Clinical trial results:
A randomized phase II study to determine the efficacy and tolerability of two doses of eribulin plus lapatinib in trastuzumab pre-treated patients with HER2-positive metastatic breast cancer

Summary

EudraCT number	2010-023237-37
Trial protocol	DE
Global end of trial date	31 March 2015

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021
Summary attachment (see zip file)	EVITA CSR SYNOPSIS (GBG 64 - E-VITA Clinical Study Report - Synopsis Version 2.pdf)

Trial information

Trial identification

Sponsor protocol code	GBG64

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01534455
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GBG Forschungs GmbH
Sponsor organisation address	Martin Behaim Str. 12, Neu-Isenburg, Germany,
Public contact	Medicine and Research, GBG Forschungs GmbH, +49 610274800, publications@gbg.de
Scientific contact	Medicine and Research, GBG Forschungs GmbH, +49 610274800, publications@gbg.de

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	22 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2015
Global end of trial reached?	Yes
Global end of trial date	31 March 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1. To assess the time to progression (TTP) of eribulin at a dose of 1.23 mg/m² IV days 1+8, q 21 and eribulin given at a dose of 1.76 mg/m² IV day 1, q d21 both in combination with lapatinib.
2. To assess the safety and toxicity of both treatment arms.

Protection of trial subjects:

The trial protocol including amendments, the patient information and the informed consent were reviewed and approved from a properly constituted IRB/IEC for each site prior to the study start. The trial was in compliance with the International Conference on Harmonization (ICH) - Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6), and the Commission Directives in the European Community as well as with the applicable German national laws and regulations, and with Declaration of Helsinki and its revisions in all aspects of preparation, monitoring, reporting, auditing, and archiving. IDMC was to ensure the ethical conduct of the trial and to protect patients' safety interests in this study

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	32
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 2.5years (Q-I 2012–Q-III 2014) in 49 sites in Germany. 43 pts were randomized, 41 started treatment (eribulin 1.23mg/m2 d1,8: 21; eribulin 1.76mg/m2 d1: 20). Study was amended in Nov 2013 to prolong recruitment for being behind planned schedule. Despite that, study was stopped on 7th July 2014 due to persistent difficulty in accrual.

Pre-assignment

Screening details:

Histologically HER2+ BC; Advanced BC not suitable for surgery or RT alone;
Previous systemic treatments eligible:
Adjuvant and <=3 CT regimen for advanced BC;
Previous trastuzumab as (neo)adjuvant for eBC and/or 1st and/or 2nd line for mBC;
Prior max. cum. dose <= 360 mg/m² for A and 720 mg/m² for E;
ECOG 0-2, normal cardiac eject. function

Pre-assignment period milestones

Number of subjects started	41
Number of subjects completed	41

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Eribulin 1.23

Arm description:

Eribulin 1.23 mg/m² IV days 1+8, q d21

Arm type	Experimental
Investigational medicinal product name	Eribulin mesylate (Halaven)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eribulin 1.23mg/m² IV as a bolus over 2-5 minutes, days 1+8, q d21

Arm title	Eribulin 1.76

Arm description:

Eribulin 1.76 mg/m² IV day 1 q d21

Arm type	Experimental
Investigational medicinal product name	Eribulin mesylate (Halaven®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eribulin 1.76 mg/m² IV as a bolus over 2-5 minutes , day 1, q d21

Number of subjects in period 1	Eribulin 1.23	Eribulin 1.76
Started	21	20
Completed	14	13
Not completed	7	7
Physician decision	2	-
Adverse event, non-fatal	1	-
Hematological tox. related to study med	-	1
Other reasons	2	3
Patient wish	-	1
Non-hematol. tox. related to study med	1	2
death (not tumor-related)	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Eribulin 1.23
Reporting group description:	
Eribulin 1.23 mg/m² IV days 1+8, q d21	
Reporting group title	Eribulin 1.76
Reporting group description:	
Eribulin 1.76 mg/m² IV day 1 q d21	

Reporting group values	Eribulin 1.23	Eribulin 1.76	Total
Number of subjects	21	20	41
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	50	60	
full range (min-max)	32 to 84	39 to 69	-
Gender categorical			
Units: Subjects			
Female	21	20	41
Male	0	0	0

End points

End points reporting groups

Reporting group title	Eribulin 1.23
Reporting group description:	
Eribulin 1.23 mg/m² IV days 1+8, q d21	
Reporting group title	Eribulin 1.76
Reporting group description:	
Eribulin 1.76 mg/m² IV day 1 q d21	

Primary: Time to progression (TTP)

End point title	Time to progression (TTP)[1]
End point description:	
Time to progression (TTP) is defined as the time period between randomization and documented disease progression or disease-related death. Patients with no progression or tumor-related death reported were censored on the date of the last contact (“last tumor assessment”, “last follow up date” or “last date in drug log”).	
End point type	Primary
End point timeframe:	
time in months between randomization and first event	

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: Kaplan-Meier estimates were presented graphically; median time to progression was reported in each arm together with the 95% confidence interval (CI). No test of significance was planned to compare treatment arms

End point values	Eribulin 1.23	Eribulin 1.76		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[2]	20[3]		
Units: month				
number (confidence interval 95%)	8.1 (4.8 to 9.4)	6.5 (4.6 to 13.4)		

Notes:

[2] - 19events

[3] - 17events

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survial

End point title	Overall survial
End point description:	
Overall survival (OS) is defined as the time period between randomization and death due to any cause. Patients with no death reported were censored on the date of the last contact (“last tumor assessment”, “last follow up date” or “last date in drug log“).	
End point type	Secondary
End point timeframe:	
time in months between randomization and death	

End point values	Eribulin 1.23	Eribulin 1.76		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[4]	20[5]		
Units: month				
number (confidence interval 95%)	23.1 (12.5 to 35.0)	23.2 (13.7 to 30.1)		

Notes:

[4] - 14 events

[5] - 12 events

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring during the study treatment period were reported

Adverse event reporting additional description:

Predefined AEs any grade (1-4) are reported per Patient.
Other AEs reported as free-text are given irrespective of preferred terms if occurring in >20%
For SAEs relatedness was not tabulated, therefore here we conservatively record all SAEs as related to treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	n.a.

Reporting groups

Reporting group title	Eribulin 1.23

Reporting group description:

Eribulin 1.23 mg/m² IV days 1+8, q d21

Reporting group title	Eribulin 1.76

Reporting group description:

Eribulin 1.76 mg/m² IV day 1 q d21

Serious adverse events	Eribulin 1.23	Eribulin 1.76	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 21 (28.57%)	8 / 20 (40.00%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 21 (0.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Confusional state			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 21 (14.29%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 21 (0.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 21 (9.52%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	0 / 21 (0.00%)	4 / 20 (20.00%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flu like symptoms			

subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macular edema			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory failure			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary mass			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
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			
Pain in lumbar spine			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sepsis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Eribulin 1.23	Eribulin 1.76	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 21 (100.00%)	20 / 20 (100.00%)	
Investigations			
Increased bilirubin			
subjects affected / exposed	1 / 21 (4.76%)	3 / 20 (15.00%)	
occurrences (all)	1	3	
Increased alkaline phosphatase			
subjects affected / exposed	7 / 21 (33.33%)	7 / 20 (35.00%)	
occurrences (all)	7	7	

Increased ASAT			
subjects affected / exposed	13 / 21 (61.90%)	15 / 20 (75.00%)	
occurrences (all)	13	15	
Increased ALAT			
subjects affected / exposed	15 / 21 (71.43%)	12 / 20 (60.00%)	
occurrences (all)	15	12	
Increased creatinine			
subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	4 / 21 (19.05%)	8 / 20 (40.00%)	
occurrences (all)	4	8	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 21 (19.05%)	6 / 20 (30.00%)	
occurrences (all)	4	6	
Sensory neuropathy			
subjects affected / exposed	13 / 21 (61.90%)	14 / 20 (70.00%)	
occurrences (all)	13	14	
Nervous system disorder			
subjects affected / exposed	5 / 21 (23.81%)	5 / 20 (25.00%)	
occurrences (all)	5	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 21 (85.71%)	15 / 20 (75.00%)	
occurrences (all)	18	15	
Leukopenia			
subjects affected / exposed	19 / 21 (90.48%)	17 / 20 (85.00%)	
occurrences (all)	19	17	
Neutropenia			
subjects affected / exposed	16 / 21 (76.19%)	16 / 20 (80.00%)	
occurrences (all)	16	16	
Febrile neutropenia			
subjects affected / exposed	1 / 21 (4.76%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Thrombopenia			

subjects affected / exposed	6 / 21 (28.57%)	2 / 20 (10.00%)	
occurrences (all)	6	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 21 (76.19%)	16 / 20 (80.00%)	
occurrences (all)	16	16	
Mucositis/esophagitis			
subjects affected / exposed	9 / 21 (42.86%)	10 / 20 (50.00%)	
occurrences (all)	9	10	
Fever without neutropenia			
subjects affected / exposed	5 / 21 (23.81%)	6 / 20 (30.00%)	
occurrences (all)	5	6	
General disorders and administration site conditions			
subjects affected / exposed	3 / 21 (14.29%)	11 / 20 (55.00%)	
occurrences (all)	3	11	
Immune system disorders			
Allergic reactions			
subjects affected / exposed	5 / 21 (23.81%)	6 / 20 (30.00%)	
occurrences (all)	5	6	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	10 / 21 (47.62%)	9 / 20 (45.00%)	
occurrences (all)	10	9	
Vomiting			
subjects affected / exposed	6 / 21 (28.57%)	4 / 20 (20.00%)	
occurrences (all)	6	4	
Diarrhoea			
subjects affected / exposed	12 / 21 (57.14%)	12 / 20 (60.00%)	
occurrences (all)	12	12	
Constipation			
subjects affected / exposed	3 / 21 (14.29%)	4 / 20 (20.00%)	
occurrences (all)	3	4	
Gastrointestinal disorders			
subjects affected / exposed	10 / 21 (47.62%)	9 / 20 (45.00%)	
occurrences (all)	10	9	
Respiratory, thoracic and mediastinal			

disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	5 / 21 (23.81%)	14 / 20 (70.00%)	
occurrences (all)	5	14	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	20 / 21 (95.24%)	18 / 20 (90.00%)	
occurrences (all)	20	18	
PPE (hand-foot syndrome)			
subjects affected / exposed	7 / 21 (33.33%)	5 / 20 (25.00%)	
occurrences (all)	7	5	
Skin and subcutaneous tissue disorders			
subjects affected / exposed	13 / 21 (61.90%)	14 / 20 (70.00%)	
occurrences (all)	13	14	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 21 (47.62%)	12 / 20 (60.00%)	
occurrences (all)	10	12	
Myalgia			
subjects affected / exposed	6 / 21 (28.57%)	7 / 20 (35.00%)	
occurrences (all)	6	7	
Musculoskeletal, connective tissue and bone disorders			
subjects affected / exposed	5 / 21 (23.81%)	9 / 20 (45.00%)	
occurrences (all)	5	9	
Infections and infestations			
Infection			
subjects affected / exposed	11 / 21 (52.38%)	10 / 20 (50.00%)	
occurrences (all)	11	10	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	5 / 21 (23.81%)	7 / 20 (35.00%)	
occurrences (all)	5	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 September 2013	There was one substantial Amendment to the protocol of E-Vita. In November 2013, given that the study recruitment was behind the planned schedule, the study was amended in order to prolong the recruitment period, as well as to allow the use of new Anti-HER2 treatment options as TDM1. Despite that the study was stopped in July 2014 due to the persistent difficulty in accrual. Amendment 1 protocol changes: Title: A randomized phase II study to determine the efficacy and tolerability of two doses of eribulin plus lapatinib in patients pre-treated with anti-HER2- therapy with HER2-positive metastatic breast cancer. Stratification factors for randomization will be: • previous line of chemotherapy for metastatic disease (0-1 vs. 2-3). Inclusion criterion no.6: The following previous systemic treatments are eligible: • Previous treatment with anti HER2 therapy either as (neo)adjuvant treatment for early breast cancer and/or first, second and/or third line treatment for metastatic breast cancer, • adjuvant and up to 3 chemotherapy regimen for metastatic breast cancer, … • radiotherapy with full recovery from clinical relevant side effects. The measurable disease must be completely outside the radiation field or there must be pathologic proof of progressive disease. Exclusion criterion no.2: Patients who have received eribulin or who have received lapatinib as part of the last therapy before entering this Trial. Enrollment period: 36 months (Q-I 2012 – Q-I 2015). Regular End of Study: The end of this study is defined as 4 years after the 1st patient entered the trial. Planned end of study is Q-I 2016.

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/30875348