Clinical trial results:
Progression-free Survival after Minimally Invasive Surgical Microwave Ablation (MIS-MWA) plus Durvalumab (MEDI4736) and Tremelimumab for Unresectable Non-metastatic Locally Advanced Pancreatic Cancer. MIMIPAC trial.

Summary

EudraCT number	2018-002852-34
Trial protocol	BE
Global end of trial date	29 January 2024

Results information

Result version number	v1 (current)
This version publication date	20 September 2024
First version publication date	20 September 2024

Trial information

Trial identification

Sponsor protocol code	S61508

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04156087
WHO universal trial number (UTN)	-
Other trial identifiers	AstraZeneca identifier: AZ ESR-17-12926

Notes:

Sponsors

Sponsor organisation name	UZLeuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Halit Topal, UZ Leuven, 0032 16346009 , halit.topal@uzleuven.be
Scientific contact	Halit Topal, UZ Leuven, 0032 16346009 , halit.topal@uzleuven.be

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	29 May 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 January 2024
Global end of trial reached?	Yes
Global end of trial date	29 January 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Median progression-free survival time was chosen as a clinically meaningful outcome. The study aimed to detect a 2-fold increase of median PFS time compared to the historical reference, i.e. from 6 to 12 months.

Protection of trial subjects:

Ethics review and approval, informed consent, prophylactic medication prior to infusions (to prevent chemotherapy known adverse events as per current practice and protocol recommendations), supportive care and routine monitoring.

Background therapy:

Systemic chemotherapy gemcitabine will be started 6 weeks after MIS-MWA. Gemcitabine will be given at a dose of 1000 mg /m², once a week for 3 weeks, followed with a week of rest. Patients will be treated with gemcitabine and durvalumab until disease progression is observed on CT-scan measurements.

Evidence for comparator:

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Actual start date of recruitment	06 January 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	5
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was included on 09-May-2020. Last patient last treatment visit was on 04-Aug-2024. Recruitment was stopped on 31-Oct-2022.

16 subjects have been screened; 4 were screening failures and 12 were enrolled and received at least one infusion of durvalumab and tremelimumab on study.

Survival data cutoff date was 29/05/2024.

Pre-assignment

Screening details:

The study target population is represented by patients with unresectable non-metastatic locally advanced pancreatic cancer, histologically or cytologically confirmed, eligible for treatment with durvalumab, tremelimumab and gemcitabine in a first line setting and fit for MIS-MWA.

Period 1

Period 1 title	Full duration = baseline to end of FU (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	MWA + D + T + Gemcitabine (SOC)

Arm description:

Durvalumab and tremelimumab are the investigational drugs. Per protocol, patients receive durvalumab (MEDI4736) 1500 mg IV every four weeks in combination with tremelimumab 75 mg IV every four weeks, starting two weeks prior to MIS-MWA. Standard gemcitabine (1g/m²) is started 6 weeks after the MIS-MWA procedure and is given weekly, in four-week cycles, three administrations followed by a week of rest as background treatment. Gemcitabine is given in combination with both tremelimumab and durvalumab (MEDI4736) on weeks 6 and 10 after MIS-MWA and in combination with durvalumab only afterwards. While only four doses of tremelimumab are foreseen, treatment with durvalumab and gemcitabine is continued until disease progression is observed on CT-scan measurements or patient withdrawal for other reason.

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	1428935-60-7
Other name	Imfinzi, MEDI4736
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

All patients will receive durvalumab (1500mg Q4W) in combination with tremelimumab (75 mg IV Q4W) until confirmed disease progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Standard infusion time for each is 60 minutes (±5 minutes). Tremelimumab will be administered first; the durvalumab infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion.

Investigational medicinal product name	Tremelimumab
Investigational medicinal product code	745013-59-6
Other name	MEDI1123
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

All patients will receive durvalumab (1500mg Q4W) in combination with tremelimumab (75 mg IV Q4W) until confirmed disease progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Standard infusion time for each is 60 minutes (±5 minutes).

Tremelimumab will be administered first; the durvalumab infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion.

Number of subjects in period 1	MWA + D + T + Gemcitabine (SOC)
Started	12
Completed	8
Not completed	4
Metastasis discovered during MWA	4

Baseline characteristics

Reporting groups	
Reporting group title	Full duration = baseline to end of FU
Reporting group description:	
All patients who consented to participate in the study and fulfilled all inclusion/exclusion criteria at baseline.	

Reporting group values	Full duration = baseline to end of FU	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
Adults (18-64 years)	5	5	
From 65-84 years	7	7	
Age continuous Units: years			
median	67.5		
full range (min-max)	34 to 81	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	8	8	
ECOG PS			
WHO EGOG performance status (PS) scale 0 Able to carry out all normal activity without restriction 1 Restricted in physically strenuous activity but ambulatory and able to carry out light work 2 Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours. 3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours 4 Completely disabled; cannot carry on any self-care; totally confined to bed or chair			
Units: Subjects			
PS 0	1	1	
PS 1	11	11	
PS 2	0	0	
Site of pancreatic tumour Units: Subjects			
Head	11	11	
Body	1	1	
Tail	0	0	
T stage Units: Subjects			
T3	0	0	
T4	12	12	
N stage Units: Subjects			
N0	4	4	
N1	6	6	
N2	2	2	
M stage at baseline			

Units: Subjects			
M0	12	12	
M stage at MIS-MWA			
Intra-abdominal metastasis discovered at laparoscopy prior to MIS-MWA procedure. Patients discontinued at this timepoint.			
Units: Subjects			
M0	8	8	
M1	4	4	

Subject analysis sets

Subject analysis set title	Intent to treat set (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who consented to participate in the study and fulfilled all inclusion/exclusion criteria at baseline.

Reporting group values	Intent to treat set (ITT)		
Number of subjects	12		
Age categorical Units: Subjects			
Adults (18-64 years)	5		
From 65-84 years	7		
Age continuous Units: years			
median	67.5		
full range (min-max)	34 to 81		
Gender categorical Units: Subjects			
Female	4		
Male	8		
ECOG PS			
WHO EGOG performance status (PS) scale 0 Able to carry out all normal activity without restriction 1 Restricted in physically strenuous activity but ambulatory and able to carry out light work 2 Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours. 3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours 4 Completely disabled; cannot carry on any self-care; totally confined to bed or chair			
Units: Subjects			
PS 0	1		
PS 1	11		
PS 2	0		
Site of pancreatic tumour Units: Subjects			
Head	11		
Body	1		
Tail	0		
T stage Units: Subjects			
T3	0		
T4	12		
N stage			

Units: Subjects			
N0	4		
N1	6		
N2	2		
M stage at baseline Units: Subjects			
M0	12		
M stage at MIS-MWA			
Intra-abdominal metastasis discovered at laparoscopy prior to MIS-MWA procedure. Patients discontinued at this timepoint.			
Units: Subjects			
M0	8		
M1	4		

End points

End points reporting groups

Reporting group title	MWA + D + T + Gemcitabine (SOC)

Reporting group description:

Durvalumab and tremelimumab are the investigational drugs. Per protocol, patients receive durvalumab (MEDI4736) 1500 mg IV every four weeks in combination with tremelimumab 75 mg IV every four weeks, starting two weeks prior to MIS-MWA. Standard gemcitabine (1g/m²) is started 6 weeks after the MIS-MWA procedure and is given weekly, in four-week cycles, three administrations followed by a week of rest as background treatment. Gemcitabine is given in combination with both tremelimumab and durvalumab (MEDI4736) on weeks 6 and 10 after MIS-MWA and in combination with durvalumab only afterwards. While only four doses of tremelimumab are foreseen, treatment with durvalumab and gemcitabine is continued until disease progression is observed on CT-scan measurements or patient withdrawal for other reason.

Subject analysis set title	Intent to treat set (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who consented to participate in the study and fulfilled all inclusion/exclusion criteria at baseline.

Primary: Progression free survival (PFS)

End point title	Progression free survival (PFS)[1]

End point description:

Standard Kaplan Meier analysis, performed with IBM SPSS statistics, version 29 0.2.0. Survival data cutoff date was 29/05/2024.

The study is exploratory and results are presented descriptively. No formal comparison was foreseen, this is a single arm study. The reference PFS time in patients with non-metastatic locally advanced pancreatic cancer treated with gemcitabine monotherapy is about 6 months.

No conclusion can be drawn due to the insufficient sample size.

End point type	Primary

End point timeframe:

From signature of informed consent to disease progression or death from any cause.

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: Standard Kaplan Meier analysis for PFS and OS, performed with IBM SPSS statistics, version 29 0.2.0. Survival data cutoff date was 29/05/2024.The study is exploratory and results are presented descriptively. No formal comparison was foreseen, this is a single arm study. The reference PFS time in patients with non-metastatic locally advanced pancreatic cancer treated with gemcitabine monotherapy is about 6 months.No conclusion can be drawn due to the insufficient sample size.

End point values	MWA + D + T + Gemcitabine (SOC)	Intent to treat set (ITT)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	12			
Units: month				
median (confidence interval 95%)	4.3 (0.0 to 15.2)	4.3 (0.0 to 15.2)		

Attachments (see zip file)	MIMIPAC_PFS_cutoff 240529_chart.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety

End point description:

Clinical and hematological toxicity (NCI CTCAE v. 5.0) of chemotherapy and immunotherapy. Summary tabulations and line listings of serious adverse events (14 SAE reported), non-serious adverse events, laboratory anomalies are attached. Also see section Adverse events.

End point type	Secondary

End point timeframe:

From signature of informed consent to 90 days post last immunotherapy dose.

End point values	MWA + D + T + Gemcitabine (SOC)	Intent to treat set (ITT)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	12	12		
Units: Occurrences	14	14		

Attachments (see zip file)	Safety A1_SAE LL.pdf Safety A2 SAE ST.pdf Safety A3 AE LL.pdf Safety A4 AE ST.pdf Safety A5 Lab ST.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Post operative complications

End point title	Post operative complications

End point description:

The number and type of postoperative complications were recorded, i.e. fistula, hemorrhage, abscess, etc... The therapy-oriented severity grading system (TOSGS) of complications were also used and complications were allocated to surgical (SSC) and non-surgical site (NSSC) complications.

Post operative complications after the MIS-MWA procedure occurred in one patient. Three occurrences were recorded as separate AEs and listed as SAE cases 9 and 10 with fatal outcome for this patient. See Safety and Adverse event sections.

End point type	Secondary

End point timeframe:

From signature of informed consent to 90 days post last immunotherapy dose.

End point values	MWA + D + T + Gemcitabine (SOC)	Intent to treat set (ITT)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	12	12		
Units: Occurrences	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of hospital stay

End point title	Length of hospital stay

End point description:

Postoperative length of hospital stay (after MIS-MWA)

End point type	Secondary

End point timeframe:

From signature of informed consent to 90 days post last immunotherapy dose.

End point values	MWA + D + T + Gemcitabine (SOC)	Intent to treat set (ITT)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	12	12		
Units: day				
median (full range (min-max))	2 (2 to 17)	2 (2 to 17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Tertiary endpoint. Standard Kaplan Meier analysis, performed with IBM SPSS statistics, version 29 0.2.0.

End point type	Secondary

End point timeframe:

From signature of informed consent to death of any cause or date of last contact for patients still alive.

End point values	MWA + D + T + Gemcitabine (SOC)	Intent to treat set (ITT)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	12	12		
Units: month				
median (confidence interval 95%)	14.9 (9.4 to 20.4)	14.9 (9.4 to 20.4)		

Attachments (see zip file)	MIMIPAC_OS_cutoff 240529_chart.jpg

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signature of ICF to 90 days post last dose of immunotherapy (mandatory safety FU)

Adverse event reporting additional description:

Only grade 3/4/5 of non serious adverse events are reported. All events including grade 1/2 are available in line listings attached.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	5

Reporting groups

Reporting group title	Total (safety set)

Reporting group description: -

Serious adverse events	Total (safety set)		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events	1		
Investigations			
Liver enzymes increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Postoperative hemorrhage			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Total (safety set)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Investigations			
Hemoglobin decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
White blood cell count decreased			

subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Absolute neutrophil count decreased			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
ALP increased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
ALT increased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
AST increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
GGT increased			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	5		
Total bilirubine increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Amylase increased			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Lipase increased			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Hyperglycaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	5		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 2 / 12 (16.67%) 2		
Eye disorders Cataract subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Ascites subjects affected / exposed occurrences (all) Diarrhea subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 2		
Renal and urinary disorders Cystocoele subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
Musculoskeletal and connective tissue disorders Generalized muscle weakness subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
Infections and infestations Absolute lymphocyte count decreased subjects affected / exposed occurrences (all)	 3 / 12 (25.00%) 3		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) Hyperglycemia	 1 / 12 (8.33%) 1 		

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2020	Substantial amendment 1 – ICF V1.2 dd 19Feb2020
14 January 2021	Substantial amendment 2 – protocol V9 dd 10 Nov 2020 and ICF V1.3 dd 13 Jan 2021
24 August 2021	Substantial amendment 3 - protocol V10 dd 20 Jul 2021 and ICF V2 dd 20 Jul 2021
24 May 2023	Substantial amendment 4 - protocol V11 dd 17 Apr 2023 and ICF V3 dd 17 Apr 2023

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Insufficient sample size due to low accrual.
Non randomised design for an efficacy endpoint

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25524417

http://www.ncbi.nlm.nih.gov/pubmed/24907635

http://www.ncbi.nlm.nih.gov/pubmed/22658128

http://www.ncbi.nlm.nih.gov/pubmed/24070507

http://www.ncbi.nlm.nih.gov/pubmed/15173017

http://www.ncbi.nlm.nih.gov/pubmed/32664183

http://www.ncbi.nlm.nih.gov/pubmed/31318392

http://www.ncbi.nlm.nih.gov/pubmed/31996388

http://www.ncbi.nlm.nih.gov/pubmed/33442411

http://www.ncbi.nlm.nih.gov/pubmed/30578687

http://www.ncbi.nlm.nih.gov/pubmed/32816849

http://www.ncbi.nlm.nih.gov/pubmed/31676670