Clinical trial results:
Feasibility study of chemoradiation, TRAstuzumab and Pertuzumab in resectable HER2+ esophageal carcinoma

Summary

EudraCT number	2013-004111-42
Trial protocol	NL
Global end of trial date	24 January 2017

Results information

Result version number	v1 (current)
This version publication date	19 August 2020
First version publication date	19 August 2020
Summary attachment (see zip file)	JCO_TRAP (JCO.19.TRAP.pdf)

Trial information

Trial identification

Sponsor protocol code	TRAP

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02120911
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AMC
Sponsor organisation address	Meibergdreef 9, Amsterdam, Netherlands, 1105AZ
Public contact	Laurien Verkleij (trialmedonc@amc.uva.nl), Amsterdam UMC, +31 205668440, trialmedonc@amc.uva.nl
Scientific contact	Laurien Verkleij (trialmedonc@amc.uva.nl), Amsterdam UMC, +31 205668440, trialmedonc@amc.uva.nl

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	19 February 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the feasibility of preoperative treatment with pertuzumab and trastuzumab combined with preoperative chemoradiation (carboplatin, paclitaxel and radiation) in terms of percentage of completion with trastuzumab and pertuzumab.

Protection of trial subjects:

Several measures were put in place to protect trial subjects:
1. If symptoms (e.g. fever, chills, headache, pruritus, nausea) occured during administration of study drugs, infusion was slowed down/interrupted.
2. Premedication was applied if patients experienced infusion-associated symptoms
; premedication was standard applied for chemoradiotherapy
3. Dose delays were permitted for presumed trastuzumab/pertuzumab related toxicity
4. Upon unacceptable toxicity, patients were withdrawn from the study
5. Patients were monitored carefully during and following each cycle

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 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)	22
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from January 2014 to Sept 2019, in 7 centers in the Netherlands (Amsterdam UMC AMC, Catharina hospital, NKI-AvL, LUMC, UMCG, Anthonius hospital, Elisabeth hospital)

Pre-assignment

Screening details:

57 patients were primarily enrolled at 7 centers in the Netherlands. 17 patients were ineligible, due to not meeting all inclusion criteria (n=11) or not wanting to participate in the trial (n=6).

Period 1

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

Arms

Arm title	TRAP cohort

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Herceptin
Investigational medicinal product code	
Other name	Trastuzumab
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was administered intravenously on day 1 of each treatment cycle, using an initial dose of 4 mg/kg on day 1, followed by doses of 2 mg/kg weekly up to week 6. From week 7 onwards trastuzumab was administered at a dose of 6 mh/kg every three weeks

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Pertuzumab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab was administered intravenously on day 1, 22, 43, 64, and 85, using a fixed dose of 840 mg.

Number of subjects in period 1	TRAP cohort
Started	40
Completed	40

Baseline characteristics

Reporting groups

Reporting group title	Baseline Characteristics

Reporting group description: -

Reporting group values	Baseline Characteristics	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	22	22	
From 65-84 years	18	18	
85 years and over	0	0	
Age continuous Units: years			
median	63		
full range (min-max)	44 to 78	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	33	33	
ECOG Performance Status			
ECOG performance status			
Units: Subjects			
ECOG PS 0	33	33	
ECOG PS 1	7	7	
HER2 status			
HER2-status			
Units: Subjects			
HER2 2+	11	11	
HER2 3+	29	29	
Clinical Tumor stage			
cT stage			
Units: Subjects			
cT2	11	11	
cT3	26	26	
cT4	1	1	
cTx	2	2	
Clinical Nodal stage			
cN stage			
Units: Subjects			

cN0	8	8	
cN1	27	27	
cN2	5	5	
Tumor length			
Tumor length in cm			
Units: cm			
arithmetic mean	6.3		
standard deviation	± 2.7	-	
LVEF			
LVEF			
Units: Percentage			
median	64		
full range (min-max)	52 to 87	-	

End points

End points reporting groups

Reporting group title	TRAP cohort
Reporting group description: -	
Subject analysis set title	Feasibility
Subject analysis set type	Per protocol
Subject analysis set description: Feasibility	

Primary: Feasibility

End point title	Feasibility
End point description:	
End point type	Primary
End point timeframe: Day 1 cycle 1 to the end of planned treatment	

End point values	TRAP cohort	Feasibility		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	40	40		
Units: Participants				
Completed all treatment cycles with study drugs	33	33		
No full completion of all treatment cycles	7	7		

Statistical analyses

Statistical analysis title	Feasibility Test
Statistical analysis description: A one-sample test was used for binomial proportion with normal approximation and a one-sided p-value of <0.05. Feasibility was defined as more than or equal to 80% of patients completing treatment with trastuzumab and pertuzumab, whereas less than or equal to 62% was unfeasible.	
Comparison groups	TRAP cohort v Feasibility
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05 [2]
Method	t-test, 1-sided
Parameter estimate	% of completion
Point estimate	80

Confidence interval	
level	95 %
sides	1-sided
lower limit	80
Variability estimate	Standard deviation

Notes:

[1] - One-sample test

[2] - P-value <0.05 was considered as statistically significant

Secondary: Survival

End point title	Survival

End point description:

End point type	Secondary

End point timeframe:

From trial initiation to a median of 32.1 months follow-up

End point values	TRAP cohort			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Percentage				
number (not applicable)				
1-year OS	90			
1-year PFS	82.5			
3-year OS	72.3			
3-year PFS	71.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Response

End point title	Response

End point description:

End point type	Secondary

End point timeframe:

Following resection

End point values	TRAP cohort			
Subject group type	Reporting group			
Number of subjects analysed	38[3]			
Units: Participants				
Mandard 1	13			
Mandard 2	10			
Mandard 3	10			
Mandard 4	3			
Mandard 5	2			

Notes:

[3] - 2 patients did not receive resection due to death of pulmonary fibrosis and interval metastases.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored from start of treatment end of follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4.3

Reporting groups

Reporting group title	Baseline Cohort4

Reporting group description: -

Serious adverse events	Baseline Cohort4		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 40 (27.50%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events	1		
Investigations			
Creatinin increase			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Anastomotic Leakage			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Flank Pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Melena			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhea			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary Fibrosis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Pneumonia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Baseline Cohort4		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 40 (100.00%)		
Investigations			
Hypophosphatemia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Cardiac disorders			
Cardiac symptoms			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	6		
Nervous system disorders			
Peripheral Sensory Neuropathy			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	30 / 40 (75.00%)		
occurrences (all)	30		
Pain			
subjects affected / exposed	18 / 40 (45.00%)		
occurrences (all)	18		
Odynophagia			
subjects affected / exposed	11 / 40 (27.50%)		
occurrences (all)	11		
Alopecia			
subjects affected / exposed	9 / 40 (22.50%)		
occurrences (all)	9		
Hoarseness			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	6		
Infusion related reaction			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
Chills			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		

Headache			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Sore throat			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Epistaxis			
subjects affected / exposed	9 / 40 (22.50%)		
occurrences (all)	9		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	28 / 40 (70.00%)		
occurrences (all)	28		
Diarrhea			
subjects affected / exposed	29 / 40 (72.50%)		
occurrences (all)	29		
Vomiting			
subjects affected / exposed	18 / 40 (45.00%)		
occurrences (all)	18		
Constipation			
subjects affected / exposed	14 / 40 (35.00%)		
occurrences (all)	14		
Dyspaghia			
subjects affected / exposed	16 / 40 (40.00%)		
occurrences (all)	16		
Dysgeusia			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	7		
Dyspepsia			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	6		
Oral mucositis			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Hematemesis			

subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnea subjects affected / exposed occurrences (all)	 4 / 40 (10.00%) 4 4 / 40 (10.00%) 4		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all)	 14 / 40 (35.00%) 14 5 / 40 (12.50%) 5		
Infections and infestations Infection subjects affected / exposed occurrences (all) Flu/Malaise subjects affected / exposed occurrences (all) Fever subjects affected / exposed occurrences (all) Esophagitis subjects affected / exposed occurrences (all)	 11 / 40 (27.50%) 11 10 / 40 (25.00%) 10 7 / 40 (17.50%) 7 5 / 40 (12.50%) 5		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all)	 11 / 40 (27.50%) 11 5 / 40 (12.50%) 5		

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