Clinical trial results:
Phase I Study of Intrathecal Radioimmunotherapy using 131I-omburtamab for Central Nervous System/Leptomeningeal Neoplasms

Summary

EudraCT number	2020-001590-68
Trial protocol	Outside EU/EEA
Global end of trial date	12 March 2020

Results information

Result version number	v1 (current)
This version publication date	10 June 2021
First version publication date	10 June 2021

Trial information

Trial identification

Sponsor protocol code	03-133

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00089245
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Y-mAbs Therapeutics Inc
Sponsor organisation address	230 Park Avenue, Suite 3350, New York NY, United States, 10169
Public contact	clinical department, Y-mAbs Therapeutics Inc, +45 70261414, info@ymabs.com
Scientific contact	clinical department, Y-mAbs Therapeutics Inc, +45 70261414, info@ymabs.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2019
Global end of trial reached?	Yes
Global end of trial date	12 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the overall survival (OS) at 3 years after the first treatment of dose 131I-omburtamab.

Protection of trial subjects:

Thyroid protection was ensured by adequate stable iodide saturation (by use of oral potassium iodide and Cytomel). Thyroid protection was initiated one week prior to 131I-omburtamab dosimetry doses and continued until two weeks after each 131I-omburtamab treatment doses.
During the administration of omburtamab, emergency support for anaphylaxis was to be readily available, including at the bedside epinephrine, diphenhydramine, hydrocortisone and/or dexamethasone. Based upon past experience with other radiolabeled monoclonal antibody infusions, symptoms of fever, nausea, vomiting, and headache could occur in the immediate few hours post-injection. It was recommended, if any of those symptoms occured, acetaminophen, hydroxyzine, ondansetron, or Ativan could be given. Patients with myelosuppression could have received support with blood products or GCSF. In addition, if the study doctor feelt it necessary, patients could have banked stem cells reinfused.

Background therapy:

To alleviate infusion-related AEs, all subjects received premedication, including oral dexamethasone or an intravenous equivalent starting 24 hours prior to 131I-omburtamab infusion twice daily for 6 doses. Furthermore, an anti-pyretic (e.g., oral acetaminophen/paracetamol [15 mg/kg, 650 mg max]), and an antihistamine (e.g., diphenhydramine [1 mg/kg, 50 mg max]) were administered within a few hours before all intracerebroventricular infusions and as needed after infusions.

Evidence for comparator:

None

Actual start date of recruitment	05 February 2004
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	15 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 109
Worldwide total number of subjects	109
EEA total number of subjects	0

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)	7
Children (2-11 years)	99
Adolescents (12-17 years)	3
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was an open-label, non-randomized trial. 107 eligible subjects received treatment. The subjects were consecutively assigned to the currently open dose level cohort. Eligibility required that the subject met all inclusion criteria and did not violate any exclusion criterion

Pre-assignment

Screening details:

Inclusion criteria: 1. Confirmed diagnosis of a malignancy known to be omburtamab reactive. 2. CNS/ leptomeningeal disease. 3. No rapidly progressing or deteriorating neurologic examination. 4. Absolute neutrophil count (ANC) > 1000/ul and a platelet count > 50,000/ul.
Exclusion criteria: Obstructive or symptomatic communicating hydrocephalus.

Pre-assignment period milestones

Number of subjects started	109
Number of subjects completed	109

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	Overall trial

Arm description:

Single-arm dose escalation part (Part 1) and a cohort expansion part (Part 2).

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

Dosage and administration details:

In Part 1, subjects received treatment doses ranging from 10 to 70 mCi administered by intracerebroventricular infusion. In Part 2, dose escalation was closed and all subjects were treated at 50 mCi with dose reductions for children less than 1 and 3 years of age

Number of subjects in period 1	Overall trial
Started	109
Completed	61
Not completed	48
Consent withdrawn by subject	1
Excessive toxicity	4
Progressive disease	12

Not applicable	31

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description:

The median age of all SAF subjects was 4.7 years with a range of 0.9 to 15.3 years old. All dose groups were consistent with the age demographic for the neuroblastoma population. The median weight of all SAF subjects was 15.1 kg, ranging from 6.9 to 71.2 kg. The majority of the subjects in the SAF were White (78.9%). The remaining subjects were Black/African American (8.3%), Asian/ Far East/ Indian Subcontinent (2.8%), Unknown (5.5%), and Patient refused to Answer (4.6%). Most of the subjects were Not Hispanic or Latino (72.5%).

Reporting group values	overall trial	Total	
Number of subjects	109	109	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	7	7	
Children (2-11 years)	99	99	
Adolescents (12-17 years)	3	3	
Age continuous Units: years			
arithmetic mean	5.245		
standard deviation	± 2.796	-	
Gender categorical Units: Subjects			
Female	37	37	
Male	72	72	
Dose group Units: Subjects			
Dose <50 mCi	10	10	
Dose 50 mCi	94	94	
Dose >50 mCi	5	5	

Subject analysis sets

Subject analysis set title	Overall trial (full analysis)
Subject analysis set type	Full analysis

Subject analysis set description:

The long-term follow-up and efficacy were primarily concerned with the subgroup of Neuroblastoma patients.
The full analysis set (FAS) included all Neuroblastoma patients enrolled in the trial who began an infusion of the treatment dose of 131I-omburtamab. The FAS included 107 neuroblastoma subjects that had CNS/LM disease. To be included in the FAS, subjects must have had to begin an infusion of the treatment dose of 131I-omburtamab. 2 subjects did not receive the treatment dose of 131I-omburtamab and were excluded from the FAS.

Subject analysis set title	Overall trial (safety analysis)
Subject analysis set type	Safety analysis

Subject analysis set description:

The analysis of safety data was based on the safety analysis set (SAF), which included all neuroblastoma subjects enrolled in the trial who began an infusion of radiolabeled omburtamab by the enrollment cut-

off date (109 subjects).

Reporting group values	Overall trial (full analysis)	Overall trial (safety analysis)	
Number of subjects	107	109	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	7	7	
Children (2-11 years)	98	99	
Adolescents (12-17 years)	2	3	
Age continuous Units: years			
arithmetic mean	5.149	5.245	
standard deviation	± 2.645	± 2.796	
Gender categorical Units: Subjects			
Female	35	37	
Male	72	72	
Dose group Units: Subjects			
Dose <50 mCi	8	10	
Dose 50 mCi	94	94	
Dose >50 mCi	5	5	

End points

End points reporting groups

Reporting group title	Overall trial

Reporting group description:

Single-arm dose escalation part (Part 1) and a cohort expansion part (Part 2).

Subject analysis set title	Overall trial (full analysis)
Subject analysis set type	Full analysis

Subject analysis set description:

The long-term follow-up and efficacy were primarily concerned with the subgroup of Neuroblastoma patients.
The full analysis set (FAS) included all Neuroblastoma patients enrolled in the trial who began an infusion of the treatment dose of 131I-omburtamab. The FAS included 107 neuroblastoma subjects that had CNS/LM disease. To be included in the FAS, subjects must have had to begin an infusion of the treatment dose of 131I-omburtamab. 2 subjects did not receive the treatment dose of 131I-omburtamab and were excluded from the FAS.

Subject analysis set title	Overall trial (safety analysis)
Subject analysis set type	Safety analysis

Subject analysis set description:

The analysis of safety data was based on the safety analysis set (SAF), which included all neuroblastoma subjects enrolled in the trial who began an infusion of radiolabeled omburtamab by the enrollment cut-off date (109 subjects).

Primary: Evaluate overall survival at 3 years

End point title	Evaluate overall survival at 3 years[1]

End point description:

Overall survival, defined as the time from first date of diagnosis of CNS relapse to the date of death. The survival time was calculated from the date of first diagnosis of CNS relapse until the date of death (event) or until the latest date confirmed alive (censored observation).

End point type	Primary

End point timeframe:

The survival rate at 3 years including its 95% confidence interval.
Additionally, the median OS time was estimated, and 95% confidence intervals were calculated.

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: This is a single arm study with no comparison groups.

End point values	Overall trial	Overall trial (full analysis)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	107	107		
Units: probability	107	107		

Attachments (see zip file)	Summary of Survival of Subjects in the FAS/Table 11.1.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: CNS/LM progression-free survival (PFS) at 12 months

End point title	CNS/LM progression-free survival (PFS) at 12 months

End point description:

CNS/LM PFS time was calculated from the date of first dose of omburtamab until the date of CNS/LM progression or death (event) or until the latest date confirmed to be progression-free (censored observation).

End point type	Secondary

End point timeframe:

Central nervous system/leptomeningeal (CNS/LM) progression-free survival (PFS) was estimated using similar methods as overall survival (OS) with events defined by CNS/LM progression or death.

End point values	Overall trial	Overall trial (full analysis)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	107	107		
Units: probability	107	107		

Attachments (see zip file)	Summary of CNS/LM Progression-Free Survival/Table 11.2.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluate long term safety

End point title	Evaluate long term safety

End point description:

Full safety and efficacy information collected in neuroblastoma subjects up to the cut-off date of 30 June 2019, with an exception for long-term follow-up data (i.e., survival, 12 March 2020). Long-term follow up data were collected as available.

End point type	Secondary

End point timeframe:

Long term safety was evaluated up to 15 years.

End point values	Overall trial	Overall trial (safety analysis)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	107	107		
Units: Probability	107	107		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics and dosimetry after first dosimetry dose

End point title	Pharmacokinetics and dosimetry after first dosimetry dose

End point description:

Dosimetry and PK will be summarized with descriptive statistics (n, mean, median, SD, minimum, maximum)

End point type	Secondary

End point timeframe:

After first dosimetry dose

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Descriptive				
arithmetic mean (standard deviation)	1.93 (± 0.718)			

Attachments (see zip file)	Summary of pharmacokinetiscs/Summary of pharmacokinetics.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the trial	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1
Reporting groups	
Reporting group title	Safety Analysis set
Reporting group description:	
Summary of treatment emergent adverse events reported for subjects in the safety analysis set	

Serious adverse events	Safety Analysis set		
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 109 (48.62%)		
number of deaths (all causes)	57		
number of deaths resulting from adverse events	0		
Investigations			
Platelet count decreased			
subjects affected / exposed	23 / 109 (21.10%)		
occurrences causally related to treatment / all	21 / 26		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	13 / 109 (11.93%)		
occurrences causally related to treatment / all	12 / 13		
deaths causally related to treatment / all	0 / 0		
White blood cell count decreased			
subjects affected / exposed	8 / 109 (7.34%)		
occurrences causally related to treatment / all	8 / 9		
deaths causally related to treatment / all	0 / 0		
Haemoglobin decreased			
subjects affected / exposed	5 / 109 (4.59%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			

subjects affected / exposed	4 / 109 (3.67%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	3 / 109 (2.75%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Acute myeloid leukaemia			
subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Meningitis chemical			
subjects affected / exposed	3 / 109 (2.75%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorder			

subjects affected / exposed	2 / 109 (1.83%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	2 / 109 (1.83%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Depressed level of consciousness				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrospinal fluid leakage				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Immune thrombocytopenic purpura				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphopenia				
subjects affected / exposed	2 / 109 (1.83%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	1 / 109 (0.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	2 / 109 (1.83%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 109 (2.75%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 109 (0.92%)		
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	2 / 109 (1.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastric infection			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infectious colitis			
subjects affected / exposed	2 / 109 (1.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	1 / 109 (0.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 109 (0.92%)		
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	Safety Analysis set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	102 / 109 (93.58%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm			
subjects affected / exposed	6 / 109 (5.50%)		
occurrences (all)	6		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	15 / 109 (13.76%)		
occurrences (all)	17		
Fatigue			
subjects affected / exposed	6 / 109 (5.50%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	29 / 109 (26.61%)		
occurrences (all)	31		
Rhinorrhoea			
subjects affected / exposed	18 / 109 (16.51%)		
occurrences (all)	19		
Psychiatric disorders			
Irritability			

subjects affected / exposed	8 / 109 (7.34%)		
occurrences (all)	10		
Investigations			
Platelet count decreased			
subjects affected / exposed	59 / 109 (54.13%)		
occurrences (all)	296		
White blood cell count decreased			
subjects affected / exposed	51 / 109 (46.79%)		
occurrences (all)	223		
Neutrophil count decreased			
subjects affected / exposed	47 / 109 (43.12%)		
occurrences (all)	157		
Haemoglobin decreased			
subjects affected / exposed	33 / 109 (30.28%)		
occurrences (all)	81		
Alanine aminotransferase increased			
subjects affected / exposed	7 / 109 (6.42%)		
occurrences (all)	11		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	23 / 109 (21.10%)		
occurrences (all)	30		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	8 / 109 (7.34%)		
occurrences (all)	8		
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 109 (24.77%)		
occurrences (all)	38		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	70 / 109 (64.22%)		
occurrences (all)	454		
Eye disorders			

Eye disorder subjects affected / exposed occurrences (all)	6 / 109 (5.50%) 6		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all)	 38 / 109 (34.86%) 64 18 / 109 (16.51%) 29 12 / 109 (11.01%) 14 12 / 109 (11.01%) 13 7 / 109 (6.42%) 7		
Skin and subcutaneous tissue disorders Petechiae subjects affected / exposed occurrences (all)	 7 / 109 (6.42%) 8		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	 10 / 109 (9.17%) 11		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypokalemia subjects affected / exposed occurrences (all)	 16 / 109 (14.68%) 16 7 / 109 (6.42%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 February 2005	• "Hyperglycemia or myelosuppression" was added to the toxicities excluded as criteria for removal from study and as criteria not to receive the second injection • Immunofluorescence of bone marrow was added as a method to confirm 8H9 expression
27 April 2005	Perchloracap was removed from the market, all references to this drug were removed
14 September 2005	• Added to pretreatment: HAMA testing recommended for patients with prior antibody exposure
25 October 2006	• Patients registered to assessment part only – no SAEs will be reported
22 August 2007	• Incorporation of 124I-8H9 instead of 131I-8H9 for dosimetry • Dose escalation 60-100 mCi/injection as no DLT was seen at 10-50 mCi. • Decrease in the cognitive function added as a long-term risk
10 December 2008	Language updated to note: • Patients with non-neuroblastic tumors would be treated at the dose escalating schema and patients with Neuroblastoma would be treated with 50 mCi • Patients could be treated either in an outpatient setting or admitted to the hospital for treatment
25 February 2009	• Increase the total accrual from 35 patients to 60 patients to reach the 100 mCi maximum dose and to accommodate for neuroblastoma patients, who may continue to be registered at the 50 mCi dose
27 January 2010	• 20 patients added to accrual to accommodate for the additional patients treated on cohorts above 60 mCi and patients with no reserved stem cells that will be treated at 50 mCi • Patients who did not have stored stem cells available would be treated at a dose of 50 mCi • Observation period was changed from 4 weeks to 3 weeks • For safety reasons, doses of 70 mCi and higher were expanded to 6 patients • Language was clarified so Grade 3 or 4 myelosuppression was not a reason to be removed from study • Explanation of MTD and DLT was changed since cohort for doses 70 mCi and higher was changed to 6 patients
26 January 2011	• Treatment stopped including dosimetry dose with 124I-8H9. Protocol used 131I-8H9 for the dosimetry dose through Amendment 6, but was changed to 124I-8H9 in Amendment 7.
12 October 2011	• Note that only neurotoxicity would be counted as a DLT • Clarification that patients treated at 50 mCi will not be counted for DLTs since there were already 3 patients treated on this dose level without experiencing DLT • A new possible side effect was added: drug extravasation
01 September 2016	• As per IRB Policy the informed consent may be delivered by mail and the consent interview can be conducted by telephone with IRB approval

12 July 2017	• Addition of neurocognitive and QOL assessment measures • Hama testing and RT-PCR testing removed • Eligibility updated to include patients diagnosed with an Embryonal tumor do not require immunohistochemical staining of tumor • Language updated to clarify when patients come off treatment, they will remain on study for life
11 April 2018	• Sponsor name changed to Y-mAbs • 8H9 name changed to burtomab
08 October 2019	• Compound name was updated to 131I-omburtamab

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.

None reported

Notes: