Clinical trial results:
Capecitabine in combination with Bendamustine in women with pretreated locally advanced or metastatic Her2-negative breast cancer, a Phase II Trial

Summary

EudraCT number	2012-005593-64
Trial protocol	AT
Global end of trial date	15 March 2018

Results information

Result version number	v1 (current)
This version publication date	23 March 2019
First version publication date	23 March 2019

Trial information

Trial identification

Sponsor protocol code	AGMT_MBC-6

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01891277
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AGMT
Sponsor organisation address	Gentzgasse 60/20, Vienna, Austria, 1180
Public contact	Daniela Wolkersdorfer, AGMT, 0043 (0)66264044411, d.wolkersdorfer@agmt.at
Scientific contact	Richard Greil, AGMT, 0043 (0)5785585801, 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	16 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2018
Global end of trial reached?	Yes
Global end of trial date	15 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The efficacy of a capecitabine plus bendamustine combination regimen in the treatment of Her2-negative advanced metastatic breast cancer, in terms of overall response rates (complete or partial Response)

Protection of trial subjects:

Safety assessments were scheduled 3-weekly during treatment until 28 days after end of study treatment. Recommendations for dose modifications in case of toxicity were done in protocol. Only patients with adequate haematology, liver and renal function could have been included. Patients with known hypersensitivity to the study drugs capecitabine and bendamustine or their excipients were excluded from study participation.

Background therapy:

Capecitabine was dosed at 1000mg/m2 twice daily for 14 days, followed by a 7-day rest period for a total cycle time of 21 days (until disease progression or unacceptable toxic effects).

Evidence for comparator:

None.

Actual start date of recruitment	09 August 2013
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: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	26
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In stage 1 of AGMT MBC-6, 20 patients were recruited from September 2013 to July 2014 in Austria. Fulfilling the efficacy criterion, the study was continued enrolling another 20 patients from October 2014 to May 2015 (Stage 2). A total of 40 patients were recruited in eight Austrian centers.

Pre-assignment

Screening details:

Female patients, age ≥ 18 years were screened. The patients had to have advanced or metastatic Her2-negative breast cancer, histologically confirmed and had to be progredient after anthracycline and/or taxane treatment (palliative or neoadjuvant or adjuvant).

Period 1

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

Arms

Arm title	Bendamustin/Capecitabine

Arm description:

Bendamustin in addition to backbone capecitabine, followed by capecitabine monotherapy.

Arm type	Experimental
Investigational medicinal product name	Bendamustin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bendamustine 80mg/m2 were administered on day 1 and 8 of a three week cycle (for a maximum of eight cycles).

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine was dosed at 1000mg/m2 twice daily for 14 days, followed by a 7-day rest period for a total cycle time of 21 days (until disease progression or unacceptable toxic effects).

Number of subjects in period 1	Bendamustin/Capecitabine
Started	40
Completed	27
Not completed	13
Adverse event, serious fatal	1
Physician decision	3
Consent withdrawn by subject	5

Therapy paused for more than 2 cylces	1
Adverse event, non-fatal	3

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	40	40	
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			
median	60		
full range (min-max)	29 to 77	-	
Gender categorical Units: Subjects			
Female	40	40	
Male	0	0	

End points

End points reporting groups

Reporting group title	Bendamustin/Capecitabine

Reporting group description:

Bendamustin in addition to backbone capecitabine, followed by capecitabine monotherapy.

Primary: Overall Response Rate

End point title	Overall Response Rate[1]

End point description:

Overall tumor response rates (complete response (CR) or partial response (PR), determined by radiologic evaluation according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1))

End point type	Primary

End point timeframe:

Best response evaluated from start of study therapy until end of study participation (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: No statistical analysis is provided as this is a one armed, open label, non-comperative study.
According to the pre-specified design, the regimen was concluded to be efficacious since 18 responses were observed in the study exceeding the efficacy criterion of 13 or more responses out of 40 at the end of trial.

End point values	Bendamustin/Capecitabine			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Patients				
CR	1			
PR	17			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All patients having received at least one dose of the study medication were followed for (serious) adverse events for 28 days after discontinuing study treatment or completion of study treatment.

Adverse event reporting additional description:

Progression of disease (including death due to the underlying malignant disease) was not to be regarded as SAE.
Due to the seriousness of the disease, certain conditions defined as SAEs were excluded from expedited reporting i.e.: elective hospitalization and surgery for treatment of disease or to simplify treatment or study procedures.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Safety population

Reporting group description:

All patients having received at least one dose of the study medication were followed for (serious) adverse events for 28 days after discontinuing study treatment or completion of study treatment.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 40 (65.00%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	1		
Vascular disorders			
Embolism			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			

subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiomyopathy				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Nervous system disorders				
Peripheral motor neuropathy				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia macrocytic				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Faecaloma				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toothache				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic failure				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Musculoskeletal chest pain				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Device related infection				

subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile infection				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth infection				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				

subjects affected / exposed	1 / 40 (2.50%)		
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	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 40 (92.50%)		
Vascular disorders			
Lymphoedema			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Thrombosis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Hot flush			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	29 / 40 (72.50%)		
occurrences (all)	58		
Oedema peripheral			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	8		
Pain			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Chills			

subjects affected / exposed occurrences (all) Non-cardiac chest pain subjects affected / exposed occurrences (all) Feeling cold subjects affected / exposed occurrences (all) General physical health deterioration subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	9 / 40 (22.50%) 10 7 / 40 (17.50%) 12		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Investigations Weight decreased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) Lymphocyte count decreased	4 / 40 (10.00%) 4 4 / 40 (10.00%) 5 4 / 40 (10.00%) 7 2 / 40 (5.00%) 2		

subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	9		
Dysgeusia			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	7		
Polyneuropathy			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	9		
Dizziness			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	9		
Presyncope			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Neuropathy peripheral			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	15 / 40 (37.50%)		
occurrences (all)	36		
Leukopenia			

subjects affected / exposed	13 / 40 (32.50%)		
occurrences (all)	35		
Anaemia			
subjects affected / exposed	9 / 40 (22.50%)		
occurrences (all)	13		
Thrombocytopenia			
subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	11		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	7		
Eye disorders			
Eyelid oedema			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	19 / 40 (47.50%)		
occurrences (all)	34		
Diarrhoea			
subjects affected / exposed	14 / 40 (35.00%)		
occurrences (all)	31		
Stomatitis			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	11		
Vomiting			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	11		
Toothache			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
Abdominal pain upper			

subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	7		
Dry mouth			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Haematochezia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Abdominal distension			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	22 / 40 (55.00%)		
occurrences (all)	54		
Night sweats			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Alopecia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	4		
Erythema			

subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Skin fissures			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
Arthralgia			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Back pain			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Musculoskeletal chest pain			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Bone pain			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Infections and infestations			
Oral herpes			
subjects affected / exposed	10 / 40 (25.00%)		
occurrences (all)	16		
Nasopharyngitis			

subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 7		
Bronchitis subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 4		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 4		
Rhinitis subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	8 / 40 (20.00%) 10		
Hypokalaemia subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported