3 / 46 (6.52%)	
occurrences (all)	6	3	
Rash			
subjects affected / exposed	3 / 44 (6.82%)	3 / 46 (6.52%)	
occurrences (all)	3	3	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	10 / 44 (22.73%)	15 / 46 (32.61%)	
occurrences (all)	10	15	
Urinary frequency			
subjects affected / exposed	5 / 44 (11.36%)	2 / 46 (4.35%)	
occurrences (all)	5	2	
Hematuria			
subjects affected / exposed	3 / 44 (6.82%)	2 / 46 (4.35%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 44 (4.55%)	3 / 46 (6.52%)	
occurrences (all)	2	3	
Infections and infestations			

Cystitis subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 4	2 / 46 (4.35%) 2	
Metabolism and nutrition disorders Loss of appetite subjects affected / exposed occurrences (all)	7 / 44 (15.91%) 7	6 / 46 (13.04%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2009	Treatment with oxaliplatin was eliminated after data presented on ASCO 2009. Minor mistakes correction. Protocol v 3.0 was generated
19 April 2010	Clarifications about RT treatment, management of toxicities and addition of a 4th sample for the sub study. Typos eliminated. Change of PI in H. de Valdecilla. Protocol v 4.0 was generated.
20 October 2010	Informative amendment, correcting inclusion criteria 5 and referring to Avastin's IB (previously: technical datasheet). Protocol v 4.1 was generated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25886378