Clinical trial results:
Open-label pilot Phase I / II study on hyperthermic intraperitoneal chemotherapy (HIPEC) after macroscopically complete resection (R0 / R1) of adenocarcinomas of the pancreas (PanHIPEC)

Summary

EudraCT number	2015-002288-41
Trial protocol	DE
Global end of trial date	31 October 2018

Results information

Result version number	v1 (current)
This version publication date	07 October 2021
First version publication date	07 October 2021

Trial information

Trial identification

Sponsor protocol code	PanHIPEC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02863471
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University hospital Tuebingen
Sponsor organisation address	Hoppe - Seyler - Straße 3, Tuebingen, Germany, 72076
Public contact	PI, Dr. med. P. Horvath, University Department of General, Visceral and Transplant Surgery Tübingen, +49 70712981222, Philip.Horvath@med.uni-tuebingen.de
Scientific contact	PI, Dr. med. P. Horvath, University Department of General, Visceral and Transplant Surgery Tübingen, +49 70712981222, Philip.Horvath@med.uni-tuebingen.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	19 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2018
Global end of trial reached?	Yes
Global end of trial date	31 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

30 days mortality after macroscopically complete resection (R0 / R1) of pancreatic adenocarcinoma in combination with HIPEC

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and the ICH Guidelines in Good Clinical Practice. The study was not started before the competent ethics committee had given a favorable opinion. Written informed consent was obtained from all patients and the study was only conducted as approved by the Ethics committee and the competent authority.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2015
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	Germany: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	20
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

16 Patients were planned + recruited in the university hospital Tuebingen. Date of first patient enrollment: 03.12.2015. Date of last patient enrollment: 04.12.2017.End of study:31.10.2018. Explanation: The system contains an error in the calculation of patients. There was no comparison arm! This was a single-arm study with 16 recruited patients!

Pre-assignment

Screening details:

20 patients were assessed, 2 patients were excluded due to extended disease,2 patients were excluded from HIPEC during surgery, 1 patient due to histologically unconfirmed PDAC diagnosis,the other for severe hemorrhagic diathesis with edema of the gut. A total of 16 patients with confirmed PDAC diagnosis received HIPEC after oncological resection.

Period 1

Period 1 title	Gemcitabin (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Gemcitabin

Arm description:

16 patients with confirmed PDAC diagnosis received HIPEC after oncological resection.

Arm type	Experimental
Investigational medicinal product name	Gemcitabin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intraperitoneal use

Dosage and administration details:

during surgery 100mg/m2 KOF, 60 minutes intraperitoneal, hypertherme lavage

Arm title	Gemcitabin

Arm description:

there was no comparison arm

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Gemcitabin	Gemcitabin
Started	16	16
Completed	16	16

Baseline characteristics

Reporting groups	
Reporting group title	Gemcitabin
Reporting group description:	
16 patients with confirmed PDAC diagnosis received HIPEC after oncological resection.	
Reporting group title	Gemcitabin
Reporting group description:	
there was no comparison arm	

Reporting group values	Gemcitabin	Gemcitabin	Total
Number of subjects	16	16	32
Age categorical			
Age 18-99			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	16	16	32
85 years and over	0	0	0
18-99	0	0	0
Gender categorical			
16 subjects were exposed to the investiagtional drug dirung the reporting period. 13 subjects are male, 6 subjects are female with an rane from 1939 to 1966.			
Units: Subjects			
Female	4	4	8
Male	12	12	24

Subject analysis sets	
Subject analysis set title	Baseline
Subject analysis set type	Full analysis

Subject analysis set description:

Sample Size Calculation: 30-day mortality rate was the primary end point for statistical analysis. A one-sided 95% exact confidence interval (CI) and a one-sided exact binomial test were used to evaluate the null hypothesis that the observed 30-day mortality rate is ≥10% versus the alternative that the 30-day mortality rate is <10%. Given a required number of 16 patients, the probability that a critical event (death within 30 days of surgery) will occur in at least one patient is 81.5% if the incidence of critical events is ≥10% in the general population. The exact one-sided binomial test was used for statistical analysis.End point assessment: The primary endpoint analyzed was the incidence of death within the mITT population (all included patients who actually underwent planned HIPEC in addition to oncologic pancreatic resection) (with 95% CI). In addition, survival probability for 30-day versus minimum acceptable probability of π 0 = 0.9 was compared by one-sided binomial test.

Reporting group values	Baseline		
Number of subjects	16		
Age categorical			
Age 18-99			
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)	16		
From 65-84 years	0		
85 years and over	0		
18-99	0		
Gender categorical			
16 subjects were exposed to the investiagtional drug dirung the reporting period. 13 subjects are male, 6 subjects are female with an rane from 1939 to 1966.			
Units: Subjects			
Female	4		
Male	12		

End points

End points reporting groups

Reporting group title	Gemcitabin
Reporting group description:	
16 patients with confirmed PDAC diagnosis received HIPEC after oncological resection.	
Reporting group title	Gemcitabin
Reporting group description:	
there was no comparison arm	
Subject analysis set title	Baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
Sample Size Calculation: 30-day mortality rate was the primary end point for statistical analysis. A one-sided 95% exact confidence interval (CI) and a one-sided exact binomial test were used to evaluate the null hypothesis that the observed 30-day mortality rate is ≥10% versus the alternative that the 30-day mortality rate is <10%. Given a required number of 16 patients, the probability that a critical event (death within 30 days of surgery) will occur in at least one patient is 81.5% if the incidence of critical events is ≥10% in the general population. The exact one-sided binomial test was used for statistical analysis.End point assessment: The primary endpoint analyzed was the incidence of death within the mITT population (all included patients who actually underwent planned HIPEC in addition to oncologic pancreatic resection) (with 95% CI). In addition, survival probability for 30-day versus minimum acceptable probability of π 0 = 0.9 was compared by one-sided binomial test.	

Primary: Overall Survival

End point title	Overall Survival
End point description:	
End point type	Primary
End point timeframe:	
30-day mortality after macroscopically complete resection of adenocarcinoma of the pancreas in combination with HIPEC.	

End point values	Gemcitabin	Gemcitabin	Baseline	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	16	16	16	
Units: not applicable				
number (not applicable)	16	16	16	

Statistical analyses

Statistical analysis title	Primary statistical analysis
Statistical analysis description:	
30d mortality rate = primary end point,a one-sided 95% exact CI and a one-sided exact binomial test were used to evaluate the null hypothesis that the observed 30-day mortality rate is ≥10% versus the alternative that the 30-day mortality rate is <10%. Given a required number of 16 patients, the probability that a critical event (death within 30 days of surgery) will occur in at least one patient is 81.5% if the incidence of critical events is ≥10% in the general population.	
Comparison groups	Gemcitabin v Gemcitabin v Baseline

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.9
Method	Kaplan-Meyer, COX-Regression,Log-Rank
Confidence interval	
level	95 %
sides	1-sided

Notes:

[1] - n.a
there is no comparison group

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Within 30 days after invention, no patient died or experienced ay adverse events higher than grade 3 that were related to HIPEC. Furthermore, treatment-related AEs were prospectively ducemnted and categorized as expected or unexpected.

Assessment type	Non-systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Considering the results of this prospective phase I/II clinical trial a subsequent investigation of a potential clinical benefit (e.g., prolonged overall survival and progression-free survival) for patients with resectable pancreatic adenocarcinoma seems feasible and is also justifiable based on the results obtained, as the HIPEC procedure is not associated with a significant increase in short-term mortality and no signal of unexpected SAEs was evident in our study.

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34131821