Clinical trial results:
Pilotstudy: Biomarker directed treatment in metastatic colorectal cancer

Summary

EudraCT number	2011-003217-41
Trial protocol	AT
Global end of trial date	03 July 2020

Results information

Result version number	v1 (current)
This version publication date	10 February 2021
First version publication date	10 February 2021

Trial information

Trial identification

Sponsor protocol code	AGMT_ERCC1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01703390
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AGMT
Sponsor organisation address	Gentzgasse 60/21, Vienna, Austria, 1180
Public contact	Dr. Daniela Wolkersdorfer, AGMT, 0043 6641422504, d.wolkersdorfer@agmt.at
Scientific contact	Dr. Richard Greil, AGMT, 0043 5 725525800, r.greil@salk.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	Final
Date of interim/final analysis	27 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 July 2020
Global end of trial reached?	Yes
Global end of trial date	03 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess treatment response (according to Response Evaluation Criteria In Solid Tumors [RECIST]) in patients with previous untreated wt RAS advanced colorectal cancer (patients with mutant KRAS and mutant NRAS are excluded) using mFOLFOX6 or FOLFIRI and cetuximab with therapy chosen using ERCC-1 gene expression assessment.

Protection of trial subjects:

Safety assessments were done on a regular basis, all patients having received at least one dose of the study medication have been followed for adverse events for at least 28 days after discontinuing study treatment or completion of study treatment. Pretreatment with antiemetics, micronutriens, atropine and corticosteroids was recommended. Recommendations for dose modifications in case of toxicities were given. Inclusion and exclusion criteria were defined.

Background therapy:

Arm A (ERCC-1 low), mFOLFOX6:
Oxaliplatin 85mg/m2 on day 1, 15 q d29 for 6 cycles; folinic acid 400mg/m2 on days 1 and 15 q d29 for 6 cycles; fluorouracil (5-FU) 2400mg/m2 46-hour infusion on days 1, 2 and 15, 16 and q d29 for 6 cycles or until unacceptable toxicity, optional: 400mg/m2 bolus on day 1 and 16 of each cycle.

Arm B (ERCC-1 high), FOLFIRI:
Irinotecan 180mg/m² on day 1, 15 q d29 for 6 cycles; folinic acid 400mg/m2 on days 1 and 15 q d29 for 6 cycles; fluorouracil (5-FU) 2400mg/m2 46-hour infusion on days 1, 2 and 15, 16 and q d29 for 6 cycles or until unacceptable toxicity, optional: 400mg/m2 bolus on day 1 and 16 of each cycle.

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 February 2012
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	Austria: 47
Worldwide total number of subjects	47
EEA total number of subjects	47

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)	27
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 04-Dec-2012 and 04-Jun-2018 47 patients were enrolled at 10 study sites in Austria.

Pre-assignment

Screening details:

83 patients with metastatic colorectal cancer were screened for eligibility. Initially 50 patients met inclusion criteria. In one patient a KRAS E3 mutation was locally tested after screening period and two further patients were not willing to start with the study. Therefore 47 patients were enrolled for the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

ERCC1-low, mFOLFOX + cetuximab followed by cetuximab maintenance

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab is administered as a 120 minute intravenous infusion at 500mg/m2 on day 1 then 500 mg/m2 bi-weekly until progression of disease for max. 2,5 years after registration of last patient.

Arm title	Arm B

Arm description:

ERCC1-high, FOLFIRI + cetuximab followed by cetuximab maintenance

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab is administered as a 120 minute intravenous infusion at 500mg/m2 on day 1 then 500 mg/m2 bi-weekly until progression of disease for max. 2,5 years after registration of last patient.

Number of subjects in period 1	Arm A	Arm B
Started	41	6
Induction therapy	25	3
Completed	15	1
Not completed	26	5
Consent withdrawn by subject	2	-
Physician decision	2	1
Resection	3	-
Adverse event, non-fatal	7	-
Death	1	-
Exon 4 mutation	1	-
Therapy postponed >4 weeks	3	-
Progressive disease before maintenance	7	4

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
ERCC1-low, mFOLFOX + cetuximab followed by cetuximab maintenance	
Reporting group title	Arm B
Reporting group description:	
ERCC1-high, FOLFIRI + cetuximab followed by cetuximab maintenance	

Reporting group values	Arm A	Arm B	Total
Number of subjects	41	6	47
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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	61.94	69.64	
standard deviation	± 10.10	± 6.01	-
Gender categorical Units: Subjects			
Female	9	2	11
Male	32	4	36

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
ERCC1-low, mFOLFOX + cetuximab followed by cetuximab maintenance	
Reporting group title	Arm B
Reporting group description:	
ERCC1-high, FOLFIRI + cetuximab followed by cetuximab maintenance	

Primary: Best overall response

End point title	Best overall response[1]
End point description:	
Patients best response from start of study until disease progression or withdrawal determined from an independent response assessment committee.	
End point type	Primary
End point timeframe:	
Start of study paticipation until disease progression or withdrawal	

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: This non-randomized study was not designed for statistical comparisons by treatment arm.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	6		
Units: Subjects				
PR (partial response)	28	2		
SD (stable disease)	7	2		
PD (progressive disease)	1	1		
NA	5	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All (serious) adverse events occurring during study treatment until 28 days after the end of study treatment were collected.

Adverse event reporting additional description:

All grades 3 and 4 AEs were documented. Additionally AEs of all grades which led to dose modification or were associated with a SAE as well as AEs that were associated with neurotoxicity or were considered relevant by the investigator were documented.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 47 (53.19%)		
number of deaths (all causes)	41		
number of deaths resulting from adverse events	0		
Investigations			
Computerised tomogram			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion related reaction			

subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Seroma			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Sciatica			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			

subjects affected / exposed	1 / 47 (2.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity				
subjects affected / exposed	3 / 47 (6.38%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 47 (2.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 47 (2.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 47 (2.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	2 / 47 (4.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 47 (2.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Proctalgia				
subjects affected / exposed	1 / 47 (2.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subileus				

subjects affected / exposed	1 / 47 (2.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mechanical ileus				
subjects affected / exposed	1 / 47 (2.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Bronchospasm				
subjects affected / exposed	1 / 47 (2.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 47 (2.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 47 (2.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	3 / 47 (6.38%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Rash				
subjects affected / exposed	2 / 47 (4.26%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Urinary retention				
subjects affected / exposed	1 / 47 (2.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile infection			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Genital herpes zoster			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sinusitis			

subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 47 (74.47%)		
Nervous system disorders			
Polyneuropathy			
subjects affected / exposed	6 / 47 (12.77%)		
occurrences (all)	7		
Neuropathy peripheral			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	8 / 47 (17.02%)		
occurrences (all)	22		
Leukopenia			
subjects affected / exposed	5 / 47 (10.64%)		
occurrences (all)	10		
Thrombocytopenia			
subjects affected / exposed	4 / 47 (8.51%)		
occurrences (all)	4		
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	6		
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all)	5 / 47 (10.64%) 9 4 / 47 (8.51%) 6		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	13 / 47 (27.66%) 28		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2013	In-/exclusion criteria were extended. Patients with mutant KRAS and NRAS (Exon 2,3) were excluded. As soon as other KRAS or NRAS mutation status analyses were available (KRAS exon 3,4 and NRAS 4) these were implemented without an amendment.

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.

none

Notes: