



Clinical trial results:

Safety and efficacy of the addition of IMM-101 Heat-Killed Whole Cell Mycobacterium obuense to standard stereotactic radiotherapy in locally advanced pancreatic cancer patients (LAPC-2 trial).

Summary

EudraCT number	2019-000216-29
Trial protocol	NL
Global end of trial date	21 September 2021

Results information

Result version number	v1 (current)
This version publication date	12 July 2024
First version publication date	12 July 2024
Summary attachment (see zip file)	Manuscript 2 (Van 't Land et al (2022). Radiotherapy and Oncology.pdf) Manuscript 1 (Van 't Land et al (2022). Cancers.pdf)

Trial information

Trial identification

Sponsor protocol code	NL68762.078.19
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	NTR: NL7578

Notes:

Sponsors

Sponsor organisation name	Erasmus MC Cancer Institute
Sponsor organisation address	Doctor Molewaterplein 40, Rotterdam, Netherlands,
Public contact	Research coordinator, Erasmus MC, 0031 650032401, f.vantland@erasmusmc.nl
Scientific contact	Research coordinator, Erasmus MC, 0631949794 650032401, f.vantland@erasmusmc.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	29 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2021
Global end of trial reached?	Yes
Global end of trial date	21 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This phase I/II study consists of 2 subsequent study parts. In the phase I part we will investigate the safety of combining IMM-101 administration with SBRT in 20 patients with locally advanced pancreatic cancer who have completed at least 4 cycles of FOLFIRINOX chemotherapy. If deemed safe and feasible (defined as max 6 out of 20 patients experiencing a grade 4/5 toxicity related to the IMM-101 intervention) we will continue inclusion in phase II with an additional 18 patients in order to be able to study efficacy of combining IMM-101 treatment with SBRT based on a 20% improvement of 1-year disease free survival.

Protection of trial subjects:

The sponsor and the trial management team will guide conduct of the trial according to Good Clinical Practice (GCP). The Principal Investigator will be responsible for the conduct within his site.

Data will be handled confidentially. Each patient will receive an anonymous identification code. To trace data back to an individual patient, a subject identification code list will be used. The PI will safeguard the key to this code for patients included at the site. The handling of personal data will comply with the Dutch Personal Data Protection Act (in Dutch: Algemene verordening gegevensbescherming (AVG)). Data will be kept as long as 15 years, according to the guidelines for Clinical Trials.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	21
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with locally advanced pancreatic cancer who had been treated with at least four cycles of (m)FOLFIRINOX and who did not show progression of disease were screened for participation in the study. Patients were classified as LAPC according to the dutch resectability guidelines defined by the

Pre-assignment

Screening details:

Patients with LAPC, following systemic chemotherapy

No progression of disease

Inclusion and exclusion criteria are shown in the online publication

Period 1

Period 1 title	Complete trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

not applicable

Arms

Arm title	Study treatment
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Arm description:

6 vaccinations of 1mg of intradermal IMM-101 over a period of three months (experimental) combined with 40 Gy of stereotactic radiotherapy (5 times 8 Gy) (standard of care)

Arm type	Experimental
Investigational medicinal product name	IMM-101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

1mg IMM-101, intradermal injection

Number of subjects in period 1	Study treatment
Started	38
Completed	38

Baseline characteristics

Reporting groups

Reporting group title	Complete trial
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Reporting group description: -

Reporting group values	Complete trial	Total	
Number of subjects	38	38	
Age categorical			
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: months			
median	63		
inter-quartile range (Q1-Q3)	59 to 71	-	
Gender categorical			
Units: Subjects			
Female	22	22	
Male	16	16	
ECOG performance score			
Units: Subjects			
ECOG 0	12	12	
ECOG 1	26	26	
Tumor location			
Units: Subjects			
Pancreatic Head	27	27	
Pancreatic body/tail	11	11	
Vessel involvement - arterial contact			
Units: Subjects			
< 90 degrees	5	5	
≥ 90 degrees	33	33	
Vessel involvement - venous contact			
Units: Subjects			
≤ 270 degrees	24	24	
> 270 degrees	14	14	
diagnostic laparoscopy at diagnosis			
Units: Subjects			
Yes	13	13	
No	25	25	

Prior biliary drainage Units: Subjects			
Yes	18	18	
No	20	20	
Treatment with (m)FOLFIRINOX Units: Subjects			
Yes	38	38	
No	0	0	
Radiological response after (m)FOLFIRINOX Units: Subjects			
Stable disease	27	27	
Partial response	10	10	
Complete response	1	1	
Body mass index Units: kg/m2			
median	24		
inter-quartile range (Q1-Q3)	21 to 27	-	
CA19-9 at inclusion Units: U/ml			
median	113		
inter-quartile range (Q1-Q3)	34 to 206	-	
CA 19-9 at diagnosis Units: U/ml			
median	508		
inter-quartile range (Q1-Q3)	126 to 1331	-	
CEA at inclusion Units: micrograms/L			
median	4.4		
inter-quartile range (Q1-Q3)	3.4 to 6.4	-	
CEA at diagnosis Units: micrograms/L			
median	5.37		
inter-quartile range (Q1-Q3)	3.53 to 9.80	-	
Tumor size at diagnosis Units: mm			
median	37		
inter-quartile range (Q1-Q3)	30 to 46	-	
Tumor size at inclusion Units: mm			
median	31		
inter-quartile range (Q1-Q3)	25 to 40	-	
Number of cycles (m)FOLFIRINOX Units: cycles			
median	8		
inter-quartile range (Q1-Q3)	8 to 8	-	

Subject analysis sets

Subject analysis set title	overall cohort
Subject analysis set type	Full analysis

Reporting group values	overall cohort		
Number of subjects	38		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: months			
median	63		
inter-quartile range (Q1-Q3)	59 to 71		
Gender categorical			
Units: Subjects			
Female	22		
Male	16		
ECOG performance score			
Units: Subjects			
ECOG 0	12		
ECOG 1	26		
Tumor location			
Units: Subjects			
Pancreatic Head	27		
Pancreatic body/tail	11		
Vessel involvement - arterial contact			
Units: Subjects			
< 90 degrees	5		
≥ 90 degrees	33		
Vessel involvement - venous contact			
Units: Subjects			
≤ 270 degrees	24		
> 270 degrees	14		
diagnostic laparoscopy at diagnosis			
Units: Subjects			
Yes	13		
No	25		
Prior biliary drainage			
Units: Subjects			
Yes	18		
No	20		
Treatment with (m)FOLFIRINOX			
Units: Subjects			

Yes	38		
No	0		
Radiological response after (m)FOLFIRINOX Units: Subjects			
Stable disease	27		
Partial response	10		
Complete response	1		
Body mass index Units: kg/m2 median inter-quartile range (Q1-Q3)	24 21 to 27		
CA19-9 at inclusion Units: U/ml median inter-quartile range (Q1-Q3)	113 34 to 206		
CA 19-9 at diagnosis Units: U/ml median inter-quartile range (Q1-Q3)	508 126 to 1331		
CEA at inclusion Units: micrograms/L median inter-quartile range (Q1-Q3)	4.4 3.4 to 6.4		
CEA at diagnosis Units: micrograms/L median inter-quartile range (Q1-Q3)	5.37 3.53 to 9.80		
Tumor size at diagnosis Units: mm median inter-quartile range (Q1-Q3)	37 30 to 46		
Tumor size at inclusion Units: mm median inter-quartile range (Q1-Q3)	31 25 to 40		
Number of cycles (m)FOLFIRINOX Units: cycles median inter-quartile range (Q1-Q3)	8 8 to 8		

End points

End points reporting groups

Reporting group title	Study treatment
Reporting group description: 6 vaccinations of 1mg of intradermal IMM-101 over a period of three months (experimental) combined with 40 Gy of stereotactic radiotherapy (5 times 8 Gy) (standard of care)	
Subject analysis set title	overall cohort
Subject analysis set type	Full analysis
Subject analysis set description: not applicable	

Primary: Adverse events

End point title	Adverse events ^[1]
End point description: All grade 4 or 5 adverse events that were possibly, probably or likely related to the study treatment were regarded as events for the endpoint. Adverse events were scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The relationship between the treatment and the adverse events were judged by the study team. The manuscript can be found online which describes this in detail.	
End point type	Primary
End point timeframe: during the complete study treatment	

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: The previously observed grade 4 toxicity rate related to SBRT in the setting of LAPC was 10%. With a sample size of 20 patients (phase I) we were able to estimate a toxicity rate of 10% within a 95% confidence interval of [1.2%, 31.7%] using binomial exact method. This meant that at most 6/20 patients were allowed to have a grade 4 toxicity in the phase I trial before moving to the phase II.

End point values	Study treatment	overall cohort		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	38	38		
Units: Adverse events				
Grade 3 - SBRT related	1	1		
Grade 4 - SBRT related	0	0		
Grade 5 - SBRT related	0	0		
Grade 3 - IMM-101 related	0	0		
Grade 4 - IMM-101 related	0	0		
Grade 5 - IMM-101 related	0	0		
Grade 3 - unrelated	12	12		
Grade 4 - unrelated	0	0		
Grade 5 - unrelated	1	1		

Attachments (see zip file)	Grade 3 or higher adverse events/2023-01-05_Van 't Land et
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Statistical analyses

No statistical analyses for this end point

Primary: One-year PFS rate

End point title	One-year PFS rate ^[2]
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End point description:

The calculated one-year progression free survival rate was 47%.

End point type	Primary
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End point timeframe:

overall study period

Notes:

[2] - 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: With previous data using SBRT, the one-year PFS rate was 45%. We hypothesized that by adding IMM-101 to SBRT, this could be improved to 65%. If the one-year PFS rate was < 65%, we would not proceed with a phase-III trial. To test this hypothesis we needed 38 patients (calculated with Fleming's test). Eventually, the one-year PFS rate was calculated in the cohort to analyze the primary end point.

End point values	Study treatment	overall cohort		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	38	38		
Units: percent	17	17		

Attachments (see zip file)	OS and PFS/2022-12-19_Figure_3_LAPC2.pdf
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

complete study period

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	5.0
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Reporting groups

Reporting group title	Overall cohort
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Reporting group description: -

Serious adverse events	Overall cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 38 (28.95%)		
number of deaths (all causes)	29		
number of deaths resulting from adverse events	0		
Investigations			
Urinary retention			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Haematemesis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Duodenal obstruction			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Cholestasis			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis	Additional description: In the manuscript this adverse event was later described, after careful consideration, as a gastro-intestinal bleeding grade 5. Please review the manuscript van 't Land et al (2022). Radiotherapy and Oncology		
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 38 (68.42%)		
Skin and subcutaneous tissue disorders			

injection site reaction			
subjects affected / exposed	26 / 38 (68.42%)		
occurrences (all)	26		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2020	The possibility of offering maintenance vaccinations was added to the protocol: If the standard of care CT scan at week 14 shows no signs of progression and the patient did not experience a SAE related to the 6 IMM101 vaccinations the patient is eligible for IMM-101 maintenance therapy for at most 12 months. The maintenance therapy will consist of a 0.05 ml dosage of IMM-101 with a 4 week interval until patients show clinical progression or withdraw from the study
21 July 2020	The protocol was ammended in order to make it possible to proceed to including more than 20 patients earlier.: Safety will be assessed when the first 20 patients have received at least 3 vaccinations (i.e. 2 weeks prior to SBRT, day 1 of SBRT and 2 weeks after SBRT). Before, the 20 patients needed to receive all the vaccinations (6 vaccinations) before we would be able to include more than 20 patients.
27 November 2020	Patients who dropped out before starting study treatment could be replaced: Patients who drop out of the study before receiving SBRT will be replaced by a new patient. The one-year PFS of 45% in the historical LAPC-1 cohort was calculated using data from only those patients who had received SBRT. To be able to perform the most accurate analysis for the PFS endpoint we can only analyze those patients who actually received SBRT. We made an amendment to make in possible to analyze samples outside the EU: Translational analysis can be performed at third parties within and outside of the European Union. In this case the Sponsor will draw up an agreement with these Parties ensuring that data and/or samples are handled according to EU legislation. Only pseudonimized data and/or samples will be shared. Data will be transferred using a secured connection.

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/36813171>

<http://www.ncbi.nlm.nih.gov/pubmed/36358718>