Clinical trial results:
Multicentre international study of capecitabine ± bevacizumab as adjuvant treatment of colorectal cancer

Summary

EudraCT number	2004-000629-32
Trial protocol	SI AT CZ
Global end of trial date	31 March 2014

Results information

Result version number	v1 (current)
This version publication date	17 November 2021
First version publication date	17 November 2021
Summary attachment (see zip file)	Adjuvant capecitabine plus bevacizumab versus capecitabine alone in patients with colorectal cancer (QUASAR 2): an open-label, randomised phase 3 trial (QUASAR2 primary publication.pdf)

Trial information

Trial identification

Sponsor protocol code	MO17092

Additional study identifiers

ISRCTN number	ISRCTN45133151
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	CTRG, Joint Research Office, 1st Floor, Boundary Brook House, Churchill Drive, Headington, Oxford, United Kingdom, OX3 7GB
Public contact	University of Oxford, Sponsor office as above., University of Oxford, Sponsor office as above., 0000 000000000, CTRG@admin.ox.ac.uk
Scientific contact	University of Oxford, Sponsor office as above., University of Oxford, Sponsor office as above., 0000 000000000, CTRG@admin.ox.ac.uk

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	31 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2014
Global end of trial reached?	Yes
Global end of trial date	31 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main study objective is to compare the efficiacy of the two regimens: standard chemotherapy with capecitabine against capecitabine + bevacizumab. Primary endpoint is disease free survival. Secondary endpoints: disease free survival for stage III patients, overall survival, safety profiles.

Protection of trial subjects:

Please see attached primary publication.

Background therapy:

Please see attached primary publication.

Evidence for comparator:

Please see attached primary publication.

Actual start date of recruitment	25 April 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovenia: 48
Country: Number of subjects enrolled	Australia: 205
Country: Number of subjects enrolled	Austria: 122
Country: Number of subjects enrolled	Czechia: 29
Country: Number of subjects enrolled	New Zealand: 15
Country: Number of subjects enrolled	United Kingdom: 1533
Worldwide total number of subjects	1952
EEA total number of subjects	199

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)	580
From 65 to 84 years	789
85 years and over	583

Subject disposition

Recruitment

Recruitment details:

Consented and Randomised. Please see primary publication.
Open-label, randomised, controlled QUASAR 2 trial, which was done at 170 hospitals in seven countries.

Pre-assignment

Screening details:

Please see attached primary publication.
Assessed for eligibility N= 7475
Exclusions N= 5523
Not meeting inclusion criteria N= 2810
Refused to participate N = 1811
Other reason N= 902

Period 1

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

Blinding implementation details:

Please see attached primary publication.

Arms

Are arms mutually exclusive?	Yes
Arm title	capecitabine alone

Arm description:

Please see primary publication.

Arm type	Please see primary publication.
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Arm A: Capecitabine 1250mg/m2, twice daily 12 hours apart (total daily dose 2500mg/m2) for 14 days [max 2500 mg b.d. (total daily dose 5000 mg)].
Treatment repeated every 3 weeks for a total of 8 cycles (24 weeks). One cycle = 3 weeks.

Arm title	capecitabine and bevacizumab

Arm description:

Please see primary publication

Arm type	Please see primary publication.
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 1250 mg/m2 twice daily, 12 hours apart (total daily dose 2500 mg/m2) for 14 days [max 2500 mg b.d. (max. total daily dose 5000 mg)]
Treatment is repeated every 3 weeks for a total of 8 cycles (24 weeks). One cycle = 3 weeks.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Bevacizumab 7.5 mg/kg was administered initially over a 90 (15) minute period, day 1. If the first infusion was well tolerated, especially without infusion-associated adverse events (fever and/or chills), the second infusion could be delivered over a 60 (10) minute period. If the 60-minute infusion was well tolerated, all subsequent infusions were delivered over a 30 (10) minute period. The drug was administered in a total volume of 100 ml, sterile saline 0.9% sodium chloride. Bevacizumab infusions should not be administered or mixed with dextrose or glucose solutions.
The dose for bevacizumab was calculated as milligrams per kilogram body weight (mg/kg). The patient's weight at screening was used to determine the dose of bevacizumab to be used for the duration of the study. If a patient's weight changed by 10% during the course of the study, the dose of bevacizumab was recalculated. The infusion was repeated every 3 weeks for a total of 16 cycles (48 weeks) 1 cycle = 3 weeks

Number of subjects in period 1	capecitabine alone	capecitabine and bevacizumab
Started	977	975
Completed	968	973
Not completed	9	2
Consent withdrawn by subject	7	2
Protocol deviation	2	-

Baseline characteristics

Reporting groups

Reporting group title	Consented and Randomised

Reporting group description: -

Reporting group values	Consented and Randomised	Total	
Number of subjects	1952	1952	
Age categorical			
Please see details as in primary publication.			
Units: Subjects			
<50	189	189	
50-59	400	400	
60-69	782	782	
70+	581	581	
Gender categorical Units: Subjects			
Female	836	836	
Male	1116	1116	

Subject analysis sets

Subject analysis set title	Please see primary publication.
Subject analysis set type	Full analysis

Subject analysis set description:
Please see primary publication.

Reporting group values	Please see primary publication.		
Number of subjects	1941		
Age categorical			
Please see details as in primary publication.			
Units: Subjects			
<50	189		
50-59	389		
60-69	782		
70+	581		
Gender categorical Units: Subjects			
Female	832		
Male	1109		

End points

End points reporting groups	
Reporting group title	capecitabine alone
Reporting group description: Please see primary publication.	
Reporting group title	capecitabine and bevacizumab
Reporting group description: Please see primary publication	
Subject analysis set title	Please see primary publication.
Subject analysis set type	Full analysis
Subject analysis set description: Please see primary publication.	

Primary: Disease free survival (3 year) Please see primary publication.	
End point title	Disease free survival (3 year) Please see primary publication.
End point description: Please see primary publication.	
End point type	Primary
End point timeframe: Please see primary publication.	

End point values	capecitabine alone	capecitabine and bevacizumab	Please see primary publication.	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	968	973	1941	
Units: Please see primary publication.	968	973	1941	

Statistical analyses

Statistical analysis title	Please see primary publication

Statistical analysis description:

Survival analyses (disease-free and overall survival) were done by intention to treat. Patients were only excluded from these analyses if at the time of randomisation the legal paperwork was not completed and current for the randomising country, they were found to have had demonstrable metastatic disease, or if they left the study and withdrew consent for the use of data. The safety analysis included all patients who received any amount of any trial drug.

Comparison groups	capecitabine alone v capecitabine and bevacizumab
Number of subjects included in analysis	1941
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.52
Method	See primary publication

Notes:

[1] - Please see primary publication.

Secondary: Disease free survival for stage III patients (3 years) Overall survival (5 year) Side effect profiles Translational science Please see primary publication.

End point title	Disease free survival for stage III patients (3 years) Overall survival (5 year) Side effect profiles Translational science Please see primary publication.

End point description:

Please see primary publication.

End point type	Secondary

End point timeframe:

Please see primary publication.

End point values	capecitabine alone	capecitabine and bevacizumab	Please see primary publication.	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	968	973	1941	
Units: Please see primary publication.	968	973	1941	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Please see primary publication.

Adverse event reporting additional description:

Please see primary publication.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Please refer to the primary publication listed in the results section

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2004	The REC requested some revisions to the protocol. Also, new data emerged at ASCO 2004 to suggest that capecitabine was as effective as 5-FU/FA and so the trial design was changed to incorporate capecitabine as the standard arm into Protocol v4.0, Capecitabine vs capecitabine+irinotecan vs capecitabine+irinotecan+bevacizumab As the original submission was still being considered by the REC, Protocol v4.0 was submitted using an amendment form.
30 September 2004	The REC sent a letter confirming their approval of the v4.0 protocol and that they had received the required favourable Site Specific Assessment from at least one study site.
31 May 2005	At ASCO 2005, results of other trials involving irinotecan were presented. These results suggested that irinotecan added no benefit to colorectal patients in the adjuvant setting and so the QUASAR 2 Trial Management Group (TMG) took the decision to amend the trial design to a two arm trial design, capecitabine vs. capecitabine+bevacizumab Recruitment was suspended on 20 May 2005 6 patients had been randomised Arm A (capecitabine) = 3 Arm B (cap + iri) = 1 Arm C (cap + iri + bev) =2 Patients randomised to receive irinotecan (n=3) were given the opportunity to discuss their treatment options with staff at their hospital. Patients were offered the chance to continue in QUASAR 2 but without irinotecan or to withdraw from the trial.
31 August 2005	Amended trial design incorporated into Protocol v6.0 and submitted to the REC as a substantial amendment. Inclusion was limited to colon cancer patients following discussions with Roche. Protocol v6.0 received favourable ethical opinion from the REC and approval from the MHRA. Recruitment reopened on 14 Sep 2006
28 April 2006	Protocol v7.0 submitted to Ethics. This version detailed the use of blister packs rather than bottles for capecitabine, and included improved capecitabine dose modification tables. Stratification by cancer stage was also amended from two groups (stage II or stage III) to four groups (stage II T3, stage II T4, stage III T2/T3, stage III T4) following feedback from other colorectal trials at National meetings.
31 January 2007	The inclusion of rectal cancer patients was agreed with Roche and the protocol amended to Protocol v8.0. This version was submitted to Ethics and the MHRA. Approval for Protocol v8.0 received from MHRA and a favourable ethical opinion from the REC. Recruitment of rectal cancer patients began from 12th Feb 2007.

30 May 2008	Protocol v9.0 submitted to the main REC and the MHRA. This version provided guidance for investigators about chest pain, bilirubinaemia and neutropenia. The Patient Information Sheet and Blood & Tissue Consent Form were also amended. Approval for Protocol v9.0 received from MHRA and a favourable ethical opinion from the REC.
31 December 2010	Protocol v10.0 submitted to the REC and the MHRA following an urgent safety measure: On 13th October 2010, the QUASAR 2 DSMC, in collaboration with the QUASAR 2 Clinical Leads, decided to withdraw Avastin (bevacizumab) from QUASAR 2 with immediate effect. This decision was made following the review of the top-line results from the AVANT study, an open-label Phase III, multicentre, multinational, randomised, 3-arm study designed to evaluate the efficacy and safety of bevacizumab in combination with either intermittent capecitabine plus oxaliplatin (XELOX) or 5-FU/LV with oxaliplatin (FOLFOX4) versus FOLFOX4 regimen alone as adjuvant chemotherapy in chemotherapy-naïve patients (stage III or high risk stage II) who undergo surgery with curative intent for colon carcinoma. A total of 3451 patients were randomized between December 2004 and June 2007. AVANT did not meet its primary endpoint of improving disease-free survival in stage III colon cancer. Adverse events were consistent with those previously observed in pivotal trials of Avastin across tumour types for approved indications. In line with the previously reported NSABP C-08 study results that also evaluated Avastin in the early-stage setting, the AVANT study showed that standard chemotherapy plus one year of Avastin is not effective in reducing the risk of relapses in early-stage colon cancer. Unlike the C-08 results, preliminary efficacy data from AVANT numerically favour chemotherapy alone (the control arm). After careful consideration of the results of AVANT, the QUASAR 2 DSMC, in collaboration with the QUASAR 2 Clinical Leads, decided to withdraw Avastin. QUASAR 2 patients still on active treatment of bevacizumab ceased bevacizumab treatment immediately and continued with capecitabine alone if they were within the first six months treatment, or continued with follow-up alone if they had already completed capecitabine. Approval of protocol v10.0 received from MHRA and a favourable ethical opinion

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 May 2005	At ASCO 2005, results of other trials involving irinotecan were presented. These results suggested that irinotecan added no benefit to colorectal patients in the adjuvant setting and so the QUASAR 2 Trial Management Group (TMG) took the decision to amend the trial design to a two arm trial design, capecitabine vs. capecitabine+bevacizumab	14 September 2006
13 October 2010	On 13th October 2010, the QUASAR 2 DSMC, in collaboration with the QUASAR 2 Clinical Leads, decided to withdraw Avastin (bevacizumab) from QUASAR 2 with immediate effect. This decision was made following the review of the top-line results from the AVANT study, an open-label Phase III, multicentre, multinational, randomised, 3-arm study designed to evaluate the efficacy and safety of bevacizumab in combination with either intermittent capecitabine plus oxaliplatin (XELOX) or 5-FU/LV with oxaliplatin (FOLFOX4) versus FOLFOX4 regimen alone as adjuvant chemotherapy in chemotherapy-naïve patients (stage III or high risk stage II) who undergo surgery with curative intent for colon carcinoma.	01 December 2010

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27660192