



Clinical trial results:

Phase I dose escalation study with expansion cohort of the addition of nab-paclitaxel to capecitabine and oxaliplatin (CapOx) as first line treatment of metastatic esophagogastric adenocarcinoma (ACTION study).

Summary

EudraCT number	2014-001333-88
Trial protocol	NL
Global end of trial date	03 August 2018

Results information

Result version number	v1 (current)
This version publication date	12 January 2020
First version publication date	12 January 2020
Summary attachment (see zip file)	ACTION article Cancers (ACTION Cancers.pdf)

Trial information

Trial identification

Sponsor protocol code	ACTION
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02273713
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amsterdam UMC, location AMC
Sponsor organisation address	Meibergdreef 9, Amsterdam, Netherlands, 1105 AZ
Public contact	Lyda ter Hofstede, Amsterdam UMC, location AMC, 0031 205668229, trialmedonc@amc.uva.nl
Scientific contact	Lyda ter Hofstede, Amsterdam UMC, location AMC, 0031 205668229, 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	02 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1: To assess the safety and tolerability of Nab-paclitaxel added to oxaliplatin and capecitabine at their currently optimal doses.

Phase 2: To determine the anti-tumor activity of Nab-paclitaxel when co-administered with oxaliplatin and capecitabine in patients with irresectable or metastasized oesophagogastric cancer in terms of progression free survival.

Protection of trial subjects:

All patients received best supportive care besides the trial regimen.

Safety was discussed in a weekly meeting. SAE's were discussed and when necessary safety was corresponded with the IRB.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2014
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	Netherlands: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	17
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between December 2014 and November 2016, 36 patients were assessed and 26 eligible patients were enrolled, all in Dutch hospitals.

Pre-assignment

Screening details:

36 patients assessed for eligibility

10 excluded before treatment

Not meeting inclusion criteria (n=7)

No measurable lesion (n=2)

Temporary inclusion stop (n=1)

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	Investigational arm
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Arm description:

This was a single-arm study where all subjects received the experimental regime of capecitabine, oxaliplatin and nab-paclitaxel up to the maximum of 6 cycles

Arm type	Experimental
Investigational medicinal product name	nab-paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage

on days 1 and 8 of a 21 day cycle

dose level 1: 60 mg/kg/m²

dose level 2: 80 mg/kg/m²

dose level 3: 100 mg/kg/m²

dose level 4: 120 mg/kg/m²

- Supply: Nab-paclitaxel is supplied by Celgene as a sterile, lyophilized powder for reconstitution.
- Solution preparation: Nab-paclitaxel (Abraxane ®) is a solvent-free, protein-bound particle form of paclitaxel for intravenous infusion with a mean particle size of approximately 130 nanometers. A 50-mL vial contains 100 mg of paclitaxel and human albumin as a stabilizer. Each vial of the lyophilized product is reconstituted

Number of subjects in period 1	Investigational arm
Started	26
Completed	20
Not completed	6
Adverse event, serious fatal	2
Adverse event, non-fatal	2

Progressive Disease	2
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Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	26	26	
Age categorical			
Units: Subjects			
Adults (18-64 years)	17	17	
From 65-84 years	9	9	
Age continuous			
Units: years			
median	63		
full range (min-max)	45 to 75	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	23	23	

Subject analysis sets

Subject analysis set title	Overall trial
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients treated with the investigational regime	

Reporting group values	Overall trial		
Number of subjects	26		
Age categorical			
Units: Subjects			
Adults (18-64 years)	17		
From 65-84 years	9		
Age continuous			
Units: years			
median	63		
full range (min-max)	45 to 75		
Gender categorical			
Units: Subjects			
Female	3		
Male	23		

End points

End points reporting groups

Reporting group title	Investigational arm
Reporting group description: This was a single-arm study where all subjects received the experimental regime of capecitabine, oxaliplatin and nab-paclitaxel up to the maximum of 6 cycles	
Subject analysis set title	Overall trial
Subject analysis set type	Full analysis
Subject analysis set description: All patients treated with the investigational regime	

Primary: RP2D

End point title	RP2D ^[1]
End point description:	
End point type	Primary
End point timeframe: entire trial, 3+3 dose escalation scheme with safety expansion cohort	
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 analyses were needed for a standard 3+3 dose escalation design with safety expansion cohort	

End point values	Investigational arm			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: mg/kg/m2	60			

Attachments (see zip file)	DLT and RP2D/Figure 2. Dose escalation and dose limiting
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Statistical analyses

No statistical analyses for this end point

Secondary: AE, SAE according to NCTCAE

End point title	AE, SAE according to NCTCAE
End point description:	
End point type	Secondary
End point timeframe: AEs and SAEs were recorded during the entire trial and at least up to 30 days after cessation of nab-paclitaxel	

End point values	Investigational arm			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: AEs in % and SAEs in N				
AEs	100			
SAEs	18			

Attachments (see zip file)	Treatment related adverse events/Table 2. Treatment Related
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Statistical analyses

No statistical analyses for this end point

Secondary: Response rate according to RECIST 1.1

End point title	Response rate according to RECIST 1.1
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End point description:

End point type	Secondary
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End point timeframe:

Best response according to RECIST 1.1 over the trial period was registered

End point values	Investigational arm			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: PD, SD, PR, CR				
Complete Response	1			
Partial Response	13			
Stable Disease	9			
Progressive Disease	2			
Non-evaluable	1			

Attachments (see zip file)	Radiological Response/Figure 3. Swimmer plot of radiological
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Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival and Overall Survival

End point title	Progression Free Survival and Overall Survival
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End point description:

End point type	Secondary
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End point timeframe:

From study start till data cut-off at may 2nd 2018

End point values	Investigational arm			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: months				
median (confidence interval 95%)				
PFS	8.0 (5.6 to 10.4)			
OS	12.8 (7.0 to 18.6)			

Attachments (see zip file)	PFS and OS/Figure 4. PFS and OS.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Self reported neurotoxicity according to the EORTC QLQ CIPN20

End point title	Self reported neurotoxicity according to the EORTC QLQ CIPN20
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End point description:

Twenty-four patients completed the baseline questionnaires before start of treatment. Compliance of follow-up questionnaires was high and all patients but one were on active CapOx-nab-paclitaxel treatment up until cycle 7. Thereafter, all patients were on capecitabine monotherapy. Four patients that were eligible for reintroduction completed questionnaires before reintroduction and after the first cycle of reintroduction. Mean global health, functioning scores, as well as symptom scores of the QLQ-C30 questionnaire remained relatively stable during treatment as well as after cessation of triple therapy. The other functioning and symptom scores also remained relatively stable. Self-reported sensory neuropathy, however, showed an increase from a mean score of 1.39 at baseline to 28.8 after 9 cycles, subsequently decreasing to 17.0 after 15 cycles. The motor- and autonomic neuropathy scores demonstrated a similar pattern albeit with a smaller amplitude.

End point type	Secondary
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End point timeframe:

Baseline questionnaires completed before start of investigational treatment, before start of the second and fourth cycle and subsequently with a 3-cycle interval.

End point values	Investigational arm			
Subject group type	Reporting group			
Number of subjects analysed	24 ^[2]			
Units: CIPN20 score				
arithmetic mean (standard deviation)	28.8 (± 17.7)			

Notes:

[2] - 2 patients did not fill in the baseline questionnaire

Attachments (see zip file)	Figure 5. Health related quality of life and neurotoxicity.pdf Supplementary figure 1. Health related quality of life and Table 4. Baseline Health Related Quality of Life and Supplementary table 2. Responses Health Related Quality of
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study until at least 30 days after last infusion of nab-paclitaxel

Adverse event reporting additional description:

Subjects with adverse event: Treatment related adverse events are all events that can (possibly) be attributed to one or more drugs of the investigational regime (capecitabine, oxaliplatin, nab-paclitaxel).

Occurrences adverse event: all occurrences regardless of attribution

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.03
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Reporting groups

Reporting group title	60 mg/kg/m2
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Reporting group description:

Ultimately this dose level was decided as RP2D

Reporting group title	80 mg/kg/m2 and 100 mg/kg/m2
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Reporting group description:

patients treated at dose levels 2 and 3

Serious adverse events	60 mg/kg/m2	80 mg/kg/m2 and 100 mg/kg/m2	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 11 (36.36%)	14 / 15 (93.33%)	
number of deaths (all causes)	11	14	
number of deaths resulting from adverse events	0	2	
Vascular disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Non-cardiac chest pain	Additional description: eventual conclusion, esophageal spasms		
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 11 (9.09%)	0 / 15 (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			
Pain	Additional description: pain of bone metastases/progressive disease		
subjects affected / exposed	1 / 11 (9.09%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ disorder	Additional description: Multi-organ failure		
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Oesophageal stenosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 11 (0.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 11 (9.09%)	0 / 15 (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			
Chylothorax			

subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Skin infection			
Additional description: cellulitis of the ear			
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 11 (0.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	60 mg/kg/m2	80 mg/kg/m2 and 100 mg/kg/m2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	15 / 15 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Thrombo-embolic event			
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	9 / 11 (81.82%)	15 / 15 (100.00%)	
occurrences (all)	14	20	
Dysgeusia			
subjects affected / exposed	6 / 11 (54.55%)	9 / 15 (60.00%)	
occurrences (all)	6	10	
Anorexia			
subjects affected / exposed	7 / 11 (63.64%)	7 / 15 (46.67%)	
occurrences (all)	8	11	
Dizziness			
subjects affected / exposed	1 / 11 (9.09%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 11 (9.09%)	2 / 15 (13.33%)	
occurrences (all)	1	3	
White blood cell count decreased	Additional description: only grade 3/4/5		
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Neutropenia	Additional description: non febrile neutropenia		
subjects affected / exposed	2 / 11 (18.18%)	4 / 15 (26.67%)	
occurrences (all)	2	7	
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	8 / 11 (72.73%)	12 / 15 (80.00%)	
occurrences (all)	9	15	
Pain			
subjects affected / exposed	2 / 11 (18.18%)	4 / 15 (26.67%)	
occurrences (all)	4	5	
Fever			
subjects affected / exposed	0 / 11 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	3	
Flu like symptoms			
subjects affected / exposed	0 / 11 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Malaise			
subjects affected / exposed	2 / 11 (18.18%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Non-cardiac chest pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 11 (63.64%)	11 / 15 (73.33%)	
occurrences (all)	11	21	
Diarrhoea			
subjects affected / exposed	9 / 11 (81.82%)	12 / 15 (80.00%)	
occurrences (all)	11	23	
Vomiting			
subjects affected / exposed	4 / 11 (36.36%)	10 / 15 (66.67%)	
occurrences (all)	7	10	
Mucositis oral			
subjects affected / exposed	1 / 11 (9.09%)	5 / 15 (33.33%)	
occurrences (all)	1	6	
Constipation			
subjects affected / exposed	3 / 11 (27.27%)	2 / 15 (13.33%)	
occurrences (all)	5	4	
Dysphagia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	5	

Abdominal pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 15 (6.67%) 1	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 15 (13.33%) 2	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) Rash maculo-papular subjects affected / exposed occurrences (all)	3 / 11 (27.27%) 3 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0	8 / 15 (53.33%) 8 2 / 15 (13.33%) 2 2 / 15 (13.33%) 2	
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	4 / 15 (26.67%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2015	due to an SAE outside of the DLT period, a further 3 patients were treated at dose level 2
22 February 2016	INR and CK were added to laboratory tests. + changes because of a change in the dutch law
20 June 2016	because of a high percentage of diarrhea/vomiting/dehydration necessitating hospitalization at dose level 2, the remainder of the safety expansion cohort were treated at dose level 1. + HER2 positive patients not eligible for trastuzumab treatment could now be included

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 June 2016	a SUSAR turned out to be a regular SAE	08 June 2016

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

a clearer, more comprehensible and completer overview of the results is provided in the article

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31207904>