



Clinical trial results:

A Multicenter Phase 2/3 Trial of the Efficacy and Safety of Intracerebroventricular Radioimmunotherapy using ¹³¹I-burtomab for Neuroblastoma Central Nervous System/Leptomeningeal Metastases

Summary

EudraCT number	2017-001828-22
Trial protocol	DK ES GB
Global end of trial date	02 June 2023

Results information

Result version number	v1 (current)
This version publication date	17 December 2023
First version publication date	17 December 2023

Trial information

Trial identification

Sponsor protocol code	101
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03275402
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Y-mAbs Therapeutics Inc.
Sponsor organisation address	230 Park Avenue, Suite 3350, New York, United States, 10169
Public contact	clinicaltrials@ymabs.com, GRS associate, 'Y-mAbs Therapeutics Inc, +45 70261414, clinicaltrials@ymabs.com, clinicaltrials@ymabs.com
Scientific contact	clinicaltrials@ymabs.com, GRS associate, 'Y-mAbs Therapeutics Inc, +45 70261414, clinicaltrials@ymabs.com, clinicaltrials@ymabs.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002101-PIP02-18
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	14 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 June 2023
Global end of trial reached?	Yes
Global end of trial date	02 June 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the overall survival (OS) rate at 3 years

Protection of trial subjects:

The trial will be conducted in accordance with the protocol, applicable regulatory requirements, ICH GCP and the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and sub-sequent versions. The trial will be conducted according to Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population (recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 November 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	United States: 36
Country: Number of subjects enrolled	Japan: 3
Worldwide total number of subjects	52
EEA total number of subjects	13

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	2

months)	
Children (2-11 years)	50
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening evaluations must be completed within 30 days before the first ¹³¹Iomburtamab dose.

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	131I-omburtamab
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Arm description:

One treatment cycle of ¹³¹I-omburtamab consists of one dosimetry dose (2 mCi) (for subjects enrolled on Version 1-7 of Protocol 101) and one treatment dose (50 mCi) for up to 2 cycles of length 5 weeks (for subjects enrolled on Version 1-7 of Protocol 101) or 4 weeks (for subject enrolled after Version 7 of Protocol 101). For Japan only, the first cycle consisted of one dosimetry dose (2 mCi) week 1 one treatment dose (50 mCi) week 2. If eligible a second cycle of 50 mCi ¹³¹I-omburtamab was given at week 6. For subjects below 3 and 1 years of age, the treatment dose was reduced by 33% and 50%, respectively.

Arm type	Experimental
Investigational medicinal product name	131I-omburtamab
Investigational medicinal product code	
Other name	131I-8H9
Pharmaceutical forms	Solution for infusion
Routes of administration	Intracerebroventricular use

Dosage and administration details:

One treatment cycle of ¹³¹I-omburtamab consists of one dosimetry dose (2 mCi) (for subjects enrolled on Version 1-7 of Protocol 101) and one treatment dose (50 mCi) for up to 2 cycles of length 5 weeks (for subjects enrolled on Version 1-7 of Protocol 101) or 4 weeks (for subject enrolled after Version 7 of Protocol 101). For Japan only, the first cycle consisted of one dosimetry dose (2 mCi) week 1 one treatment dose (50 mCi) week 2. If eligible a second cycle of 50 mCi ¹³¹I-omburtamab was given at week 6. For subjects below 3 and 1 years of age, the treatment dose was reduced by 33% and 50%, respectively.

Number of subjects in period 1	131I-omburtamab
Started	52
Completed	13
Not completed	39
Death	17
Study terminated by sponsor	21
Withdrawal by subject	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description:	
One treatment cycle of 131I-omburtamab consists of 1 dose at 50mCi at week 1. For Japan only one treatment cycle of 131I-omburtamab consists of 2 doses: 2mCi at week 1 and 50mCi at week 2. First cycle is initiated right after confirmation of eligibility at week 1. At week 5 (week 6 for Japan) the participant will be evaluated for safety and if eligible, receive a second cycle of 131I-omburtamab. Secondary efficacy endpoints will be evaluated at week 26 and primary efficacy endpoint will be evaluated at week 156. 131I-omburtamab: Murine IgG1 monoclonal antibody radiolabeled with iodine-131	

Reporting group values	Overall trial	Total	
Number of subjects	52	52	
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)	2	2	
Children (2-11 years)	50	50	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	4.7		
standard deviation	± 2.45	-	
Gender categorical			
Units: Subjects			
Female	22	22	
Male	30	30	
Ethnicity			
Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic or Latino	38	38	
Unknown or Not reported	9	9	
Race			
Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	9	9	
Black or African American	1	1	
White	38	38	
Unknown or not reported	3	3	
Region enrollment			
Units: Subjects			
United States	36	36	

Japan	3	3	
Denmark	1	1	
Spain	12	12	

End points

End points reporting groups

Reporting group title	131I-omburtamab
Reporting group description:	
One treatment cycle of 131I-omburtamab consists of one dosimetry dose (2 mCi) (for subjects enrolled on Version 1-7 of Protocol 101) and one treatment dose (50 mCi) for up to 2 cycles of length 5 weeks (for subjects enrolled on Version 1-7 of Protocol 101) or 4 weeks (for subject enrolled after Version 7 of Protocol 101). For Japan only, the first cycle consisted of one dosimetry dose (2 mCi) week 1 one treatment dose (50 mCi) week 2. If eligible a second cycle of 50 mCi 131I-omburtamab was given at week 6. For subjects below 3 and 1 years of age, the treatment dose was reduced by 33% and 50%, respectively.	

Primary: Overall Survival Rate

End point title	Overall Survival Rate ^[1]
End point description:	
Overall survival rate at 3 years after the first treatment dose of 131I-omburtamab.	
End point type	Primary
End point timeframe:	
3 years	

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 survival time was calculated from first dose of 131I-omburtamab until date of death. Subjects alive was censored at the date the subject was last confirmed alive. Kaplan-Meier methods was used to analyse the survival data and to estimate the 3-years overall survival rate.

End point values	131I-omburtamab			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Rate				
median (confidence interval 95%)	0.65 (0.49 to 0.78)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From 1st dose until 3 weeks after the last IMP administration

Adverse event reporting additional description:

Adverse events were reported from 1st dose until 3 weeks after the last IMP administration. From 3 weeks after last IMP administration and during the 3-year long term follow-up only SAEs considered related to IMP and new onset for cancers were reported

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	131I-omburtamab
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Reporting group description:

One treatment cycle of 131I-omburtamab consists of 1 dose at 50mCi at week 1. For Japan only one treatment cycle of 131I-omburtamab consists of 2 doses: 2mCi at week 1 and 50mCi at week 2. First cycle is initiated

right after confirmation of eligibility at week 1. At week 5 (week 6 for Japan) the participant will be evaluated for safety and if eligible, receive a second cycle of 131I-omburtamab.

Secondary efficacy endpoints will be evaluated at week 26 and primary efficacy endpoint will be evaluated at week 156.

131I-omburtamab: Murine IgG1 monoclonal antibody radiolabeled with iodine-131

Serious adverse events	131I-omburtamab		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 52 (38.46%)		
number of deaths (all causes)	17		
number of deaths resulting from adverse events	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphocyte count decreased			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	8 / 52 (15.38%)		
occurrences causally related to treatment / all	8 / 9		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Meningitis chemical			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 52 (1.92%)		
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	131I-omburtamab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 52 (94.23%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	5		
Hypertension			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	8		
Hypotension			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	9		
General disorders and administration site conditions			

<p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 52 (7.69%)</p> <p>4</p>		
<p>Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 52 (11.54%)</p> <p>20</p>		
<p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>8 / 52 (15.38%)</p> <p>9</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Bronchospasm</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasal congestion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 52 (5.77%)</p> <p>6</p> <p>7 / 52 (13.46%)</p> <p>8</p> <p>5 / 52 (9.62%)</p> <p>5</p>		
<p>Psychiatric disorders</p> <p>Irritability</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 52 (7.69%)</p> <p>4</p>		
<p>Investigations</p> <p>Alanine aminotransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Aspartate aminotransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lymphocyte count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neutrophil count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 52 (7.69%)</p> <p>4</p> <p>3 / 52 (5.77%)</p> <p>4</p> <p>16 / 52 (30.77%)</p> <p>19</p> <p>22 / 52 (42.31%)</p> <p>43</p>		

Platelet count decreased subjects affected / exposed occurrences (all)	22 / 52 (42.31%) 26		
Protein total decreased subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3		
White blood cell count decreased subjects affected / exposed occurrences (all)	23 / 52 (44.23%) 34		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	4 / 52 (7.69%) 10		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Neuralgia subjects affected / exposed occurrences (all)	12 / 52 (23.08%) 20 5 / 52 (9.62%) 10		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	15 / 52 (28.85%) 22		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea	4 / 52 (7.69%) 4 3 / 52 (5.77%) 3		

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 52 (5.77%)</p> <p>3</p> <p>19 / 52 (36.54%)</p> <p>21</p> <p>18 / 52 (34.62%)</p> <p>25</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash maculo-papular</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urticaria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 52 (5.77%)</p> <p>5</p> <p>3 / 52 (5.77%)</p> <p>3</p> <p>7 / 52 (13.46%)</p> <p>7</p>		
<p>Endocrine disorders</p> <p>Hypothyroidism</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 52 (7.69%)</p> <p>4</p>		
<p>Metabolism and nutrition disorders</p> <p>Decreased appetite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hyponatraemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 52 (11.54%)</p> <p>6</p> <p>3 / 52 (5.77%)</p> <p>3</p>		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2017	2.0 - Amendment issued before first subject visit.
01 August 2018	3.0 - Internal version only
17 September 2018	4.0 - Amendment issued before first subject visit
12 April 2019	<p>5.0 - Updated trial objectives to evaluate ORR at 6 months instead of up to 3 years and evaluate CNS/LM progression instead of CNS progression free survival. Also deleted objective comparing the OS to historical controls.</p> <p>Added instruction on dosing potassium iodine and referred to FDA and European Association of Nuclear Medicine guidelines on potassium iodide dosing in the "treatment" section to ensure subject safety</p> <p>Added clarification for difference between treatment before and after interim analysis throughout protocol</p> <p>Added to safety considerations section a minimum of one week is an adequate time period between support for myelosuppression and IMP administration</p> <p>Changed follow-up to include SAEs considered related to 131Iomburtamab or new onset of cancers regardless of causality</p> <p>Changed inclusion criteria</p> <ul style="list-style-type: none">- Clarified life expectancy as judged by investigator- Deleted time period between hematological support and 131Iomburtamab administration (referred to in protocol text instead)- Narrowed liver function criteria to appropriate levels and exclude subjects with Hy's law criteria at screening <p>Changed exclusion criteria to permit CSF flow study be made with several different 111Indium.</p> <p>Updated secondary endpoints to reflect changes made in the objectives.</p> <p>Added text on location and characterization of metastatic lesions to "medical and surgical history" section so that important medical history information are specified and collected</p>
10 September 2019	6.0 - internal version only
11 September 2019	<p>7.0 -Change of no. of non-MSK patients in the interim analysis</p> <ul style="list-style-type: none">- Specify removal of dosimetry doses after completion of the interim analysis- Specify when informed consent must be obtained In case the indwelling intracerebroventricular access device (e.g., Ommaya) is placed in connection with the tumor resection- Updated text on thyroid protection- Dose of dexamethasone changed- Text added for clarification re. patient treatment discontinuation- Addition of chemical meningitis to pre-defined AEs of special interest
12 December 2019	8.0 - internal version

18 December 2019	<p>9.0 - 3 new assessments were added to distinguish between CNS/LM progression and systemic progression</p> <p>A new secondary objective was added: To evaluate CNS/LM progression-free survival (CNS/LM PFS) at 12 months (primary interim objective)</p> <p>Text and sections have been deleted for treatment and procedures required before the interim analysis until 31 December 2019 to reflect that dosimetry is not part of the protocol after 01 January 2020.</p>
01 May 2020	<p>10.0 -Addition of two efficacy objectives</p> <ul style="list-style-type: none"> - To evaluate CNS/LM progression-free survival (CNS/LM PFS) at 6 months - To evaluate Overall Survival (OS) at 12 months <p>The following endpoints were added to address the above efficacy objectives:</p> <ul style="list-style-type: none"> - CNS/LM PFS at 6 months will be estimated based on time from first treatment dose to CNS/LM progression or death from any cause. Subjects alive without CNS/LM progression at time of analysis will be censored at last date of disease evaluation without evidence of progression. - OS at 12 months will be estimated – based on the time from first treatment dose to death by any cause. Subjects alive at time of analysis, are censored at last date known to be alive <p>Furthermore, the objective “To evaluate CNS/LM progression-free survival (CNS/LM PFS) at 12 months” was changed from an interim objective to an overall objective.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 June 2023	The trial was terminated early due to a business strategy decision.	-

Notes:

Limitations and caveats

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

The trial was terminated early due to a business strategy decision.

Notes: