



Clinical trial results:

PETRARCA / FLOT6

FLOT vs. FLOT/Herceptin/Perjeta for perioperative therapy of adenocarcinoma of the stomach and gastroesophageal junction expressing HER-2

A phase II/III trial of the AIO

Summary

EudraCT number	2014-002695-86
Trial protocol	DE
Global end of trial date	17 July 2020

Results information

Result version number	v1 (current)
This version publication date	21 September 2023
First version publication date	21 September 2023

Trial information

Trial identification

Sponsor protocol code	ML29452
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02581462
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest
Sponsor organisation address	Steinbacher Hohl 2-26, Frankfurt, Germany, 60488
Public contact	Dr. Claudia Pauligk, Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, petrarca@ikf-khnw.de
Scientific contact	Dr. Claudia Pauligk, Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, petrarca@ikf-khnw.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	26 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 January 2020
Global end of trial reached?	Yes
Global end of trial date	17 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this trial was to evaluate the efficacy and safety of the perioperative treatment of patients with HER-2 expressing adenocarcinoma of the stomach and gastroesophageal junctions with the anti-Her-2 antibody pertuzumab (Perjeta®) in addition to the anti-Her-2 antibody trastuzumab (Herceptin®) plus FLOT chemotherapy versus patients treated with FLOT alone (Phase II). The primary efficacy objective was the rate of pathological complete responses. Secondary efficacy endpoints were disease-free survival, overall survival and R0 resection rate.

Protection of trial subjects:

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the AMG (Arzneimittelgesetz), the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki. The trial was authorized/approved by the competent authority (Paul-Ehrlich-Institut, PEI) and the competent ethics committee responsible for the trial ("federführende Ethikkommission").

Before recruitment into the clinical trial, each patient was informed that participation in the study is completely voluntary, and that he or she may withdraw his or her participation in the trial at any time without any declaration of reasons, which will not lead to any disadvantage for the respective patient. The eligibility of a new patient was determined by the local investigator during regular clinical visits. The examinations for the study and the inclusion of the patient were done after detailed written and oral education about aims, methods, anticipated benefits and potential hazards of the study by use of the informed consent forms and after given written consent of the patient.

Safety of FLOT/Herceptin/Perjeta was monitored continuously by careful monitoring of all adverse events (AEs) and serious adverse events (SAEs) reported. An independent data safety and monitoring board (DSMB) was responsible for assessment of reports summarizing safety data or study results and gave recommendations for planned protocol.

Background therapy: -

Evidence for comparator:

FLOT, a docetaxel-based triple combination consisting of 5-FU, leucovorin, oxaliplatin and docetaxel, is one of the most intensively evaluated regimen for gastric and GEJ cancer. It has been evaluated in the metastatic and limited metastatic settings, elderly and operable patients. FLOT is regarded a standard chemotherapy regimen for gastric cancer in Germany.

The receptor protein HER-2 is overexpressed in many types of human cancer promoting cell proliferation and cancer development upon activation. Thus, it became an interesting point of attack for targeted therapies. The combination of FLOT chemotherapy with the anti-HER-2 antibody trastuzumab (Herceptin®) already yielded promising relapse-free and overall survival compared to FLOT alone in patients with HER-2 positive advanced gastric cancer (ToGa - NCT01041404, HER-FLOT - NCT01472029). The combination of Herceptin with the anti-HER-2 antibody pertuzumab (Perjeta®) resulted in augmented anti-proliferative activity in vitro as well as in vivo. Furthermore, the addition of Perjeta to the chemotherapy/Herceptin combination improved the invasive-disease-free survival of patients with breast cancer (APHINITY - NCT01358877).

Actual start date of recruitment	30 June 2016
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	Germany: 81
Worldwide total number of subjects	81
EEA total number of subjects	81

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)	53
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

100 patients for phase II and approx. 304 additional patients for phase III were planned. Due to slow recruitment the phase II part has been reduced to n=80 planned patients and trial was terminated after phase II without transition into phase III. The recruitment period was 26 months, June 2016 - August 2018 and took place in 60 centers in Germany

Pre-assignment

Screening details:

patients with HER-2 positive, locally advanced esophagogastric adenocarcinoma with exclusion of distant metastases were included.

185 patients were screened, 104 were refused participation due to screening failure. Predominant screening failure was HER-2 negativity or missing HER-2 immunohistochemistry and/or in situ hybridisation data.

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	FLOT

Arm description:

Patients received 4 pre-operative treatments of FLOT (docetaxel, oxaliplatin, leucovorin & 5-fluorouracil) on d1, d15, d29 and d43. Surgery was recommended to occur 4 weeks after last FLOT dose (4 weeks after d43 = day 71). Patients received additional 4 post-operative FLOT treatments after surgery (start 6 to 8 weeks after surgery) on d1, d15, d29, d43 of the post-operative treatment phase.

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion, Concentrate for solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

Administration 50 mg/m², iv over 1 h d1, d15, d29, d43 pre- and post-operative

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

85 mg/m², iv over 2-6 h; d1, d15, d29, d43 pre- and post-operative

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	folinic acid
Pharmaceutical forms	Solution for injection/infusion, Powder for solution for injection/infusion
Routes of administration	Infusion , Injection , Intramuscular and intravenous use

Dosage and administration details:

200 mg/m², iv, d1, d15, d29, d43 pre- and post-operative

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	5-FU
Pharmaceutical forms	Solution for injection/infusion, Concentrate for solution for infusion
Routes of administration	Infusion , Injection , Intravenous use
Dosage and administration details: 2600 mg/m ² , iv over 24 h, on d1, d15, d29, d43 pre- and post-operative	
Arm title	FLOT/Herceptin/Perjeta
Arm description: Patients received the FLOT regimen identical to Arm A (FLOT alone) in conjunction with three-weekly Herceptin at 8mg/kg initial dose (Day 1, loading dose) followed by subsequent doses of Herceptin at 6mg/kg on d22 and d43 and Perjeta at 840mg on d1, d22, and d43. Surgery was recommended to occur 4 weeks after last FLOT/Herceptin/Perjeta dose (4 weeks after d43 = day 71). Patients received 3 additional doses of Herceptin and Perjeta on d1, d22, and d43 of the post-operative treatment phase, together with the postoperative chemotherapy (start 6 to 8 weeks after surgery). Moreover, patients received 9 three-weekly additional doses of Herceptin and Perjeta after the end of post-operative FLOT	
Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	RO0452317
Other name	Herceptin
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Infusion , Intravenous use
Dosage and administration details: Herceptin was administered with a „loading dose“ of 8 mg/kg for the initial dose (d1 preoperative and d1 postoperative), followed by doses of 6 mg/kg, three-weekly cycles. Herceptin was given followed by a 30-60 minute post-infusion observation period	
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	RO4368451
Other name	Perjeta
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion , Intravenous use
Dosage and administration details: Perjeta was administered intravenously at a flat dose of 840 mg every 3 weeks Perjeta was given followed by a 30-60 minute post infusion observation period	
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion, Concentrate for solution for infusion
Routes of administration	Infusion , Intravenous use
Dosage and administration details: Administration 50 mg/m ² , iv over 1 h d1, d15, d29, d43 pre- and post-operative	
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion , Intravenous use
Dosage and administration details: 85 mg/m ² , iv over 2-6 h; d1, d15, d29, d43 pre- and post-operative	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	folinic acid
Pharmaceutical forms	Powder for solution for injection/infusion, Solution for injection/infusion

Routes of administration	Infusion , Injection , Intramuscular and intravenous use
Dosage and administration details:	
200 mg/m ² , iv, d1, d15, d29, d43 pre- and post-operative	
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	5-FU
Pharmaceutical forms	Concentrate for solution for infusion, Solution for injection/infusion
Routes of administration	Infusion , Injection , Intravenous use

Dosage and administration details:

2600 mg/m², iv over 24 h, on d1, d15, d29, d43 pre- and post-operative

Number of subjects in period 1	FLOT	FLOT/Herceptin/Perjeta
Started	41	40
started pre-OP treatment	40	39
underwent surgery	40	39
started post-OP treatment	26	25
started maintenance treatment	0 ^[1]	17
Completed	23	16
Not completed	18	24
Patient's wish	6	12
Death	1	2
Other reasons	5	4
Unacceptable toxicity	3	2
Lost to follow-up	1	-
Lack of efficacy	2	4

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: No maintenance phase was planned in the FLOT only Arm

Baseline characteristics

Reporting groups

Reporting group title	FLOT
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Reporting group description:

Patients received 4 pre-operative treatments of FLOT (docetaxel, oxaliplatin, leucovorin & 5-fluorouracil) on d1, d15, d29 and d43. Surgery was recommended to occur 4 weeks after last FLOT dose (4 weeks after d43 = day 71). Patients received additional 4 post-operative FLOT treatments after surgery (start 6 to 8 weeks after surgery) on d1, d15, d29, d43 of the post-operative treatment phase.

Reporting group title	FLOT/Herceptin/Perjeta
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Reporting group description:

Patients received the FLOT regimen identical to Arm A (FLOT alone) in conjunction with three-weekly Herceptin at 8mg/kg initial dose (Day 1, loading dose) followed by subsequent doses of Herceptin at 6mg/kg on d22 and d43 and Perjeta at 840mg on d1, d22, and d43. Surgery was recommended to occur 4 weeks after last FLOT/Herceptin/Perjeta dose (4 weeks after d43 = day 71). Patients received 3 additional doses of Herceptin and Perjeta on d1, d22, and d43 of the post-operative treatment phase, together with the postoperative chemotherapy (start 6 to 8 weeks after surgery). Moreover, patients received 9 three-weekly additional doses of Herceptin and Perjeta after the end of post-operative FLOT

Reporting group values	FLOT	FLOT/Herceptin/Perjeta	Total
Number of subjects	41	40	81
Age categorical Units: Subjects			

Age continuous Units: years median full range (min-max)	61 24 to 77	59.5 36 to 83	-
Gender categorical Units: Subjects			
Female	7	10	17
Male	34	30	64
ECOG Performance Status Units: Subjects			
Status 0	29	31	60
Status 1	11	8	19
Status 2	1	1	2
Localisation of Primarius Units: Subjects			
GEJ Siewert type 1	14	17	31
GEJ Siewert type 2 or 3	16	14	30
Stomach, corpus or antrum	11	9	20
Barrett carcinoma of the distal oesophagus Units: Subjects			
Missing	2	0	2
Yes	11	6	17
No	26	30	56
Unclear	2	4	6
cT-stage			
Clinical tumor stage and clinical nodal stage were assessed by endoscopic ultrasound and CT or MRI and			

classified according to the seventh version of the International Union against Cancer tumor-node-metastasis (TNM) classification			
Units: Subjects			
cT2	6	5	11
cT3	31	28	59
cT4	2	4	6
cT4a	2	3	5
cN stage			
Clinical tumor stage and clinical nodal stage were assessed by endoscopic ultrasound and CT or MRI and classified according to the seventh version of the International Union against Cancer tumor-node-metastasis (TNM) classification			
Units: Subjects			
cN-	7	5	12
cN+	34	35	69
Laurén Classification			
Units: Subjects			
Diffuse	5	4	9
Intestinal or mixed	21	24	45
Not evaluable according to Lauren	8	10	18
Missing	7	2	9
Singet ring cells			
Units: Subjects			
Missing values	3	1	4
with signet ring cells	7	4	11
Without signet ring cells	31	35	66
WHO grade			
Units: Subjects			
G1	3	2	5
G2	23	21	44
G2-3	2	3	5
G3	13	13	26
Missing	0	1	1
HER2 Status			
Units: Subjects			
HER2 2+ and FISH+	7	8	15
HER3+	34	32	66

End points

End points reporting groups

Reporting group title	FLOT
Reporting group description:	
Patients received 4 pre-operative treatments of FLOT (docetaxel, oxaliplatin, leucovorin & 5-fluorouracil) on d1, d15, d29 and d43. Surgery was recommended to occur 4 weeks after last FLOT dose (4 weeks after d43 = day 71). Patients received additional 4 post-operative FLOT treatments after surgery (start 6 to 8 weeks after surgery) on d1, d15, d29, d43 of the post-operative treatment phase.	
Reporting group title	FLOT/Herceptin/Perjeta
Reporting group description:	
Patients received the FLOT regimen identical to Arm A (FLOT alone) in conjunction with three-weekly Herceptin at 8mg/kg initial dose (Day 1, loading dose) followed by subsequent doses of Herceptin at 6mg/kg on d22 and d43 and Perjeta at 840mg on d1, d22, and d43. Surgery was recommended to occur 4 weeks after last FLOT/Herceptin/Perjeta dose (4 weeks after d43 = day 71). Patients received 3 additional doses of Herceptin and Perjeta on d1, d22, and d43 of the post-operative treatment phase, together with the postoperative chemotherapy (start 6 to 8 weeks after surgery). Moreover, patients received 9 three-weekly additional doses of Herceptin and Perjeta after the end of post-operative FLOT	

Primary: Pathological complete response rate

End point title	Pathological complete response rate
End point description:	
The pathological complete response (pCR) rate was chosen as primary endpoint for the phase II part of the trial and was defined as the proportion of patients with pCR as evaluated blinded, separately by two central pathologist referring to the total number of patients of the ITT population (missing data were considered as failure) as denominator in the primary analysis. The relevant time point for the primary study endpoint was reached upon completion of surgery. Patients with a pCR at this timepoint added to the rate of the primary endpoint.	
End point type	Primary
End point timeframe:	
The relevant time point for the primary study endpoint was reached upon completion of surgery. Patients with a pCR at this timepoint added to the rate of the primary endpoint.	

End point values	FLOT	FLOT/Herceptin/Perjeta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	40		
Units: Subjects				
No	36	26		
Yes	5	14		

Statistical analyses

Statistical analysis title	Fishers Exact Test
Statistical analysis description:	
The pCR rate was evaluated and reported in an explorative or descriptive manner. Analysis of the primary endpoint was additionally carried out using Fisher's exact test	
Comparison groups	FLOT/Herceptin/Perjeta v FLOT

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0193
Method	Fisher exact

Secondary: Best overall pathological response, subgroup HER2 IHC3+

End point title	Best overall pathological response, subgroup HER2 IHC3+
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End point description:

The subgroup of patients with IHC 3+ consisted of 66 patients, 34 in arm A, and 32 in arm B. Within this subgroup, two patients did not undergo surgery because of early progression and premature EOT (patient lost). Thus, information on pathological response is documented and analysed as missing value. Pathological responses were assessed by central pathology according to the Becker criteria.

End point type	Secondary
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End point timeframe:

The relevant time point was reached upon completion of surgery.

End point values	FLOT	FLOT/Herceptin /Perjeta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	32		
Units: Subjects				
Missing values	1	1		
Complete Response	4	13		
Subtotal Response	5	2		
Partial Response	9	8		
Minor Response	13	8		
No Response	1	0		
Not evaluable	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall pathological response, subgroup HER2 not IHC3+

End point title	Best overall pathological response, subgroup HER2 not IHC3+
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End point description:

The subgroup of patients with other cases than IHC 3+ consisted of 15 patients, 7 in arm A, and 8 in arm B.

End point type	Secondary
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End point timeframe:

The relevant time point was reached upon completion of surgery

End point values	FLOT	FLOT/Herceptin /Perjeta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Subjects				
Complete Response	1	1		
Subtotal Response	0	2		
Partial Response	3	3		
Minor Response	3	0		
No Response	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Resection rate (R0), ITT

End point title	Resection rate (R0), ITT
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End point description:

R0 resection rate was defined as the percentage of patients achieving a R0 (margin-free) resection referring to the total number of patients randomized into the respective treatment arm. Classification of residual tumor as R0, R1 or other was evaluated according to documentation in the reports of the local pathologists. Reports were centrally reviewed by medical experts of the sponsor. Patients with no R0 resection either were those who had no resection at all, for whom no data for residual tumor was documented (both shown as missing), or those who were not resected margin-free and had R1 resection. No R2 resection was documented

End point type	Secondary
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End point timeframe:

The relevant time point was reached upon completion of surgery

End point values	FLOT	FLOT/Herceptin /Perjeta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	40		
Units: percent				
number (not applicable)				
Missing values	4.9	5		
R0	90.2	92.5		
R1	4.9	2.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease free survival, ITT

End point title	Disease free survival, ITT
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End point description:

Disease-free survival (DFS) was defined as the time from randomization to the first occurrence of disease progression or disease recurrence after surgery, as determined by the investigator using CT criteria, or death from any cause. Patients without event were censored at the date of their last tumor assessment.

In arm A, the median DFS was 26 months, in arm B the median was not yet reached at database closure.

End point type	Secondary
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End point timeframe:

Tumors were assessed before randomization & prior to surgery and then every 3 months thereafter until progression/relapse, death or end of follow-up (was set at 1 year after last patient in ,but did not end earlier than 3 months after last dose)

End point values	FLOT	FLOT/Herceptin /Perjeta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	40		
Units: Subjects				
Event	19	12		
Censored	22	28		

Attachments (see zip file)	Disease-free survival/1.png
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Statistical analyses

Statistical analysis title	Log Rank Test
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Statistical analysis description:

Event related data like disease-free and overall survival were estimated by the product limit method providing the numbers of events and censored cases and compared using the log-rank test. Additional hazard ratios (HR) and 95% confidence intervals (CI) were estimated using a Cox regression model. Patients without any documentation of events, lost to follow-up or with early drop-out were censored at last observation i.e., the date of last tumor assessment for disease-free survival.

Comparison groups	FLOT v FLOT/Herceptin/Perjeta
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Logrank

Secondary: Disease free survival, subgroup HER2 IHC3+

End point title	Disease free survival, subgroup HER2 IHC3+
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End point description:

Median DFS was 26 months in arm A within this subgroup and was not yet reached in arm B until the end of follow-up period

End point type	Secondary
End point timeframe:	
Tumors were assessed before randomization & prior to surgery and then every 3 months thereafter until progression/relapse, death or end of follow-up (was set at 1 year after last patient in ,but did not end earlier than 3 months after last dose)	

End point values	FLOT	FLOT/Herceptin /Perjeta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	32		
Units: Subjects				
Event	16	11		
Censored	18	21		

Statistical analyses

Statistical analysis title	Log Rank Test
Comparison groups	FLOT/Herceptin/Perjeta v FLOT
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2497
Method	Logrank

Secondary: Disease free survival, subgroup HER2 not IHC3+

End point title	Disease free survival, subgroup HER2 not IHC3+
End point description:	
Median DFS was 31 months in arm A within this subgroup and was not yet reached in arm B until the end of follow-up period.	
End point type	Secondary
End point timeframe:	
Tumors were assessed before randomization & prior to surgery and then every 3 months thereafter until progression/relapse, death or end of follow-up (was set at 1 year after last patient in ,but did not end earlier than 3 months after last dose)	

End point values	FLOT	FLOT/Herceptin /Perjeta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Subjects				
Event	3	1		
Censored	4	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival, ITT

End point title	Overall survival, ITT
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End point description:

The follow-up time at the final analysis was a median of 21 months in arm A and 25 months in arm B. The maximum observation period was 42 months.

One patient in arm B was lost to follow-up immediately after randomization.

At the time of analysis, 11 deaths were observed in arm A (i.e. 27% of the patients) and 7 in arm B (18%) within the ITT population. The rest of the patients was censored at indicated time points.

The median OS was not reached in both treatment arms at the time of the final analysis.

End point type	Secondary
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End point timeframe:

Overall survival (OS) was defined as the time from randomization to death from any cause. Patients without the respective event being observed at the time of maximum follow-up are censored at this time point.

End point values	FLOT	FLOT/Herceptin/Perjeta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	40		
Units: Subjects				
Death	11	7		
Censored	30	33		

Attachments (see zip file)	Overall survival/2.png
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Statistical analyses

Statistical analysis title	Log Rank Test
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Statistical analysis description:

Event related data like disease-free and overall survival were estimated by the product limit method providing the numbers of events and censored cases and compared using the log-rank test. Additional hazard ratios (HR) and 95% confidence intervals (CI) were estimated using a Cox regression model. Patients without any documentation of events, lost to follow-up or with early drop-out were censored at last observation i.e., the last known alive date for overall survival

Comparison groups	FLOT v FLOT/Herceptin/Perjeta
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Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2278
Method	Logrank

Secondary: Overall survival, subgroup HER2 IHC3+

End point title	Overall survival, subgroup HER2 IHC3+
End point description: At the time of analysis, 10 deaths (29% of the patients) were observed in arm A versus 6 deaths (19%) in arm B. Median OS was not yet reached in arm A and arm B until the end of follow-up period	
End point type	Secondary
End point timeframe: Overall survival (OS) was defined as the time from randomization to death from any cause. Patients without the respective event being observed at the time of maximum follow-up are censored at this time point	

End point values	FLOT	FLOT/Herceptin/Perjeta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	32		
Units: Subjects				
Death	10	6		
Censored	24	26		

Statistical analyses

Statistical analysis title	Log Rank Test
Comparison groups	FLOT v FLOT/Herceptin/Perjeta
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1621
Method	Logrank

Secondary: Overall survival, subgroup HER2 not IHC3+

End point title	Overall survival, subgroup HER2 not IHC3+
End point description: Median OS was not yet reached in arm A and arm B until the end of follow-up period. At the time of analysis, 1 patient (14%) in arm A died versus 1 patient (13%) in arm B.	
End point type	Secondary

End point timeframe:

Overall survival (OS) was defined as the time from randomization to death from any cause. Patients without the respective event being observed at the time of maximum follow-up are censored at this time point

End point values	FLOT	FLOT/Herceptin /Perjeta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Subjects				
Death	1	1		
Censored	6	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical morbidity

End point title	Surgical morbidity
End point description:	
End point type	Secondary
End point timeframe: up to 60 days after surgery	

End point values	FLOT	FLOT/Herceptin /Perjeta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	39		
Units: Subjects				
Any surgical or medical complication	17	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical mortality

End point title	Surgical mortality
End point description:	
End point type	Secondary

End point timeframe:
up to 60 days after surgery

End point values	FLOT	FLOT/Herceptin /Perjeta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: Subjects				
deaths 30 days after surgery	0	0		
deaths 60 days after surgery	1	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Best overall pathological response, ITT

End point title	Best overall pathological response, ITT
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End point description:

The ITT population includes all patients who were randomized. Treatment assignment is based on the randomized treatment (primary population). The ITT population is the primary population for the description of the patient and treatment characteristics and is used for the primary efficacy analysis.

End point type	Other pre-specified
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End point timeframe:

The relevant time point for the pathological response was reached upon completion of surgery

End point values	FLOT	FLOT/Herceptin /Perjeta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	40		
Units: Subjects				
Complete Response	5	14		
Subtotal Response	5	4		
Partial Response	12	11		
Minor Response	16	8		
No Response	1	2		
Not evaluable	1	0		
Not applicable	1	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Best overall pathological response, PP

End point title	Best overall pathological response, PP
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End point description:

The Per-Protocol Analysis Set (PP) contains all eligible patients, who fulfilled all inclusion/exclusion criteria, and who underwent surgery and experienced no other major protocol violations such as wrong treatment received. Treatment assignment is based on the treatment received. This set is used in efficacy evaluation for comparison to the full analysis set.

End point type	Other pre-specified
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End point timeframe:

The relevant time point for the pathological response was reached upon completion of surgery

End point values	FLOT	FLOT/Herceptin /Perjeta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Subjects				
Complete Response	4	14		
Subtotal Response	5	4		
Partial Response	12	11		
Minor Response	15	8		
No Response	1	2		
Not evaluable	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Patients were assessed for adverse events at each visit during the study. Adverse event monitoring continued for at least 30 days (FLOT) and 90 days (monoclonal antibodies) following the last dose of study treatment

Adverse event reporting additional description:

Toxicity was assessed by non-directive questioning of patients as well as physical examination and laboratory tests of patients at each visit during the study. Toxic effects were graded according to NCI-CTCAE v4.0. A relationship of an AE to the study treatment was determined by the Investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	NCI CTCAE
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Dictionary version	4
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Reporting groups

Reporting group title	FLOT
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Reporting group description:

Patients received at least one dose of FLOT

Reporting group title	FLOT/Herceptin/Perjeta
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Reporting group description:

Patients received at least one dose of FLOT plus Herceptine and Perjeta

Serious adverse events	FLOT	FLOT/Herceptin/Perjeta	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 40 (57.50%)	26 / 39 (66.67%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	1	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hospitalisation	Additional description: prolonged hospitalisation after surgery		

subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secretion via local drainage			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 40 (5.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Specific frailty			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Aspiration			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 40 (2.50%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder	Additional description: caused by anastomoic leak		
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Creatinine increased			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight loss			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ductus thoracicus leak			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic leak			
subjects affected / exposed	3 / 40 (7.50%)	3 / 39 (7.69%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic rupture			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom	Additional description: with unclear cerebral lesions		
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Middle ear inflammation			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 40 (2.50%)	7 / 39 (17.95%)	
occurrences causally related to treatment / all	1 / 1	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dysphagia			
subjects affected / exposed	4 / 40 (10.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric necrosis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invagination			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 40 (5.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 40 (2.50%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic prolapsed jejunum			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Abscess	Additional description: left foot		
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal colic			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Catheter site infection			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
infection of unknown origin			
subjects affected / exposed	1 / 40 (2.50%)	3 / 39 (7.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 40 (7.50%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 40 (5.00%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 40 (0.00%)	3 / 39 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal infection			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 40 (2.50%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 40 (5.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	FLOT	FLOT/Herceptin/Perjeta	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 40 (100.00%)	39 / 39 (100.00%)	
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 40 (2.50%)	5 / 39 (12.82%)	
occurrences (all)	1	6	

Hypotension subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	2 / 39 (5.13%) 2	
Hypertension subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	2 / 39 (5.13%) 2	
General disorders and administration site conditions Chills subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	4 / 39 (10.26%) 4	
Limbal swelling subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3	4 / 39 (10.26%) 4	
Fatigue subjects affected / exposed occurrences (all)	19 / 40 (47.50%) 28	23 / 39 (58.97%) 40	
Fever subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 5	2 / 39 (5.13%) 2	
Pain subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 10	9 / 39 (23.08%) 14	
Creatine increased subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	3 / 39 (7.69%) 3	
General physical health deterioration subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4	3 / 39 (7.69%) 4	
Immune system disorders Allergic reaction subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	5 / 39 (12.82%) 5	
Reproductive system and breast disorders Pneumothorax subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	0 / 39 (0.00%) 0	

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 40 (10.00%)	2 / 39 (5.13%)	
occurrences (all)	7	3	
Epistaxis			
subjects affected / exposed	2 / 40 (5.00%)	6 / 39 (15.38%)	
occurrences (all)	2	9	
Pleural effusion			
subjects affected / exposed	3 / 40 (7.50%)	4 / 39 (10.26%)	
occurrences (all)	3	4	
Pharyngeal mucositis			
subjects affected / exposed	0 / 40 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	5	
Respiratory failure			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Cough			
subjects affected / exposed	2 / 40 (5.00%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Hiccups			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 40 (2.50%)	2 / 39 (5.13%)	
occurrences (all)	2	2	
Depression			
subjects affected / exposed	2 / 40 (5.00%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	14 / 40 (35.00%)	15 / 39 (38.46%)	
occurrences (all)	37	26	
Platelet count decreased			
subjects affected / exposed	2 / 40 (5.00%)	6 / 39 (15.38%)	
occurrences (all)	2	15	

Weight decreased subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 8	15 / 39 (38.46%) 17	
White blood cell count decreased subjects affected / exposed occurrences (all)	15 / 40 (37.50%) 30	18 / 39 (46.15%) 40	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3	0 / 39 (0.00%) 0	
C-reactive protein increased subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 5	4 / 39 (10.26%) 4	
Lymphocyte count decreased subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3	1 / 39 (2.56%) 2	
Injury, poisoning and procedural complications Anastomotic leak subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	2 / 39 (5.13%) 2	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3	3 / 39 (7.69%) 3	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	5 / 39 (12.82%) 6	
Dysgeusia subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 6	4 / 39 (10.26%) 6	
Paraesthesia subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 6	6 / 39 (15.38%) 13	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	19 / 40 (47.50%) 29	14 / 39 (35.90%) 25	

Headache subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	2 / 39 (5.13%) 2	
Dysesthesia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	2 / 39 (5.13%) 2	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	9 / 40 (22.50%) 9	11 / 39 (28.21%) 25	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	2 / 39 (5.13%) 2	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	9 / 40 (22.50%) 11	5 / 39 (12.82%) 5	
Constipation subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 8	2 / 39 (5.13%) 2	
Diarrhoea subjects affected / exposed occurrences (all)	20 / 40 (50.00%) 32	35 / 39 (89.74%) 105	
Dysphagia subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 9	6 / 39 (15.38%) 8	
Flatulence subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	3 / 39 (7.69%) 3	
Gastrointestinal pain subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	1 / 39 (2.56%) 1	
Mucositis oral subjects affected / exposed occurrences (all)	9 / 40 (22.50%) 11	13 / 39 (33.33%) 14	
Nausea			

subjects affected / exposed	24 / 40 (60.00%)	24 / 39 (61.54%)	
occurrences (all)	39	47	
Toothache			
subjects affected / exposed	3 / 40 (7.50%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
Vomiting			
subjects affected / exposed	11 / 40 (27.50%)	13 / 39 (33.33%)	
occurrences (all)	15	19	
Obstruction gastric			
subjects affected / exposed	2 / 40 (5.00%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	15 / 40 (37.50%)	16 / 39 (41.03%)	
occurrences (all)	15	20	
Dry skin			
subjects affected / exposed	4 / 40 (10.00%)	3 / 39 (7.69%)	
occurrences (all)	6	3	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 40 (2.50%)	3 / 39 (7.69%)	
occurrences (all)	1	6	
Pruritus			
subjects affected / exposed	0 / 40 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	4	
Rash acneiform			
subjects affected / exposed	1 / 40 (2.50%)	6 / 39 (15.38%)	
occurrences (all)	1	7	
Rash maculo-papular			
subjects affected / exposed	2 / 40 (5.00%)	3 / 39 (7.69%)	
occurrences (all)	2	7	
Exanthema			
subjects affected / exposed	0 / 40 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
Endocrine disorders			

Hyperthyroidism subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	2 / 39 (5.13%) 2	
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3	1 / 39 (2.56%) 1	
Infections and infestations Catheter site infection subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all) Port infection subjects affected / exposed occurrences (all) Wound infection subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1 4 / 40 (10.00%) 4 3 / 40 (7.50%) 3 2 / 40 (5.00%) 2	3 / 39 (7.69%) 3 1 / 39 (2.56%) 2 0 / 39 (0.00%) 0 0 / 39 (0.00%) 0	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	9 / 40 (22.50%) 13 1 / 40 (2.50%) 2 1 / 40 (2.50%) 3	13 / 39 (33.33%) 17 5 / 39 (12.82%) 5 11 / 39 (28.21%) 25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 January 2018	non-substantial amendment: transition of sponsor's institution; no formal approval of authorities necessary
25 May 2018	reduction of sample size to 80 patients in phase II
01 October 2018	reduction of follow-up time, new background information as rationale for no continuation as phase III trial, termination as phase II trial

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/35709415>