



## Clinical trial results:

**Preoperative combined radiochemotherapy for patients with newly diagnosed, primary operable and locally advanced rectal carcinoma (cT3, Nx, M0) of the lower and middle rectum**

### Summary

EudraCT number	2004-002358-72
Trial protocol	AT
Global end of trial date	

### Results information

Result version number	v1
This version publication date	10 September 2021
First version publication date	10 September 2021

### Trial information

#### Trial identification

Sponsor protocol code	ABCSG R02 (95)/TAKO 05
-----------------------	------------------------

#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00297141
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	ABCSG (Austrian Breast & Colorectal Cancer Study Group)
Sponsor organisation address	Nußdorfer Platz 8/12, Vienna, Austria, 1190
Public contact	Hannes Fohler (Trial Office Director), ABCSG (Austrian Breast & Colorectal Cancer Study Group), +43 14089230, info@abcsbg.at
Scientific contact	Prof. Dietmar Oefner-Velano, ABCSG (Austrian Breast & Colorectal Cancer Study Group), +43 14089230, info@abcsbg.at

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	Interim
Date of interim/final analysis	16 November 2006
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2006
Global end of trial reached?	No

Notes:

## General information about the trial

Main objective of the trial:

Rate of T-downstaging (Reduction of the T-stadium) at the time of final surgery following the preoperative combined radiochemotherapy (chemotherapy: Oxaliplatin, Capecitabine)

Protection of trial subjects:

A Data Monitoring Committee (DMC) was established to obtain Patient Safety. The responsibility of the DMC was to evaluate deviations of medical relevance and safety issues. The DMC decided on whether or not the patient should continue the study treatment due to safety issues. Major protocol deviations include all deviations endangering the basal medical concept of the study jeopardizing the safety of the patient. Minor protocol deviations include all other protocol deviations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 December 2004
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	38
From 65 to 84 years	22
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 8 trial sites participated and had the possibility to recruit patients in this trial in Austria. A total of 60 patients were enrolled between Dec 2004 and Dec 2005.

### Pre-assignment

Screening details:

Time period of max. 21 days for screening (from diagnosis to therapy start) in which inclusion and exclusion criteria were assessed and clinical laboratory tests were performed.

### Pre-assignment period milestones

Number of subjects started	60
Number of subjects completed	60

### Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Combined radio chemotherapy
------------------	-----------------------------

Arm description:

Preoperative Chemoradiation with therapy start within 21 days after MRI. Radiotherapy: 5 x 5 days 1.8 Gy; total dose 45 Gy; Chemotherapy: Capecitabine 825mg/m<sup>2</sup> bid, on radiotherapy days (week 1-4), Oxaliplatin 50mg/m<sup>2</sup> iv., d 1, 8, 15, 22.

Arm type	Experimental
Investigational medicinal product name	Xeloda
Investigational medicinal product code	RO 09-1978
Other name	Capecitabine
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

825 mg/m<sup>2</sup>/bid, on radiotherapy days (week 1-4)

Investigational medicinal product name	Eloxatin
Investigational medicinal product code	SR 96669
Other name	Oxaliplatin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50mg/m<sup>2</sup> BSA per day (d1, d8, d15, d22)

<b>Number of subjects in period 1</b>	Combined radio chemotherapy
Started	60
Completed	59
Not completed	1
retrospectively stated ineligible	1

## Baseline characteristics

### Reporting groups

Reporting group title	overall trial
-----------------------	---------------

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	60	60	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	38	38	
From 65-84 years	22	22	
85 years and over	0	0	
Age continuous			
Units: years			
median	61		
full range (min-max)	34 to 76	-	
Gender categorical			
Units: Subjects			
Female	19	19	
Male	41	41	
WHO Performance Status			
Units: Subjects			
0 (Zero)	55	55	
1 (One)	5	5	
Tumor differentiation			
Units: Subjects			
G1-2	42	42	
G3	9	9	
not classified	9	9	
Histologic type			
Units: Subjects			
adenocarcinoma	51	51	
mucinous	5	5	
others	4	4	
Tumor stage			
Units: Subjects			
cT2	1	1	
cT3	59	59	

## Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat population (ITT) consisted of all patients who received at least one dose of study medication. All efficacy and safety analyses were performed on this population.

Reporting group values	ITT		
Number of subjects	59		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	38		
From 65-84 years	22		
85 years and over	0		
Age continuous Units: years			
median	61		
full range (min-max)	34 to 76		
Gender categorical Units: Subjects			
Female	19		
Male	40		
WHO Performance Status Units: Subjects			
0 (Zero)	54		
1 (One)	5		
Tumor differentiation Units: Subjects			
G1-2	41		
G3	9		
not classified	9		
Histologic type Units: Subjects			
adenocarcinoma	50		
mucinous	5		
others	4		
Tumor stage Units: Subjects			
cT2	0		
cT3	59		

## End points

### End points reporting groups

Reporting group title	Combined radio chemotherapy
Reporting group description: Preoperative Chemoradiation with therapy start within 21 days after MRI. Radiotherapy: 5 x 5 days 1.8 Gy; total dose 45 Gy; Chemotherapy: Capecitabine 825mg/m <sup>2</sup> bid, on radiotherapy days (week 1-4), Oxaliplatin 50mg/m <sup>2</sup> iv., d 1, 8, 15, 22.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: The intent-to-treat population (ITT) consisted of all patients who received at least one dose of study medication. All efficacy and safety analyses were performed on this population.	

### Primary: Tumor down-categorization

End point title	Tumor down-categorization <sup>[1]</sup>
End point description: The primary efficacy variable was the rate of tumor down-categorization (defined as a decrease of $\geq 1$ point(s)) at the T level. The extent of residual tumor in the resected specimen was classified according to the TNM staging system of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC). In case of a complete pathological response (pCR; i.e., ypT0ypN0M0), an independent pathologist re-evaluated the tumor tissue. All efficacy parameters were analyzed descriptively.	
End point type	Primary
End point timeframe: At the time of final surgery following the preoperative combined radio chemotherapy (chemotherapy: Oxaliplatin, Capecitabine).	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Single arm study based on descriptive analysis only.	

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: Subjects	31			

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Pathological Complete Response (pCR)

End point title	Pathological Complete Response (pCR)
End point description: The extent of residual tumor in the resected specimen was classified according to the TNM staging system of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC). In case of a complete pathological response (pCR; i.e., ypT0ypN0M0), an independent pathologist re-evaluated the tumor tissue. All efficacy parameters were analyzed descriptively.	
End point type	Other pre-specified
End point timeframe: At the time of final surgery following the preoperative combined radio chemotherapy (chemotherapy:	

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: Subjects	6			

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Confirmed Pathological Complete Response (pCR)

End point title	Confirmed Pathological Complete Response (pCR)
-----------------	--

End point description:

The extent of residual tumor in the resected specimen was classified according to the TNM staging system of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC). In case of a complete pathological response (pCR; i.e., ypT0ypN0M0), an independent pathologist re-evaluated the tumor tissue. All efficacy parameters were analyzed descriptively.

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

At the time of final surgery following the preoperative combined radio chemotherapy (chemotherapy: Oxaliplatin, Capecitabine).

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: Subjects	4			

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Tumor status

End point title	Tumor status
-----------------	--------------

End point description:

The extent of residual tumor in the resected specimen was classified according to the TNM staging system of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC). In case of a complete pathological response (pCR; i.e., ypT0ypN0M0), an independent pathologist re-evaluated the tumor tissue. All efficacy parameters were analyzed descriptively.

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

At the time of final surgery following the preoperative combined radio chemotherapy (chemotherapy: Oxaliplatin, Capecitabine).



End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: Subjects				
0 (Zero)	6			
1 (One)	2			
2 (Two)	23			
3 (Three)	26			
4 (Four)	2			

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Nodal status

End point title	Nodal status
-----------------	--------------

End point description:

The extent of residual tumor in the resected specimen was classified according to the TNM staging system of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC). In case of a complete pathological response (pCR; i.e., ypT0ypN0M0), an independent pathologist re-evaluated the tumor tissue. All efficacy parameters were analyzed descriptively.

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

At the time of final surgery following the preoperative combined radio chemotherapy (chemotherapy: Oxaliplatin, Capecitabine).

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: Subjects				
0 (Zero)	43			
1 (One)	10			
2 (Two)	6			

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Metastasis

End point title	Metastasis
-----------------	------------

---

**End point description:**

The extent of residual tumor in the resected specimen was classified according to the TNM staging system of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC). In case of a complete pathological response (pCR; i.e., ypT0ypN0M0), an independent pathologist re-evaluated the tumor tissue. All efficacy parameters were analyzed descriptively.

---

End point type	Other pre-specified
----------------	---------------------

---

**End point timeframe:**

At the time of final surgery following the preoperative combined radio chemotherapy (chemotherapy: Oxaliplatin, Capecitabine).

---

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: Subjects				
0 (Zero)	59			
1 (One)	0			

---

**Statistical analyses**

No statistical analyses for this end point

---

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first administration of radiochemotherapy until surgery

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	10.1
--------------------	------

### Reporting groups

Reporting group title	Combined radiochemotherapy
-----------------------	----------------------------

Reporting group description: -

Serious adverse events	Combined radiochemotherapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 59 (20.34%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertensive crisis	Additional description: Hypertensive crisis		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	3 / 59 (5.08%)		
occurrences causally related to treatment / all	5 / 6		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper	Additional description: Abdominal pain upper		

subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Constipation	Additional description: Constipation		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	5 / 59 (8.47%)		
occurrences causally related to treatment / all	12 / 13		
deaths causally related to treatment / all	0 / 0		
Proctitis	Additional description: Proctitis		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism	Additional description: Pulmonary embolism		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Erythema	Additional description: Erythema		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Renal failure	Additional description: Renal failure		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion	Additional description: Intervertebral disc protrusion		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Combined radiochemotherapy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 59 (94.92%)		
Injury, poisoning and procedural complications			
Radiation skin injury	Additional description: Radiation skin injury		
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	8		
Vascular disorders			
Hypertension	Additional description: Hypertension		
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	13		
Nervous system disorders			

Neurotoxicity subjects affected / exposed occurrences (all)	Additional description: Neurotoxicity		
	22 / 59 (37.29%)		
	57		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all)	Additional description: Leukopenia		
	7 / 59 (11.86%)		
	17		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)  Fatigue subjects affected / exposed occurrences (all)  Pyrexia subjects affected / exposed occurrences (all)	Additional description: Asthenia		
	4 / 59 (6.78%)		
	10		
	Additional description: Fatigue		
	7 / 59 (11.86%)		
	9		
	Additional description: Pyrexia		
	7 / 59 (11.86%)		
	8		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)  Constipation subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Gastrointestinal toxicity subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)  Painful defaecation subjects affected / exposed occurrences (all)	Additional description: Abdominal pain		
	3 / 59 (5.08%)		
	6		
	Additional description: Constipation		
	6 / 59 (10.17%)		
	11		
	Additional description: Diarrhoea		
	26 / 59 (44.07%)		
	69		
	Additional description: Gastrointestinal toxicity		
	8 / 59 (13.56%)		
	8		
	Additional description: Nausea		
	19 / 59 (32.20%)		
	37		
	Additional description: Painful defaecation		
	3 / 59 (5.08%)		
	11		

Vomiting subjects affected / exposed occurrences (all)	Additional description: Vomiting		
	5 / 59 (8.47%) 6		
Skin and subcutaneous tissue disorders Skin toxicity subjects affected / exposed occurrences (all)	Additional description: Skin toxicity		
	7 / 59 (11.86%) 11		
Psychiatric disorders Mental disorder subjects affected / exposed occurrences (all)	Additional description: Mental disorder		
	4 / 59 (6.78%) 4		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)  Micturition urgency subjects affected / exposed occurrences (all)	Additional description: Dysuria		
	6 / 59 (10.17%) 16		
	Additional description: Micturition urgency		
	5 / 59 (8.47%) 8		
Infections and infestations Infection subjects affected / exposed occurrences (all)	Additional description: Infection		
	3 / 59 (5.08%) 6		
Metabolism and nutrition disorders Weight fluctuation subjects affected / exposed occurrences (all)	Additional description: Weight fluctuation		
	12 / 59 (20.34%) 21		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2010	According to Protocol Amendment #1, collection of prolonged (after surgery) follow up survival data was done. This data should enable estimation of survival curves for overall survival, cancer specific survival and relapse-free survival. Additionally, relationship between study primary endpoints tumor stage downstaging and yPCR and survival endpoints was examined. It should be stated that study was not powered for comparison between chemotherapy response and survival endpoint.

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Limitation of a nonrandomized design.

Notes:

---

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/21267531>