^{131}I-Omburtamab for CNS/LM Metastases From Neuroblastoma

U.S. Food & Drug Administration

October 28, 2022

Y-mAbs Therapeutics, Inc.

Introduction

Rikke Valentin Oxholm Lillesø, Vice President Regulatory Affairs

Thomas Gad, Founder

Y-mAbs Therapeutics

Introduction to Y-mAbs

"My goal is to have these antibodies available worldwide, so that everyone has the same options my daughter and family had."

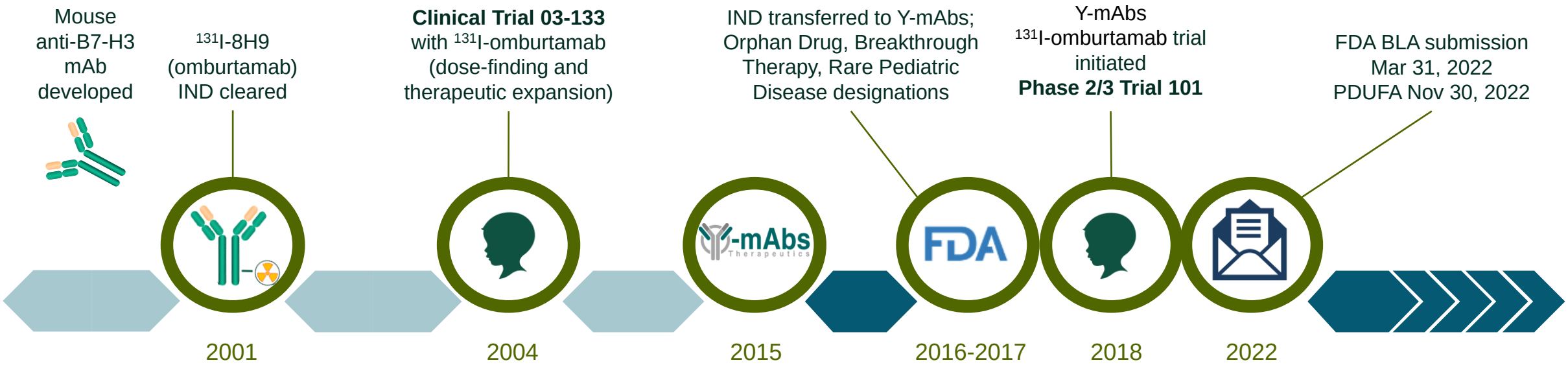
Thomas Gad,
Founder of Y-mAbs, 2015

Daniella Gad
Long-term survivor of
high-risk neuroblastoma

History of ^{131}I-Omburtamab Clinical Development

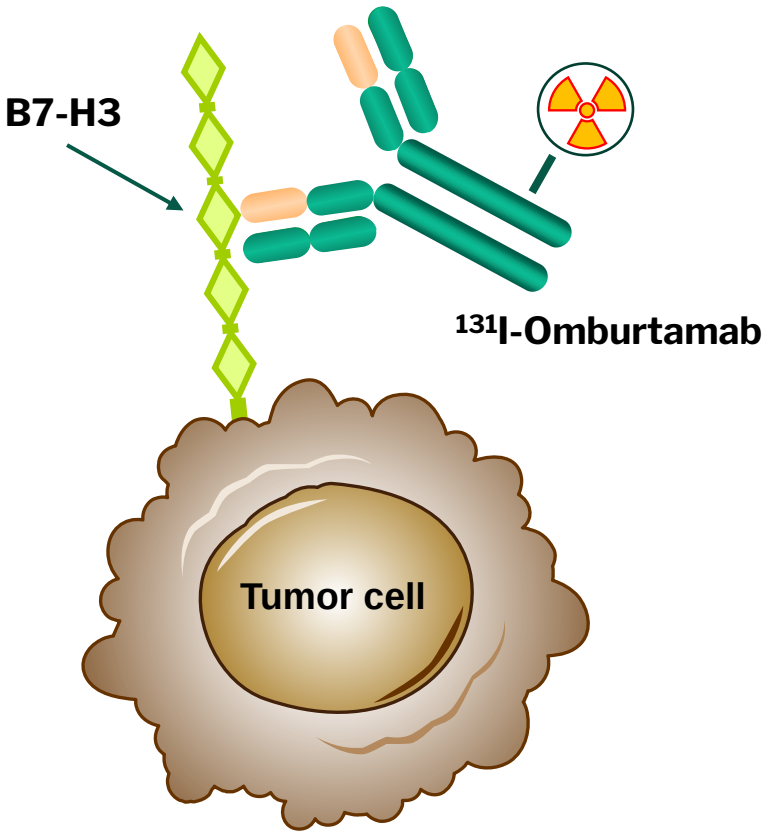
Initial development: MSKCC (NY, USA)

Y-mAbs worldwide exclusive license with MSKCC for commercial development of ^{131}I-omburtamab



Abs=antibodies; BLA=Biologics License Application; IND=Investigational New Drug; mAb=monoclonal antibody; MSKCC=Memorial Sloan Kettering Cancer Center.

Mode of Action for ^{131}I-Omburtamab: Radiolabeled Anti-B7-H3 Monoclonal Antibody

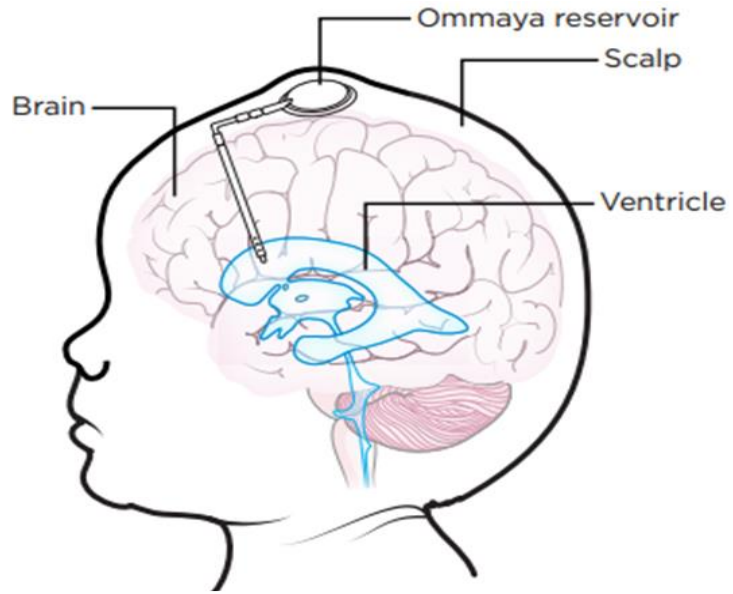


- Binds transmembrane protein B7-H3
- B7-H3 is highly overexpressed in a wide range of human solid tumors, including neuroblastoma
  - Minimal expression in normal tissues
- Beta-emission from iodine-131 induces cellular damage and tumor cell death
  - Tumor-specific localized radiation
- Targets and destroys measurable or micrometastatic central nervous system disease

Modak S, et al. *Cancer Res*. 2001;61:4048-4054.

^{131}I-Omburtamab: Compartmental Radioimmunotherapy (cRIT)

- Delivered directly into the ventricle via an Ommaya reservoir
- Cerebral spinal fluid flow functions as a conduit for delivery to all tumor sites



Administration of radiolabeled omburtamab via Ommaya reservoir

Image reprinted from Frequently Asked Questions About Ommaya Reservoirs and Ommaya Taps for Pediatric Patients. Accessed September 22, 2022. https://www.mskcc.org/cancer-care/patient-education/faq-about-ommaya-reservoirs-and-ommaya-taps-pediatric

^{131}I-Omburtamab: Clinical Trials Included in the BLA

Trial 03-133
Initiated by MSKCC

- Initiated 2004
- Single center at MSKCC
- Dose escalation + expansion into confirmatory trial
- 109 neuroblastoma patients

Trial 101
Initiated by Y-mAbs

- Initiated December 2018 (ongoing)
- International, multicenter trial
- Supporting efficacy and reproducibility at multiple sites
- 50 neuroblastoma patients

Proposed Indication & Dosing

- Proposed Indication:

  OMBLASTYS is indicated for the treatment of central nervous system (CNS)/leptomeningeal (LM) metastases in pediatric patients with neuroblastoma following standard multimodality treatment for CNS disease.

- Dosage:

  Two age-based doses administered 4 weeks apart

  - Age <1 year: 25.0 mCi
  - Age 1 to <3 years: 33.5 mCi
  - Age ≥ 3 years: 50.0 mCi

What You Will Hear Today

Unmet Need	• Neuroblastoma with CNS/LM metastases is a rare disease with a high unmet need • Associated with a poor prognosis despite multimodal treatment • No treatments currently approved for CNS/LM neuroblastoma
Efficacy	• In consultation with FDA, we defined an external control arm for comparison to Trial 03-133 • Clinically meaningful 42% improvement in OS compared to the external control arm • Results of Trial 101 are consistent and supportive for OS and PFS and demonstrated single-agent activity
Safety	• Most common AEs were lab abnormalities related to myelosuppression and were manageable
Benefit/Risk	• The totality of data demonstrates substantial evidence of effectiveness and a positive benefit/risk profile in the context of this rare and life-threatening disease with a clear unmet medical need

Agenda

Introduction	Rikke Valentin Oxholm Lillesø Y-mAbs Therapeutics
Disease Background & Unmet Need	Kim Kramer, MD Memorial Sloan Kettering Cancer Center
Efficacy	Vignesh Rajah, MD René dePont Christensen, MSc, PhD Y-mAbs Therapeutics
Safety	Vignesh Rajah, MD Y-mAbs Therapeutics
Clinical Perspective	Daniel A. Morgenstern, MB BChir, PhD Hospital for Sick Children, Toronto

Disease Background & Unmet Need

Kim Kramer, MD

Attending, Memorial Sloan Kettering Cancer Center

Professor of Pediatrics, Weill-Cornell Medical Center

Director, Faculty Development and Wellness

New York, New York

Children With CNS/LM Have a Dismal Prognosis

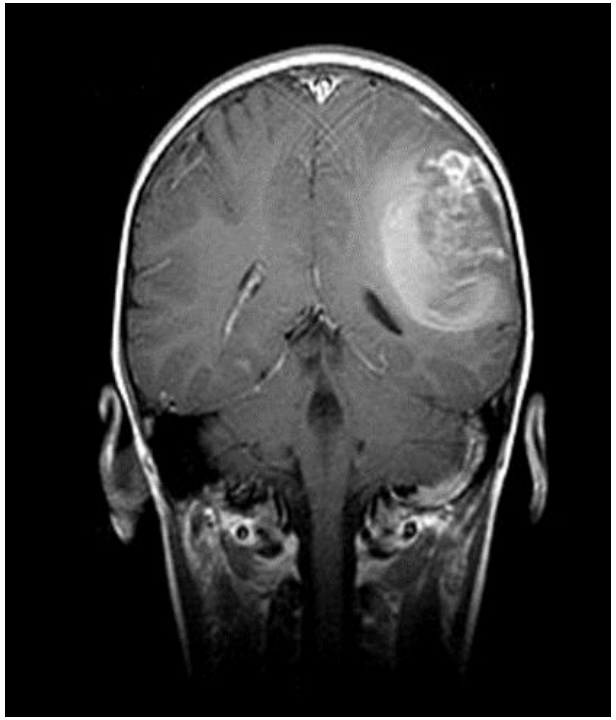


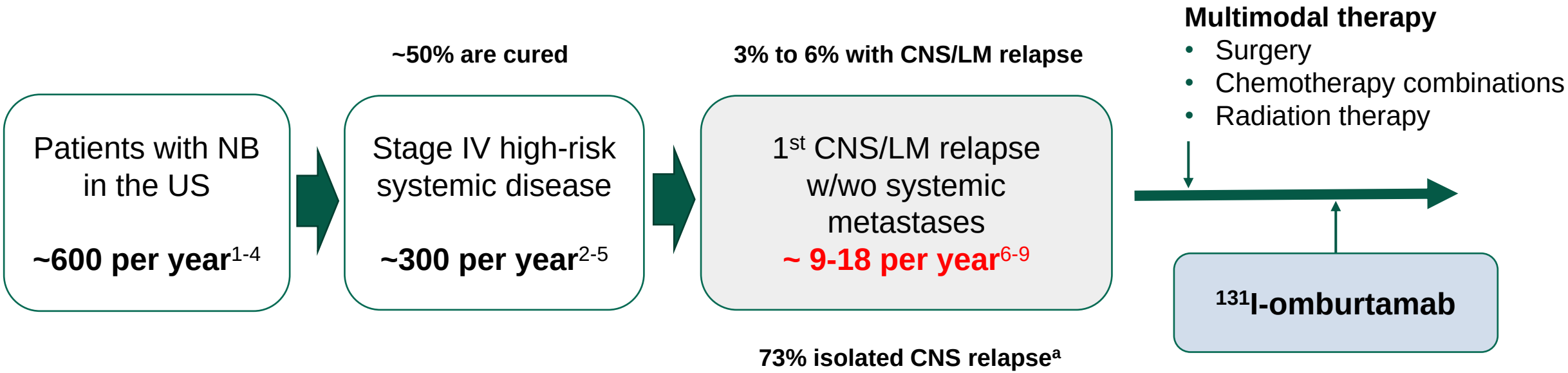
Image courtesy of MSKCC

Bulky Hemorrhagic Parenchymal Metastasis of Neuroblastoma

- Neuroblastoma is a rare embryonal tumor
  - ~6% of childhood cancers
  - Average age at diagnosis: 1-2 years
- A small proportion of patients develop CNS/LM metastases
  - Symptoms include headaches, nausea, vomiting, double vision, focal neurologic deficit, and seizures
  - Most patients ultimately die of their disease

https://www.cancer.net/cancer-types/neuroblastoma-childhood/statistics

CNS/LM Is an Ultra-Rare Disease With No Approved Targeted Treatments



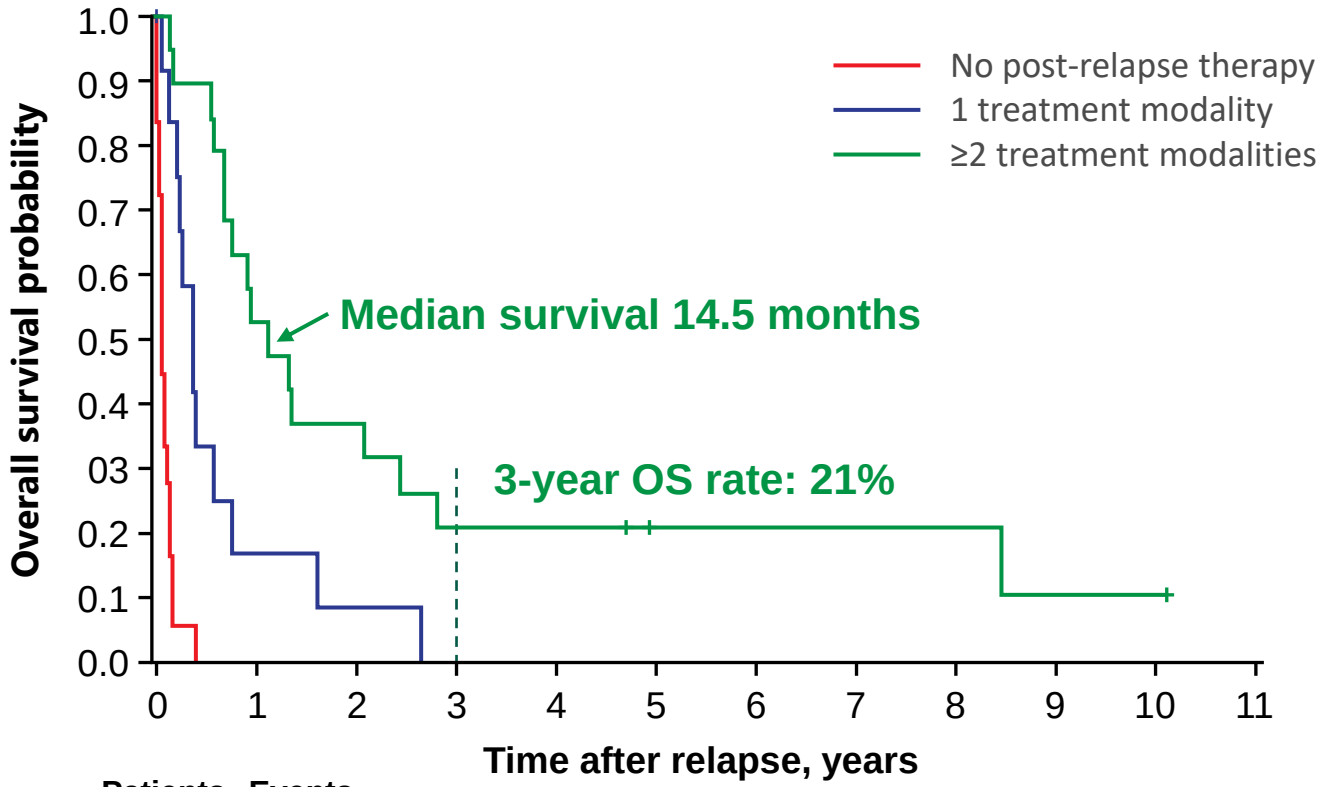
[a] Based on data from Trials 03-133 and 101.

1. Berthold F, et al *Pediatr Drugs*. 2017;19:577-593; 2. Gutierrez JC, et al. *Pediatr Surg Int*. 2007;23(7):637-634; 3. Schroeder H, et al. *Br J Cancer*. 2009;100(5):853-857; 4. Tas ML, et al. *Eur J Cancer*. 2020;124:47-55; 5. Pinto NR, et al. *J Clin Oncol*. 2015;33(27):3008-3017; 6. Kramer K, et al. *Cancer*. 2001;91(8):1510-1519; 7. Matthay KK, et al. *Cancer*. 2003;98(1):155-165; 8. Berlanga P, et al. *Eur J Cancer*. 2021;144:1-8; 9. Hu H, et al. *Clin Neurol Neurosurg*. 2019;184:105372.

Multimodal Therapy Improves OS in Patients at First Recurrence, But Outcomes Remain Poor

European International Society of Pediatric Oncology Neuroblastoma Group (SIOPEN, 2021)

- Among 53 patients at first recurrence, **median OS = 4 months (range, 0-82 months)** from CNS relapse to death
- **Overall 3-year OS rate = 8%**



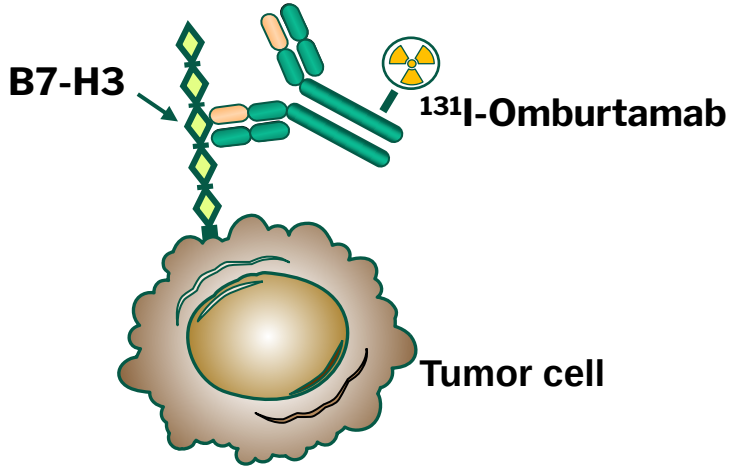
Reprinted from *Eur J Cancer*, 144, Berlanga P, et al, Central nervous system relapse in high-risk stage 4 neuroblastoma: the HR-NBL1/SIOPEN trial experience, 1-8, Copyright 2021, with permission from Elsevier.

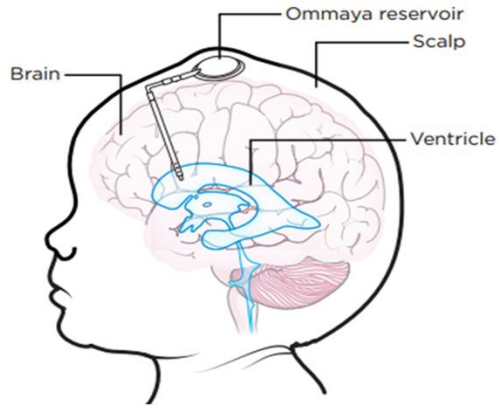
The CNS Sanctuary Site Can Be Addressed

Surgery

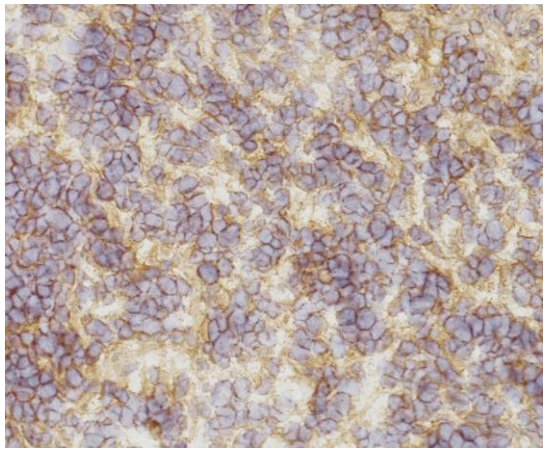
Chemotherapy combinations

Radiation therapy





B7-H3 staining of NB



Antibody linked to radio-isotope directly targets and kills tumor cells in the CNS

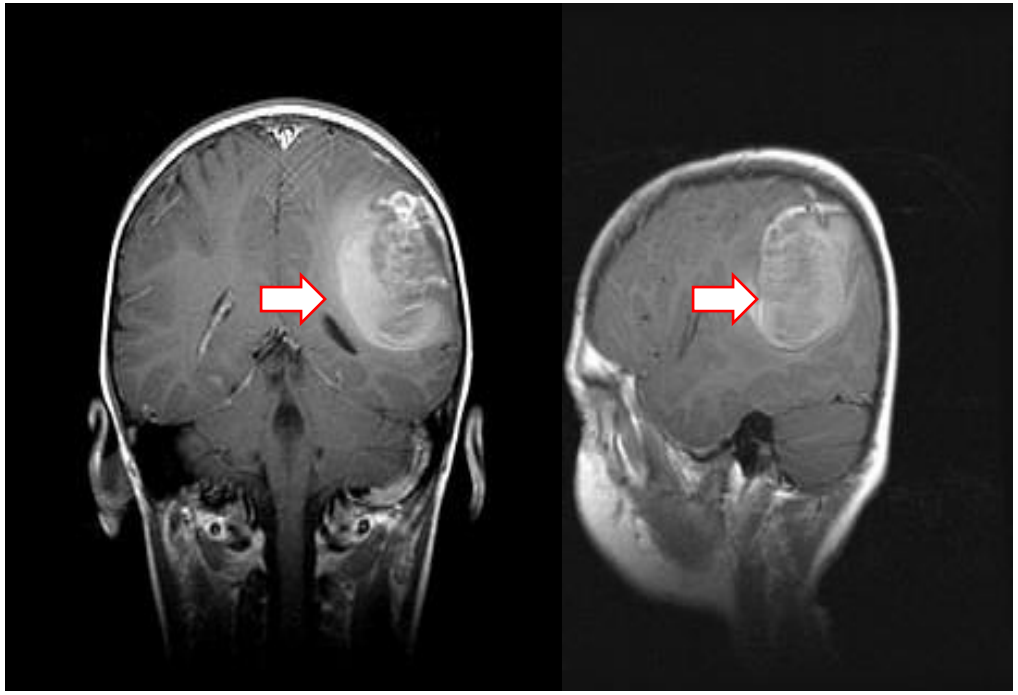
GOAL: Eradicate residual or micrometastatic CNS disease to increase chance of cure

Kramer K, et al. *Pediatr Blood Cancer*. 2014;61(9):1590-1592.

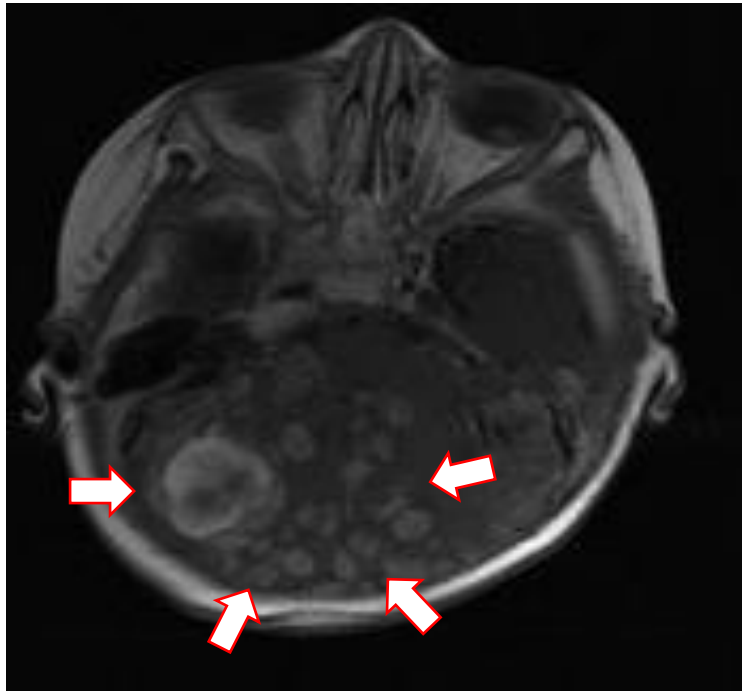
Far-right image reprinted from Frequently Asked Questions About Ommaya Reservoirs and Ommaya Taps for Pediatric Patients. Accessed September 22, 2022. https://www.mskcc.org/cancer-care/patient-education/faq-about-ommaya-reservoirs-and-ommaya-taps-pediatric

Compartmental Radioimmunotherapy Targets Parenchymal Lesions and Micrometastatic Disease

Unifocal CNS NB



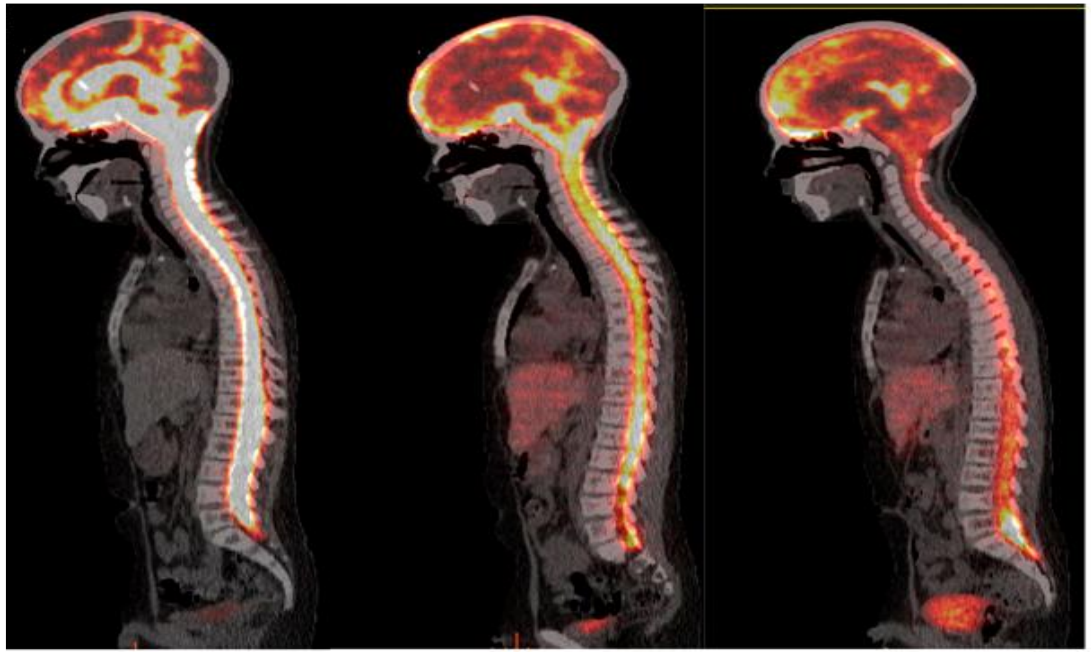
Multifocal CNS NB



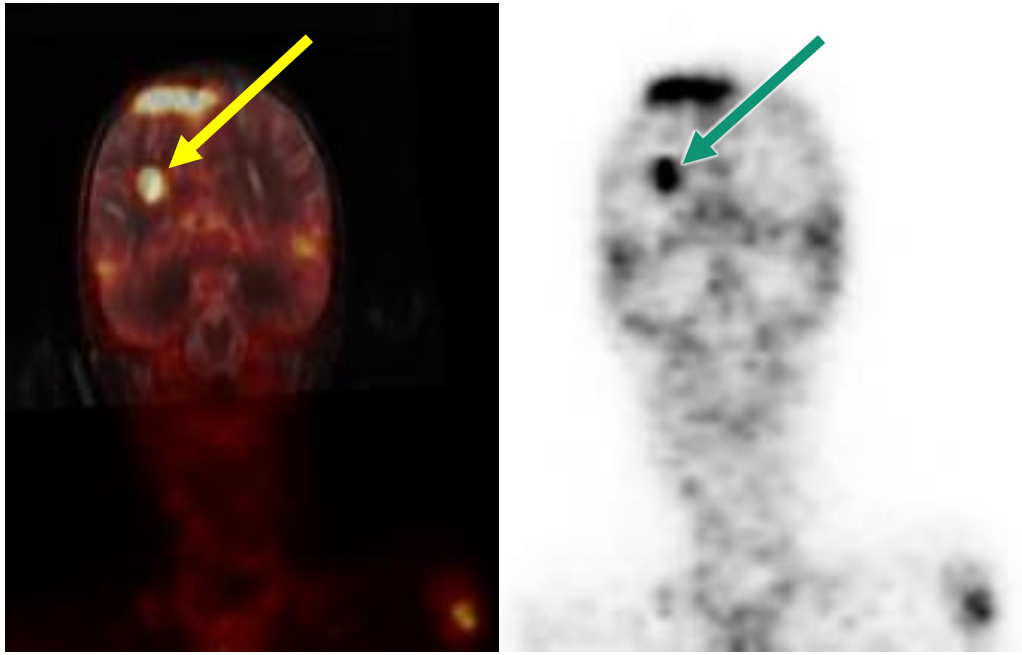
Images courtesy of MSKCC

^{131}I-Omburtamab Is Distributed Throughout CNS and Penetrates Parenchymal Tumors

The radiolabeled antibody is distributed throughout the entire CSF, delivering β radiation directly to tumor cells in the CNS and leptomeninges



Distribution of ^{124}I-Omburtamab 2, 24, and 48 hours



Images courtesy of MSKCC

Penetration of Radiolabeled Omburtamab Into a Parenchymal Frontal Parietal Lesion

Left-hand images reprinted from Pandit-Taskar N, et al. *J Nucl Med*. 2019;60(12):1794-1801.

Convenient Administration in the Outpatient Setting

Image courtesy of MSKCC

- Delivered by physician or nurse practitioner
- Children as young as 6 months
- Patients are awake
- Patients can often go home later the same day

Conclusions

- CNS neuroblastoma is devastating disease with a dismal prognosis despite all conventional treatment multimodalities
- Improved systemic therapies highlight CNS as a sanctuary site that poses an impediment to cure for this rare subset of children with CNS neuroblastoma
- No targeted CNS-directed therapy approved
- High unmet need for effective agents to supplement existing treatment modalities
- Compartmental radioimmunotherapy is feasible with a predictable and manageable adverse event profile
- ^{131}I-Omburtamab can improve overall survival and increase chance of cure

Why We Are Here Today

Image courtesy of MSKCC

Y-mAbs Therapeutics, Inc.

Efficacy

Vignesh Rajah, MD
Chief Medical Officer
Y-mAbs Therapeutics

Clinical Development of ^{131}I-Omburtamab for CNS/LM Metastases From Neuroblastoma

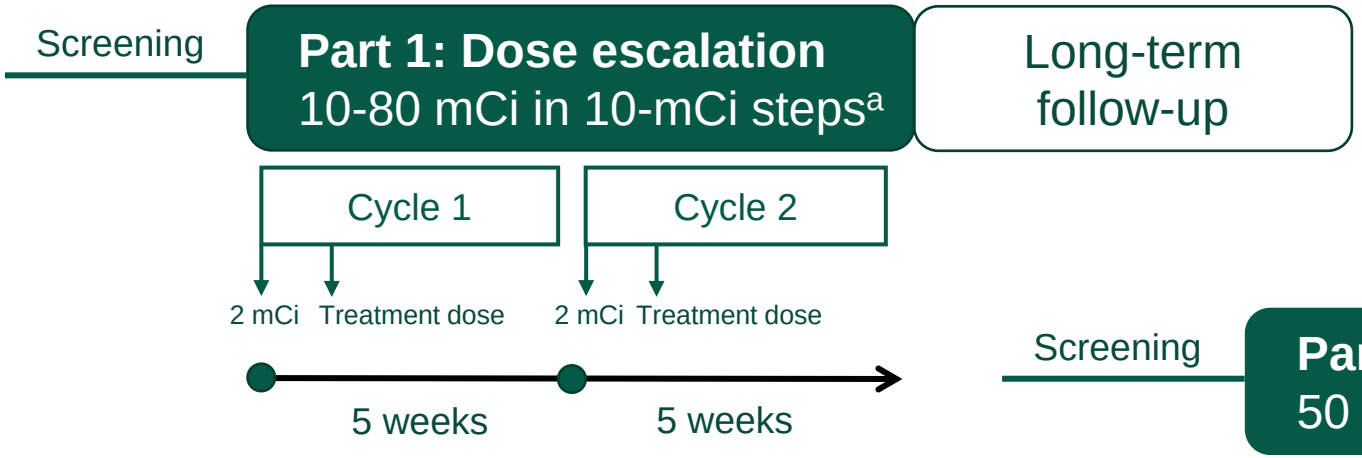
Trial 03-133 MSKCC initiated

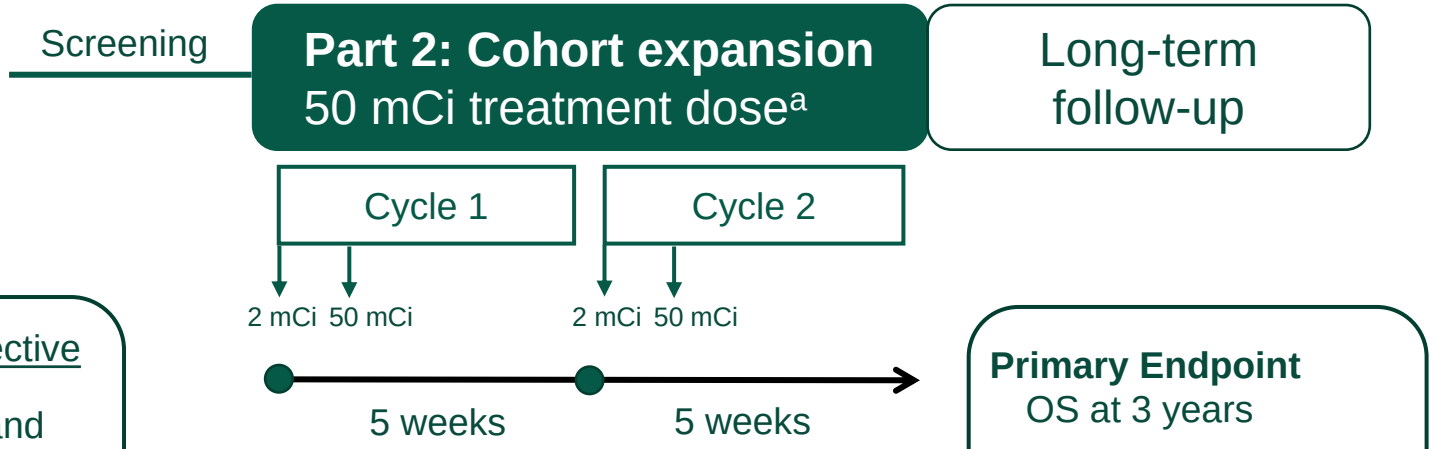
- Single-center trial initiated in 2004 at MSKCC
- 109 NB patients with CNS/LM metastases
- Enrolment over 14 years

Trial 101 Y-mAbs initiated

- International multicenter trial initiated in Dec 2018
- 50 NB patients with CNS/LM metastases – enrollment ongoing

Design of Trial 03-133 (Pivotal Trial)





Part 1 – Primary Objective

To define clinical toxicities of ^{131}I-omburtamab and determine maximum tolerated dose for Part 2

Part 2 – Primary Objective

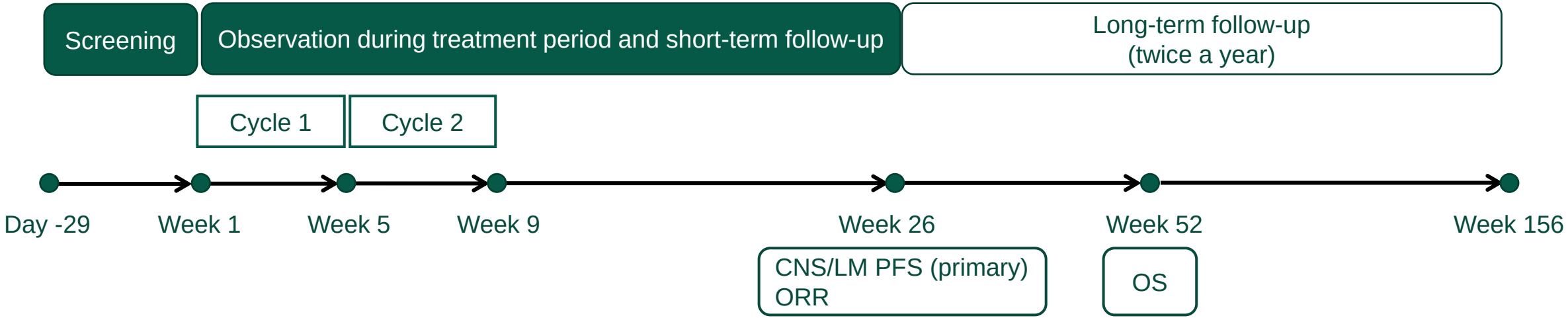
To evaluate efficacy and safety of ^{131}I-omburtamab

Primary Endpoint
OS at 3 years

Secondary Endpoint
CNS/LM PFS at 12 months

[a] Treatment dose was reduced depending on age.

Design of Global Multicenter Trial 101



Primary Endpoint

CNS/LM PFS at 6 months

Secondary Endpoint

- OS at 12 months
- ORR at 6 months

Additional Endpoints

- Safety
- Pharmacokinetics
- Dosimetry

Trial sites

- US (5 sites) - MSKCC, CHLA, Nationwide Children's, Riley Hospital for Children, MDACC
- Spain (1 site)
- Denmark (1 site)
- Japan (1 site)

Key Inclusion and Exclusion Criteria

Trial 03-133	Trial 101
Inclusion	**Inclusion**
High-risk NB or histologically confirmed omburtamab-reactive malignancy with CNS/LM disease[a]	NB with relapse in the CNS/LM
May have active systemic disease outside CNS	Stable systemic disease not requiring chemo/immunotherapy
Age: any	Age: 0 to 18 years of age
Exclusion	**Exclusion**
Obstructive or symptomatic communicating hydrocephalus	Obstructive or symptomatic communicating hydrocephalus
Uncontrolled life-threatening infection	Uncontrolled life-threatening infection
Rapidly progressing or deteriorating neurologic examination	Worsening of neurologic function according to assessment by investigator
Prior cranial or spinal irradiation or systemic chemotherapy <3 weeks before study entry	Prior cranial or spinal irradiation or systemic chemo/immunotherapy <3 weeks prior to first dose of omburtamab
	Primary neuroblastoma in CNS

[a] Refractory to conventional therapies or no conventional therapy exists.

Baseline Characteristics

Trial 03-133 and Trial 101 - Full Analysis Set

Characteristic	Trial 03-133 (N=107)	Trial 101 (N=50)
Median age, years (range)	4.7 (0.85-13)	4.0 (0-11)
Mean body weight, kg	17.3	17.6
Sex, %		
Male	67	58
Female	33	42
Race, %		
White	79	76
Black or African American	8	2
Asian	3	14
American Indian or Alaska Native	0	2
Unknown/Other	10	6

Disease Characteristics

Trial 03-133 and Trial 101 - Full Analysis Set

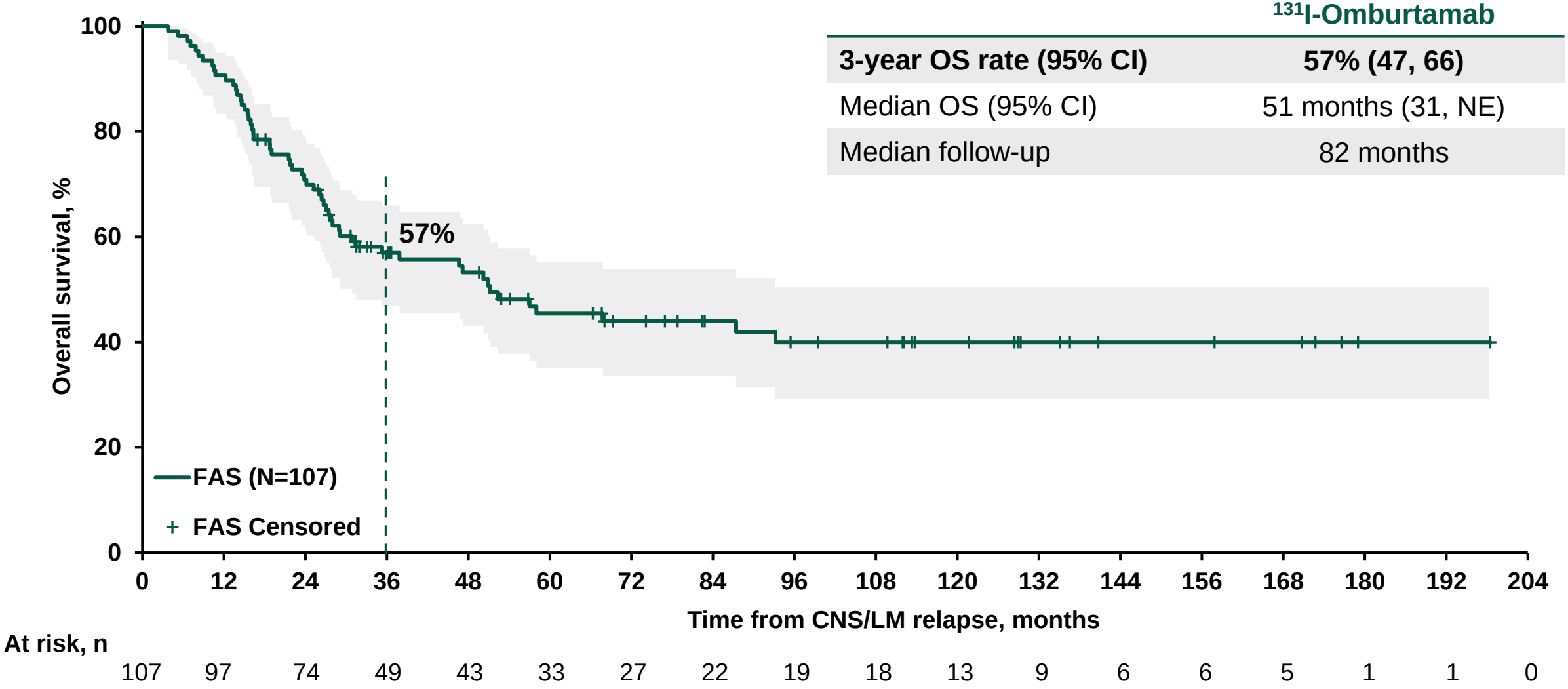
Characteristics	Trial 03-133 (N=107)	Trial 101 (N=50)
Site of metastases at CNS/LM relapse, %		
Unifocal PM	48	—
Multifocal PM	15	—
LM	9	—
PM + LM	8	—
Unknown	10	—
Not reported	9	—
Site of CNS/LM metastases at treatment baseline, %		
PM	—	10
LM	—	12
PM + LM	—	16
PM/LM[a]	—	2
No evaluable LM/PM disease	—	60
***MYCN* amplification, %**	51	42
Prior therapy for CNS/LM metastases, %		
Surgery	78	74
Radiotherapy	92	92
Chemotherapy	100	92

[a] Lesion at baseline: By independent radiologists. If not adjudicated, then the Radiologist 1 and Radiologist 2 results have been concatenated with a slash.

Overall Survival

Trial 03-133 - Full Analysis Set

	^{131}I-Omburtamab
3-year OS rate (95% CI)	**57% (47, 66)**
Median OS (95% CI)	51 months (31, NE)
Median follow-up	82 months

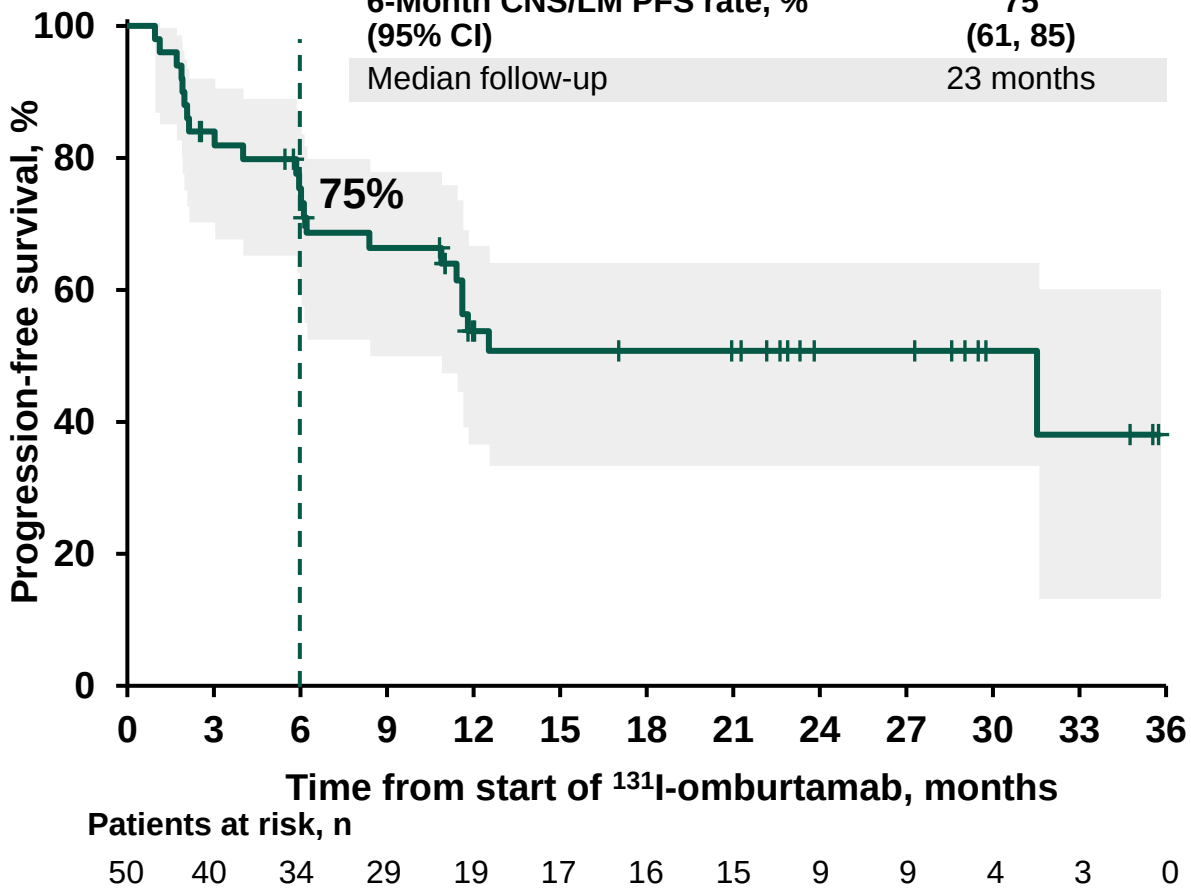


Progression-Free and Overall Survival From Start of ^{131}I-Omburtamab

Trial 101 (N=50)

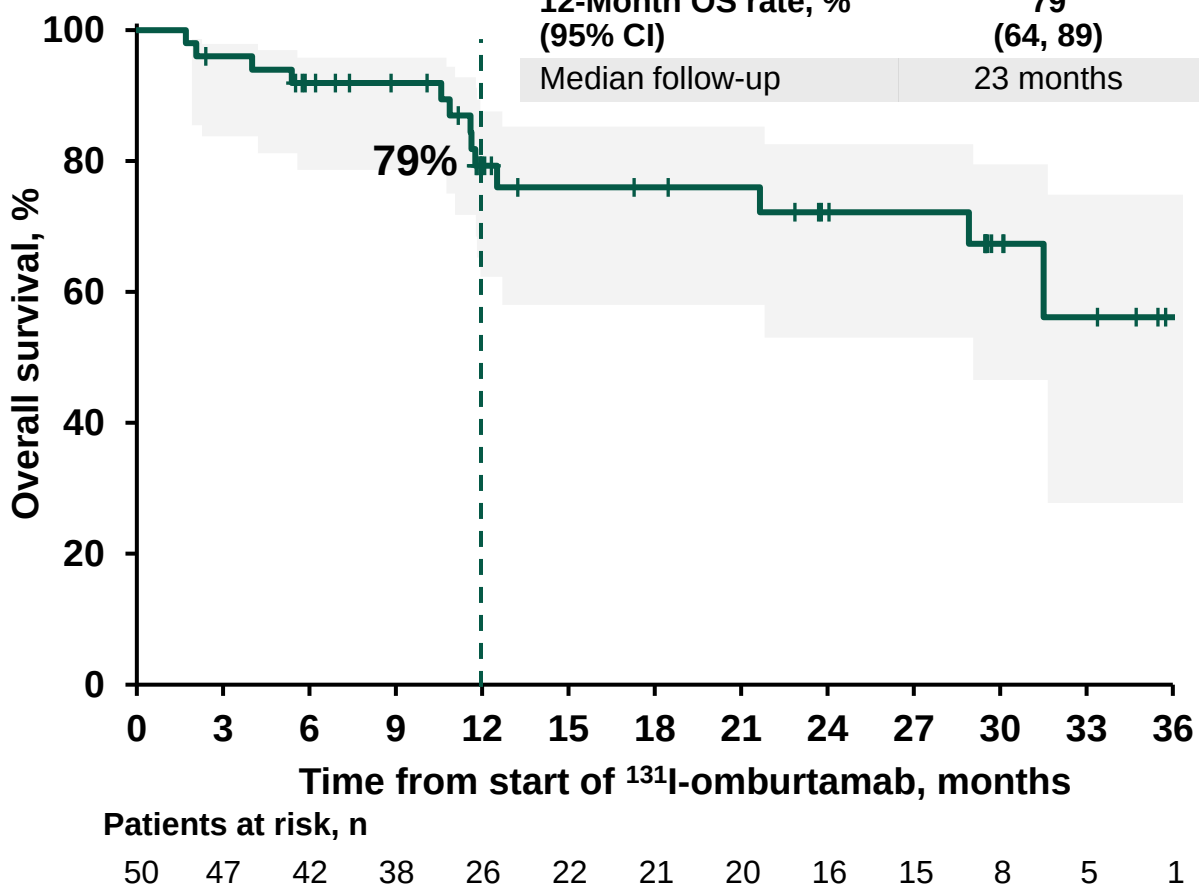
CNS/LM Progression-Free Survival

	^{131}I-Omburtamab
Progression or death event, n (%)	23 (46)
6-Month CNS/LM PFS rate, % (95% CI)	**75 (61, 85)**
Median follow-up	23 months



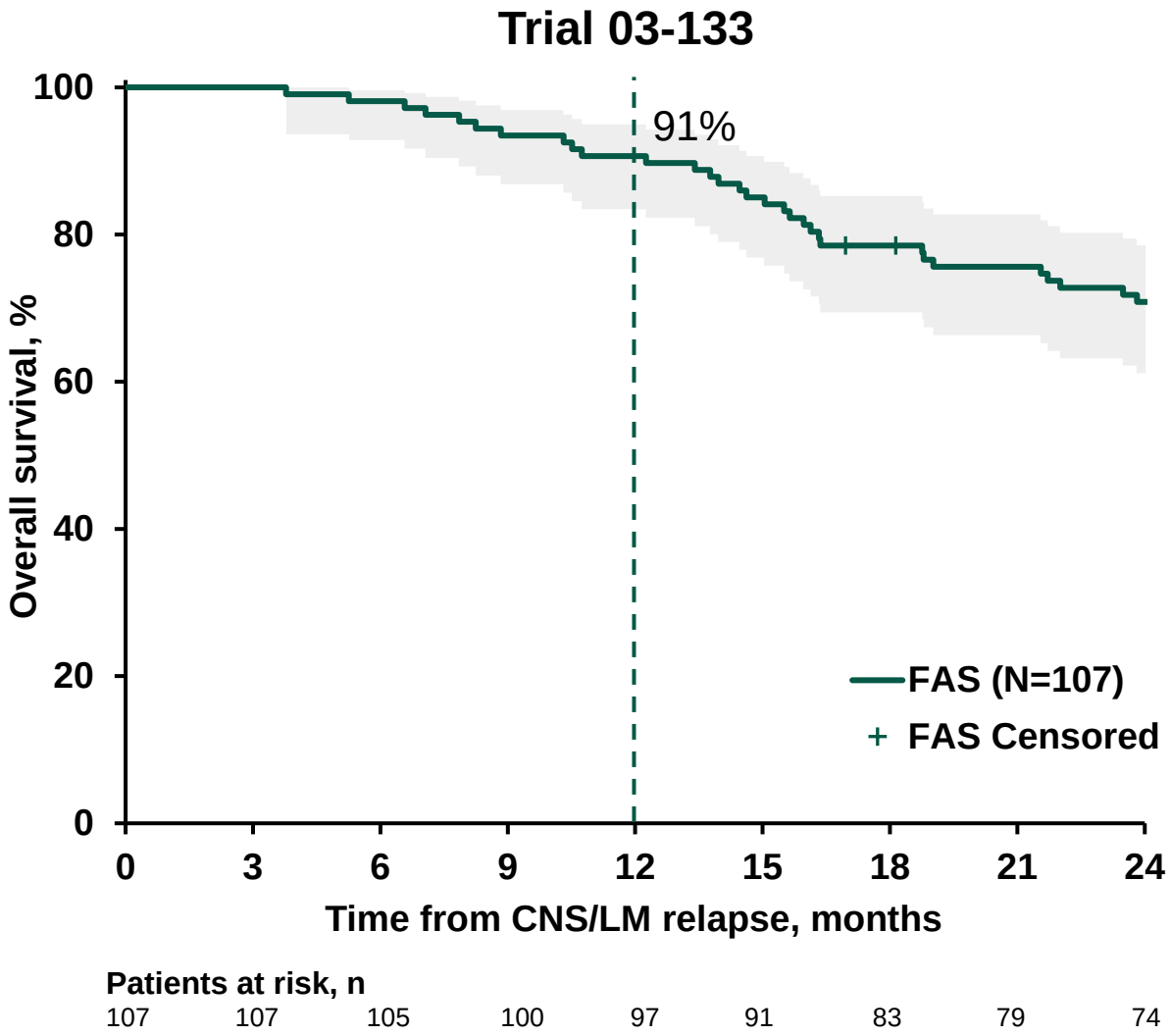
Overall Survival

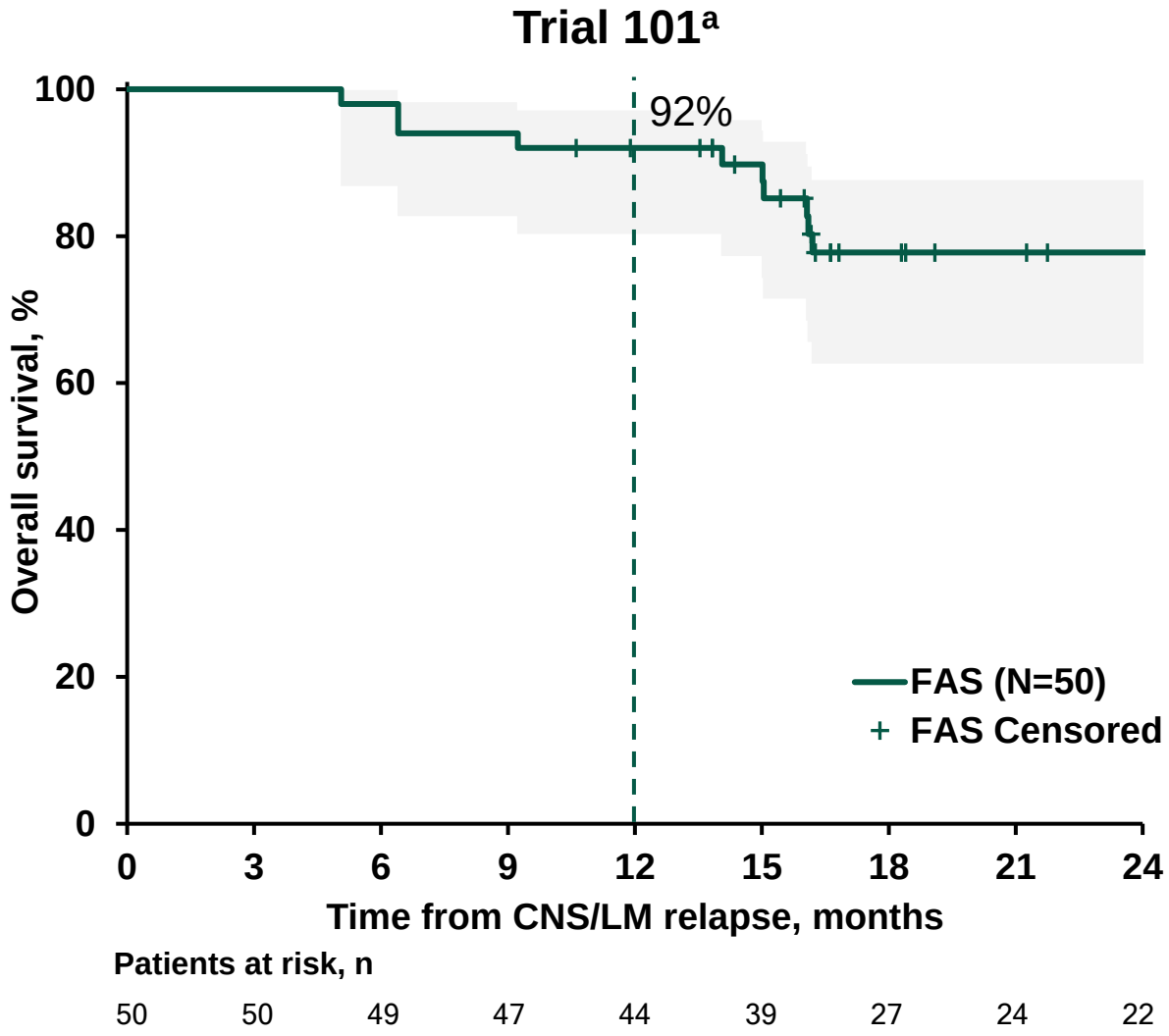
	^{131}I-Omburtamab
Death event, n (%)	13 (26)
12-Month OS rate, % (95% CI)	**79 (64, 89)**
Median follow-up	23 months



Similar Overall Survival Outcomes

Trial 03-133 and Trial 101





[a] Not a prespecified analysis.

Objective Response

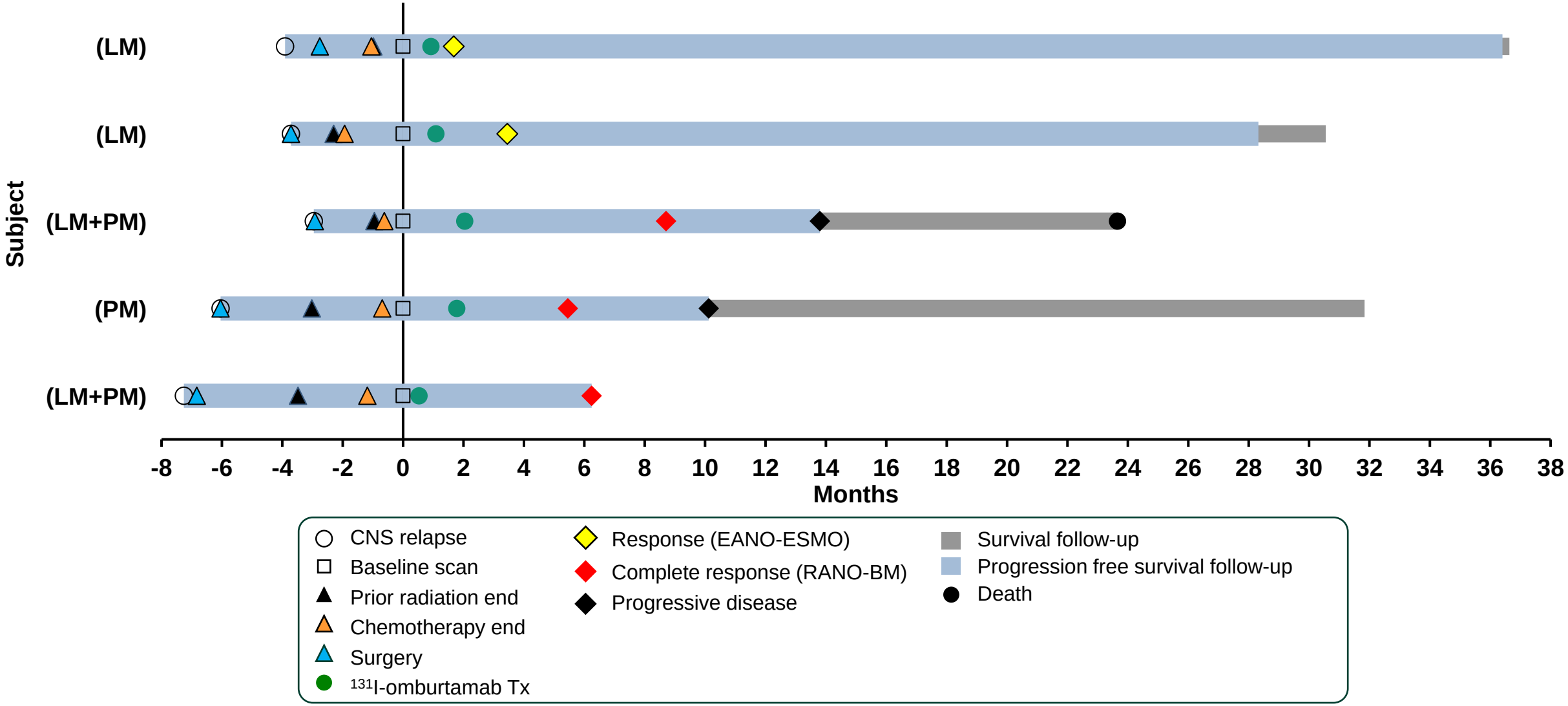
Trial 101

Up to Week 26	Patients, n (%)
Patients with evaluable disease at baseline	**20**
Objective response[a] [95% CI]	**7 (35) [15, 59]**
Best overall response	
Complete response	5 (25)
Partial response	2 (10)
Stable disease	7 (35)
Progressive disease	5 (25)
Not evaluable	1 (5)
Duration of response (N=7)	
Median, days	143
Disease control rate	**14 (70)**

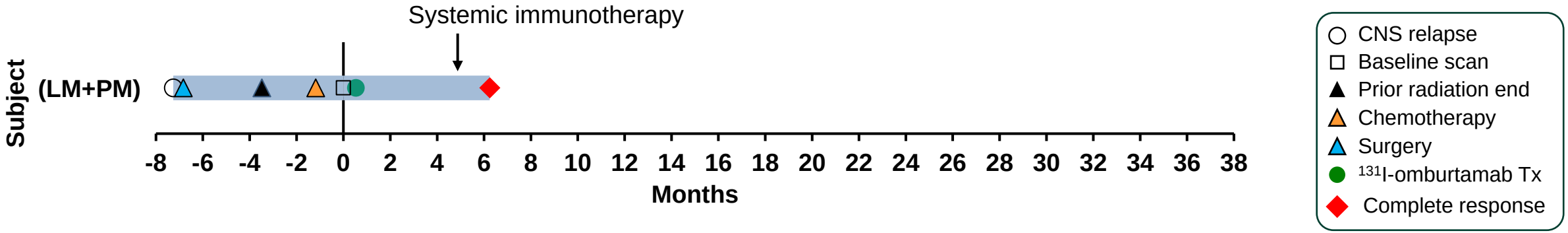
[a] Objective response = CR + PR. Central review based on RANO and EANO/ESMO Criteria.

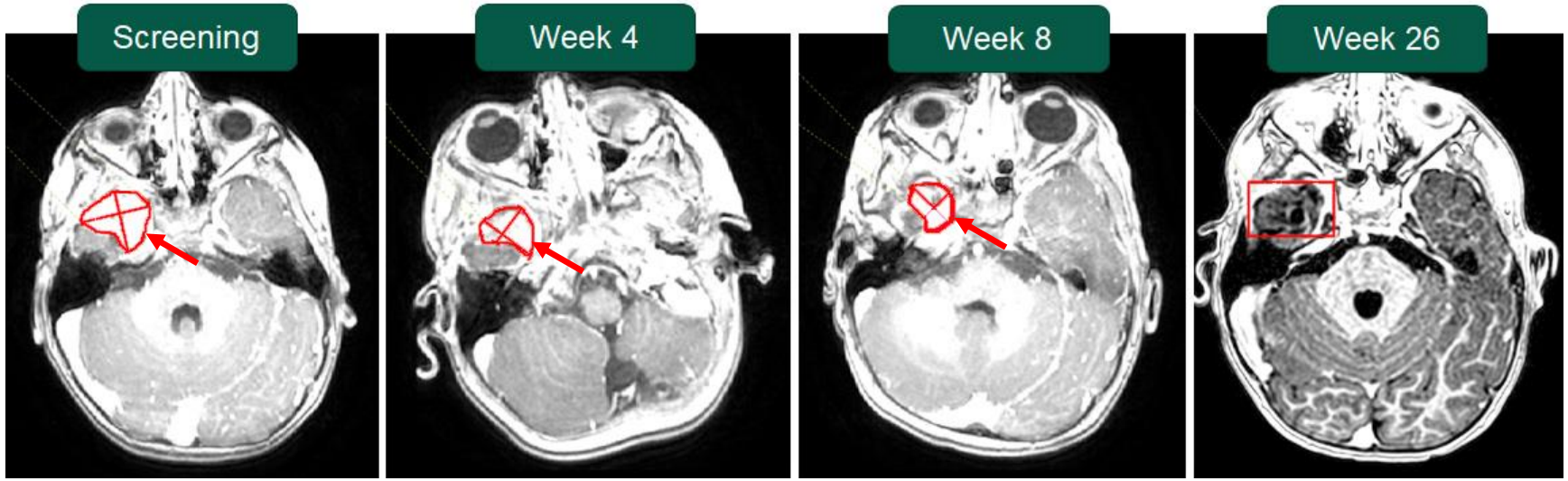
Response to ^{131}I-Omburtamab Treatment

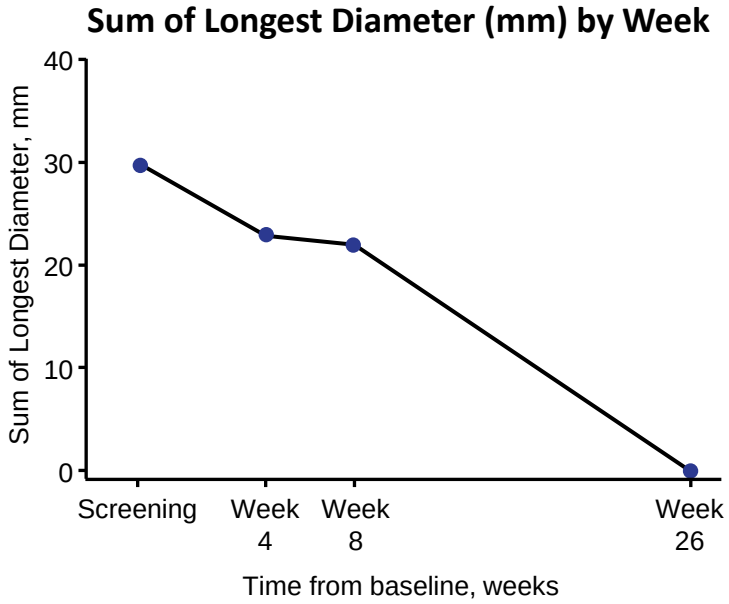
Trial 101



^{131}I-Omburtamab Demonstrated Single-Agent Activity in Parenchymal Disease







Summary of Trials 03-133 and 101

- Trial 03-133 represents the largest clinical trial experience, enrolling ~1/3 of all US patients with CNS/LM metastases from NB
- Trial **03-133** demonstrated
  - 3-year OS rate: 57%
  - Median OS: 51 months
- Trial **101** is supportive, and demonstrated similar results in a multicenter setting
  - 1-year OS rate: 79% from start of ^{131}I-omburtamab
  - Clinically meaningful 35% ORR in patients with evaluable disease at baseline
  - Evidence of single-agent activity in both parenchymal and leptomeningeal lesions

Y-mAbs Therapeutics, Inc.

External Control Arm

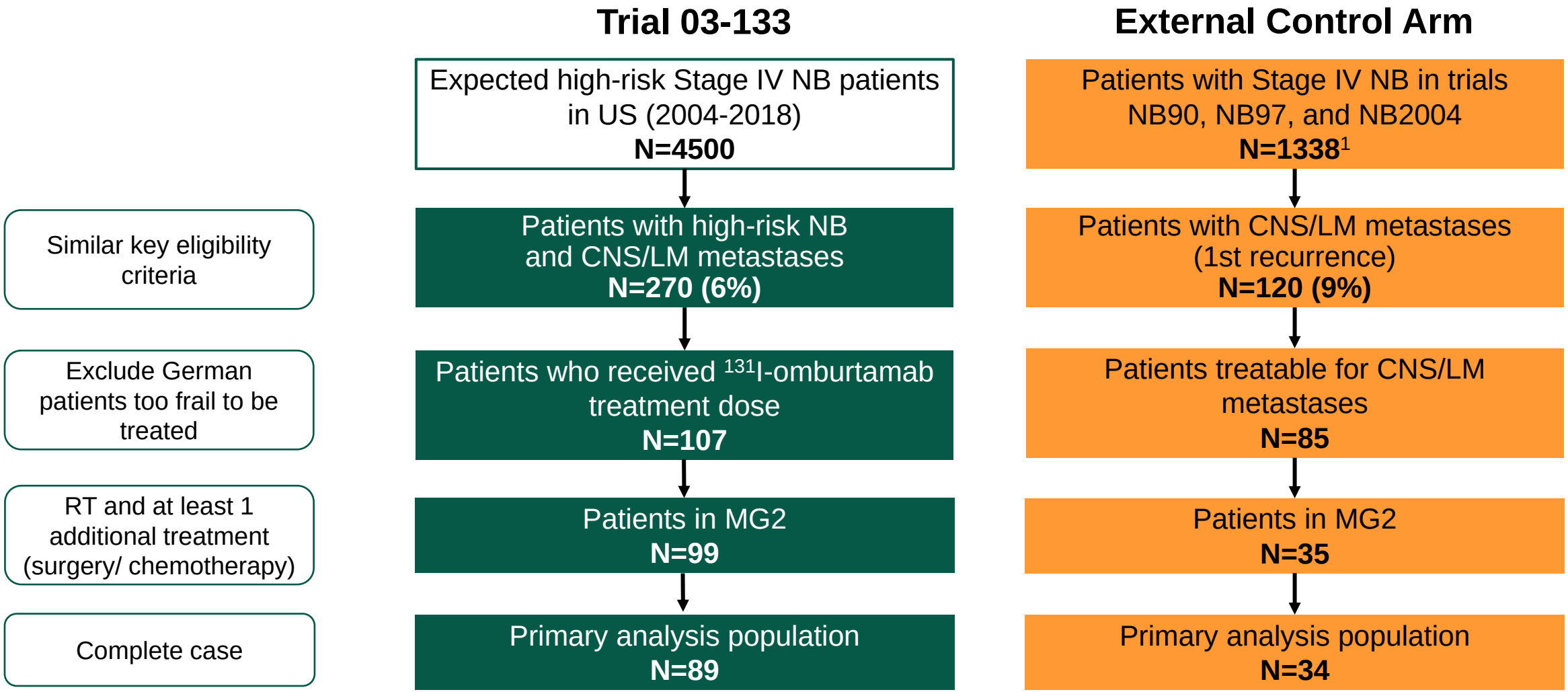
René dePont Christensen, MSc, PhD
Vice President Biometrics
Y-mAbs Therapeutics

A Suitable External Control Group Was Identified

- Only 2 comprehensive repositories of patient-level data for NB patients with CNS/LM metastases available outside of our own trials
  - Registry data from Study Center for Neuroblastoma in Cologne, Germany (N=120)
  - International Society of Pediatric Oncology Europe Neuroblastoma Group (SIOPEN) database (N=53)[1]

Berlanga P, et al. *Eur J Cancer*. 2021;144:1-8.

Key Eligibility Criteria Were Aligned



1. Berthold F, et al. *Pediatr Drugs.* 2017;19:577-593.

Propensity Score Model Successfully Balanced All Available Parameters

Parameter	Statistic	Primary Analysis (MG2, weighted, no imputation) Trial 03-133 (N=89)	ECA (N=34[a])
Age at NB diagnosis, years	Mean (SD)	2.9 (2)	2.8 (3)
MYCN Status	Amplified, %	61	57
	Not amplified, %	39	43
Time from NB diagnosis to CNS relapse, months	Mean (SD)	21.3 (14)	21.9 (8)
Time from CNS relapse to the start of post-CNS relapse treatments, days	Mean (SD)	9.6 (12)	9.4 (11)
Post-CNS relapse chemotherapy	Yes, %	99	99
Post-CNS relapse surgery	Yes, %	79	76
Number of post-CNS relapse treatments	2, %	23	25
	3, %	78	75

[a] The 34 patients were propensity score weighted according to their similarity to the Trial 03-133 patients at baseline and represent a weighted sample size of 29; percentages are based on the weighted analysis.

The Degree of Complete Resection Was Comparable

- In Trial 03-133 MG2, 51% had a unifocal PM lesion likely to undergo complete surgical resection
- In the ECA
  - 52% achieved macroscopic complete resection
  - 29% of surgeries were macro- and microscopic complete

Surgery Result	ECA MG2, n (%) (N=35)
Macro- and microscopic complete	10 (29)
Macroscopic complete and microscopic unclear/incomplete	8 (23)
Macroscopic incomplete	7 (20)
No surgery	10 (29)

52%

The Presence of Systemic Disease Was Similar

- Pattern of relapse: Isolated CNS/LM or combined with systemic disease
  - Measured at time of relapse in ECA and at time of first ^{131}I-omburtamab infusion in Trial 03-133
  - We may assume that the patients in Trial 03-133 with systemic disease at time of infusion also had systemic disease at time of relapse
  - Very similar distribution, but not directly possible to include in propensity score model due to timing issue

	Patients, n (%)	
	Trial 03-133 MG2 (N=99)	ECA MG2 (N=35)
Isolated CNS disease	72 (73)	28 (80)
Combined CNS and systemic disease	25 (25)	7 (20)
Unknown	2 (2.0)	0

More ECA Patients Were in First Recurrence

	Patients, n (%)	
	Trial 03-133 MG2 (N=99)	ECA MG2 (N=35)
First recurrence	57 (58)	32 (91)
Second recurrence	34 (34)	2 (5.7)
Third or more recurrence	4 (4.0)	1 (2.9)
Unknown	4 (4.0)	0

Treatment Intensity Was Comparable Within Modality Group 2

	Patients, n (%)	
	Trial 03-133 MG2 (N=99)	ECA MG2 (N=35)
Radiotherapy	99 (100)	35 (100)
Chemotherapy	98 (99)	31 (89)
Surgery	78 (79)	25 (71)

- All patients in the ECA received CNS-directed focal or whole-brain radiotherapy
- 93% of patients in Trial 03-133 received craniospinal irradiation

Trial 03-133 and ECA MG2 Populations Are Comparable

- We evaluated all available sources for external patient level data
- We identified a comparable external control arm (ECA) through alignment of eligibility criteria and balancing of baseline conditions with propensity score (PS) methods
- Prognostic factors not included in the PS model were shown to be similar or in favor of the ECA:
  - Surgical radicality
  - Presence of systemic disease
  - Number of prior recurrence
- Treatment intensity immediately following CNS relapse was comparable
- Data suggest that the ECA patients have a similar prognosis to, or even tend to have a more favorable prognosis than, the Trial 03-133 population

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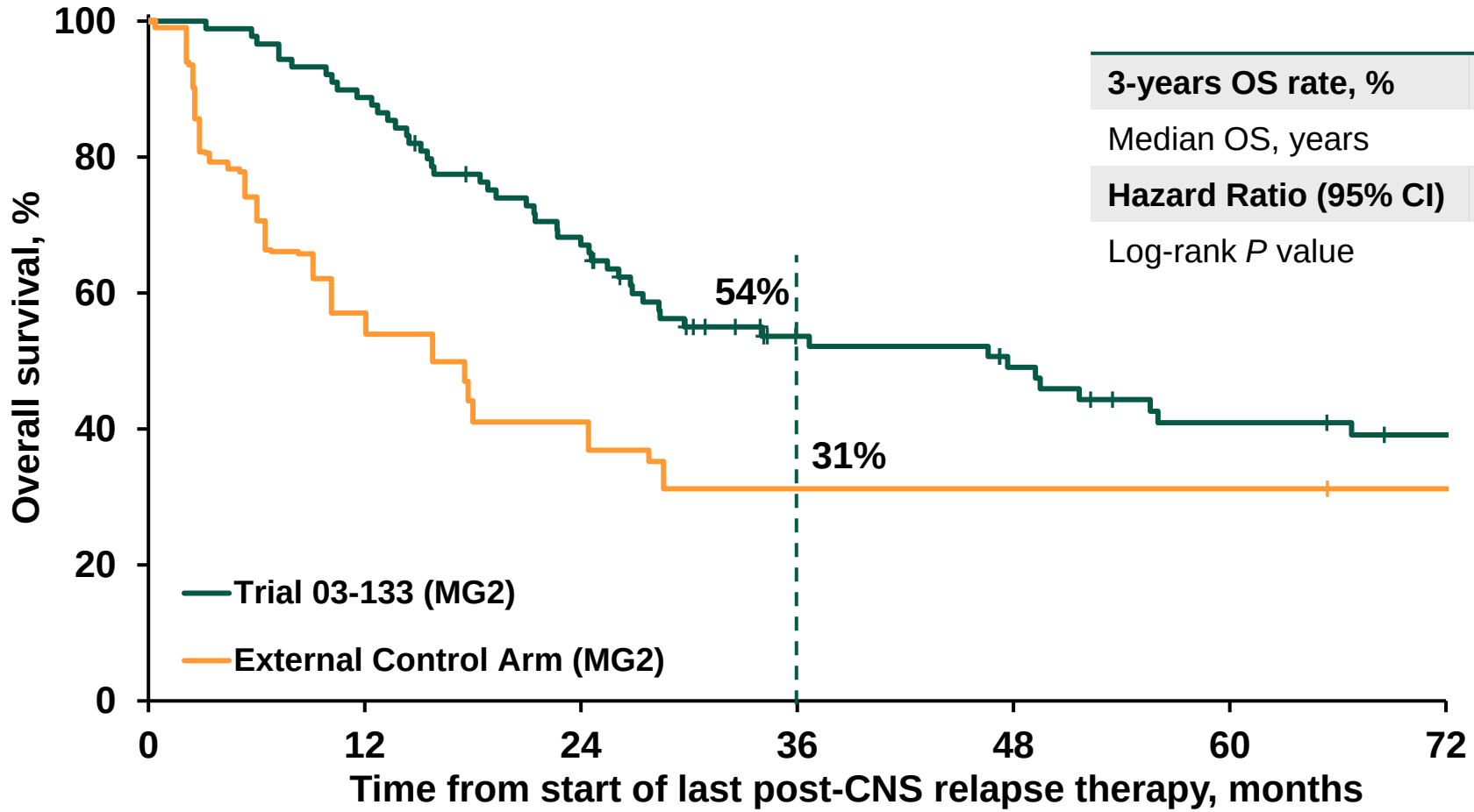
Comparison of Trial 03-133 and ECA

René dePont Christensen, MSc, PhD
Vice President Biometrics
Y-mAbs Therapeutics

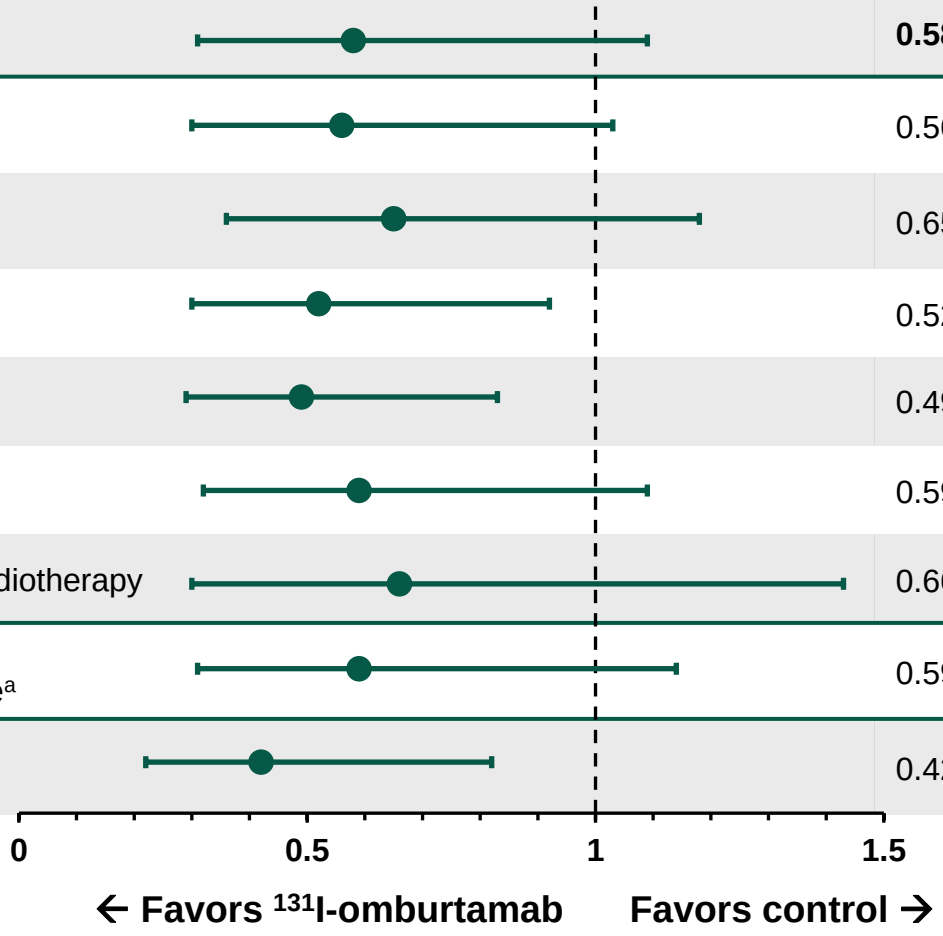
^{131}I-Omburtamab Demonstrated a Clinically Meaningful 42% Improvement in Overall Survival vs External Control Arm (MG2)



	Trial 03-133 ^{131}I-omburtamab	External Control Arm
3-years OS rate, %	**54**	**31**
Median OS, years	4.0	1.3
Hazard Ratio (95% CI)	**0.58 (0.31, 1.09)**	
Log-rank *P* value	0.0544	

Sensitivity Analyses Show Consistent Treatment Effect

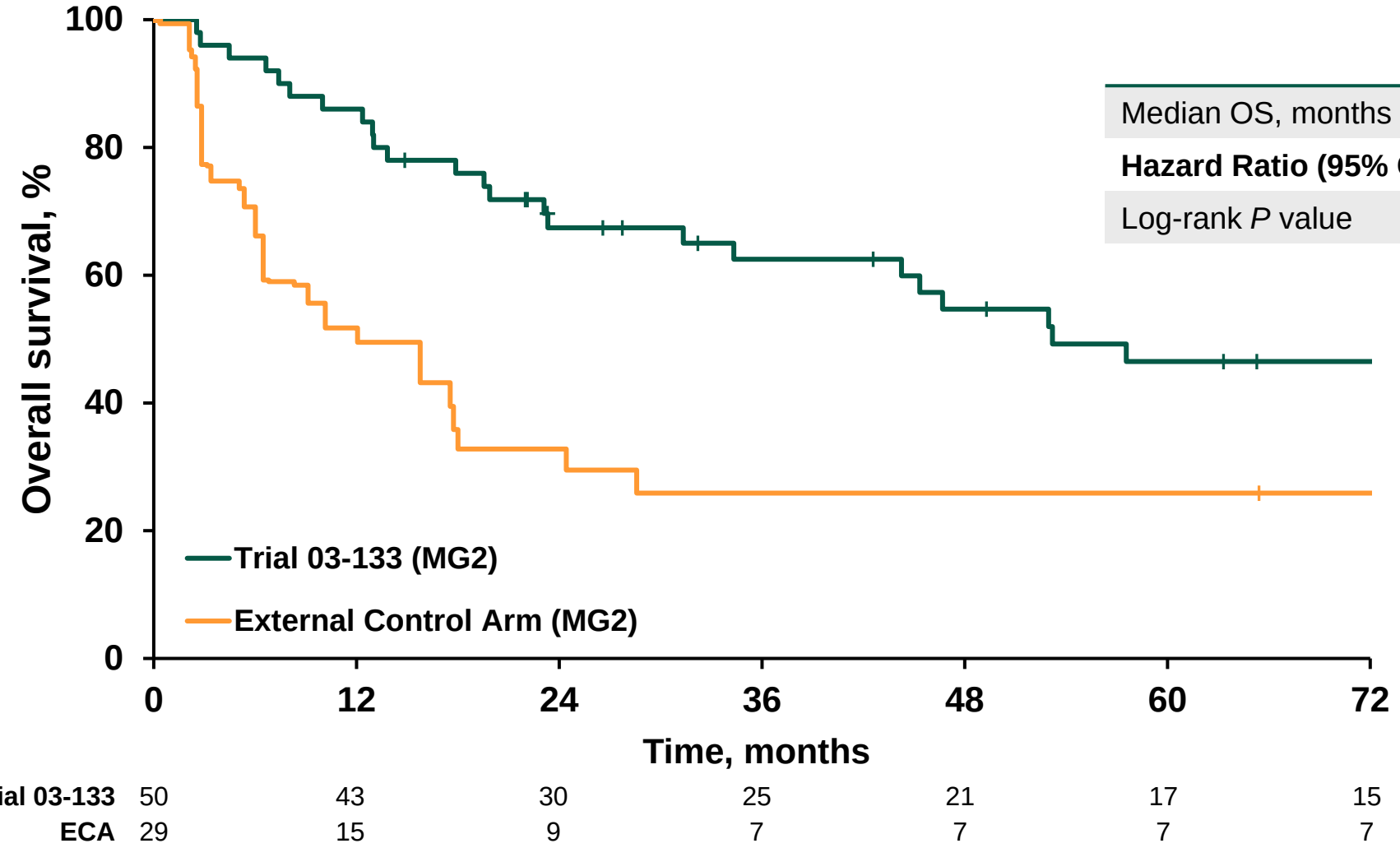
Objective	Description	OS Hazard ratio (95% CI)	N (03-133/ECA)
	Primary Analysis	**0.58 (0.31, 1.09)**	**89/34**
Test consistency despite missing data	Baseline covariate imputation	0.56 (0.30, 1.03)	99/35
Test consistency despite index date	Start of ^{131}I-omburtamab infusion (Trial 03-133) (index date A vs D to address immortal time bias)	0.65 (0.36, 1.18)	89/34
	First post CNS/LM metastases treatment	0.52 (0.30, 0.92)	89/34
	CNS/LM metastases diagnosis	0.49 (0.29, 0.83)	89/34
Test consistency despite modality group	Patients receiving at least radiotherapy	0.59 (0.32, 1.09)	90/36
	Patients receiving surgery, chemotherapy, and radiotherapy	0.66 (0.30, 1.43)	69/21
Test impact of pattern of relapse	Pattern of relapse (isolated CNS vs combined CNS and systemic disease) included as covariate[a]	0.59 (0.31, 1.14)	89/34
Test impact of prior recurrence	Patients treated at first recurrence	0.42 (0.22, 0.82)	50/29



[a] Assumed that in Trial 03-133, the pattern at time of relapse was the same at time of first ^{131}I-omburtamab infusion.

Overall Survival in Patients Treated at First Recurrence

Trial 03-133 and ECA, MG2, Index Dates A+D

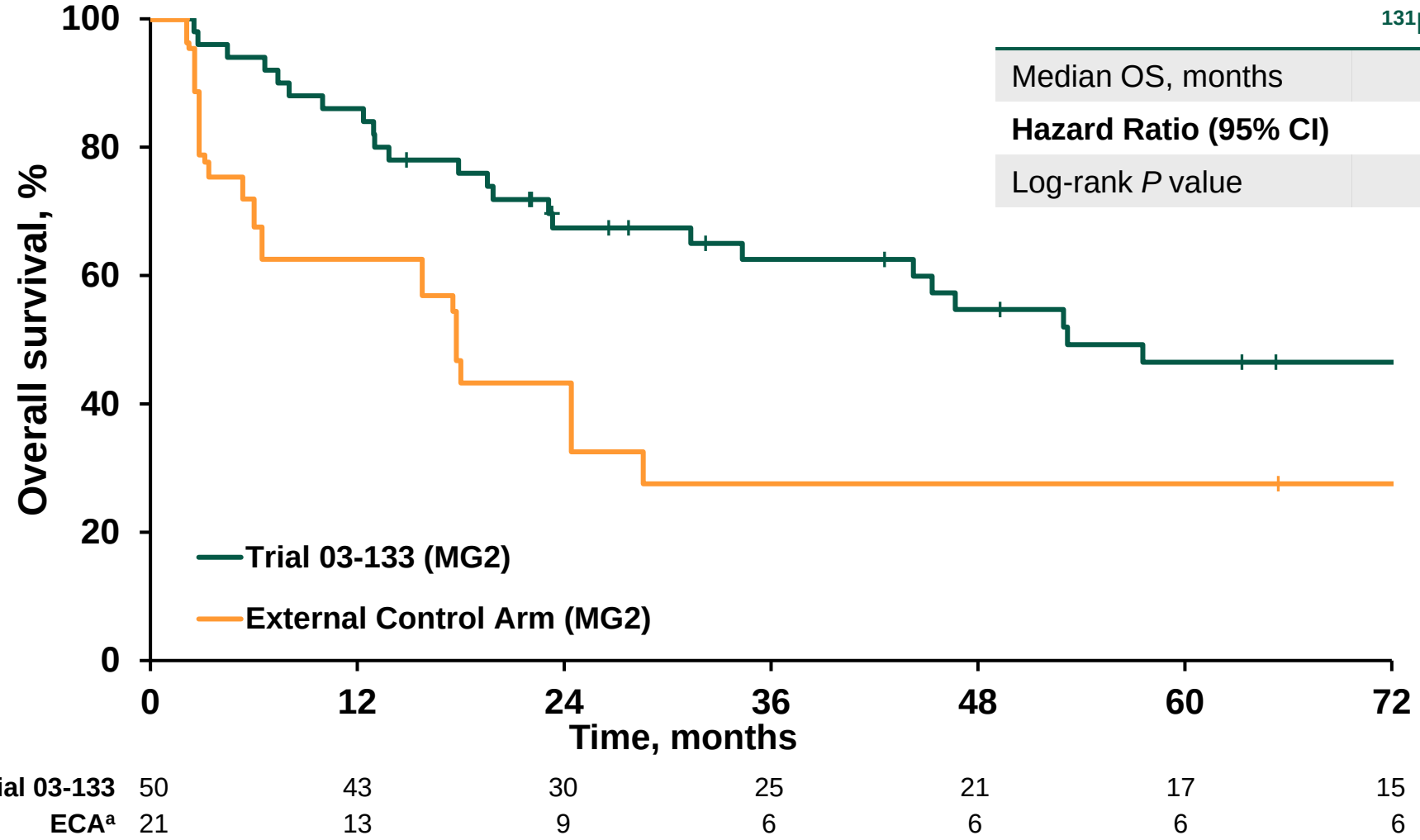


	Trial 03-133 ^{131}I-Omburtamab (N=50)	External Control Arm (N=29)
Median OS, months	53	12
Hazard Ratio (95% CI)	**0.42 (0.22, 0.82)**	
Log-rank *P* value	0.007	

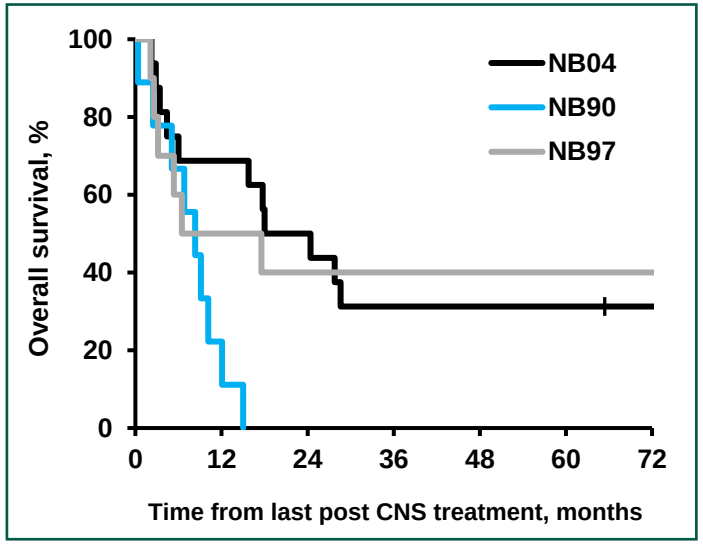
Trial 03-133	50	43	30	25	21	17	15
ECA	29	15	9	7	7	7	7

Overall Survival in Patients Treated at First Recurrence, Temporal Trend

Trial 03-133 and ECA, MG2, Index Dates A+D, Excluding NB90 From ECA



	Trial 03-133 ^{131}I-Omburtamab	External Control Arm
Median OS, months	53	18
Hazard Ratio (95% CI)	**0.48 (0.24, 0.96)**	
Log-rank *P* value	0.0333	



Trial 03-133	50	43	30	25	21	17	15
ECA[a]	21	13	9	6	6	6	6

[a] Excluding NB90 protocol.

External Control Arm Is Fit for Purpose

- There are 3 major concerns raised by the FDA and 1 key confounder identified by Y-mAbs
  - Treatment intensity
  - Immortal time bias
  - Era of therapy
  - Number of prior recurrence
- These concerns have been addressed, maintaining a consistent treatment effect
- Analysis in the subgroup of patients in first recurrence offers a like-for-like comparison, which is robust to both immortal time and era

Conclusions

- External control arm of high quality and fit for purpose
- Important prognostic factors were sufficiently balanced
- Compared with the ECA, treatment with ^{131}I-omburtamab resulted in clinically meaningful improvements in OS
  - 42% relative reduction in the risk of death (HR=0.58; 95% CI: 0.31, 1.09)
  - Improved median OS by 32 months (48 vs 16 months)
  - Improved 3-year OS rate by 23% (54% vs 31%)
- Sensitivity analyses showed a consistent clinically meaningful effect favoring ^{131}I-omburtamab
- Subgroup of patients in first recurrence shows a large, significant and robust effect of ^{131}I-omburtamab added to conventional treatments, which cannot be ignored

Y-mAbs Therapeutics, Inc.

Safety

Vignesh Rajah, MD
Chief Medical Officer
Y-mAbs Therapeutics

Safety Evaluation: Treatment Exposure by Study

Trials 03-133 and 101

	Patients, n (%)				
	Trial 03-133				Trial 101
Treatment dose received	<50 mCi N=10	50 mCi N=94	>50 mCi N=5	All patients N=109	50 mCi N=50
0	2 (20)[a]	0	0	2 (1.8)[a]	0
1	1 (10)	45 (48)	4 (80)	50 (46)	20 (40)
2	7 (70)	47 (50)	1 (20)	55 (50)	30 (60)
>2	0	2 (2.1)	0	2 (1.8)	0

[a] Received dosimetry dose only.

Overview of Safety Profile

Trials 03-133 and 101

	Patients, n (%)	
	Trial 03-133 N=109	Trial 101 N=50
At least 1 TEAE	**102 (94)**	**49 (98)**
Grade ≥3 TEAE	93 (85)	33 (66)
Serious TEAE	54 (50)	18 (36)
TEAE leading to discontinuation of study drug[a]	11 (10)	7 (14)
TEAE leading to death	0	1 (2.0)

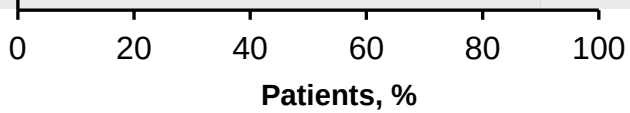
TEAE=treatment-emergent adverse event.

[a] Predominantly related to myelosuppression.

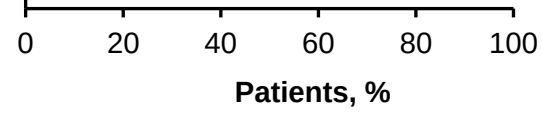
Grade ≥3 TEAEs

Trials 03-133 and 101 (>1 Patient)

Trial 03-133 Preferred Term	Patients, n (%) N=109
Patients with any Grade ≥3 TEAE	**93 (85)**
Laboratory TEAEs	
Lymphopenia	70 (64)
Platelet count decreased	60 (55)
White blood cell count decreased	51 (47)
Neutrophil count decreased	47 (43)
Hemoglobin decreased	33 (30)
Hypokalemia	7 (6.4)
ALT increased	7 (6.4)
AST increased	3 (2.8)
Clinical TEAEs	
Vomiting	3 (2.8)
Myelodysplastic syndrome	3 (2.8)
Acute myeloid leukemia	2 (1.8)
Meningitis chemical	2 (1.8)
Device-related infection	2 (1.8)



Trial 101 Preferred Term	Patients, n (%) N=50
Patients with any Grade ≥3 TEAE	**33 (66)**
Laboratory TEAE	
Platelet count decreased	16 (32)
Lymphocyte count decreased	14 (28)
Neutrophil count decreased	12 (24)
White blood cell count decreased	12 (24)
Anemia	2 (4.0)
Clinical TEAE	
Intracranial hemorrhage	4 (8.0)

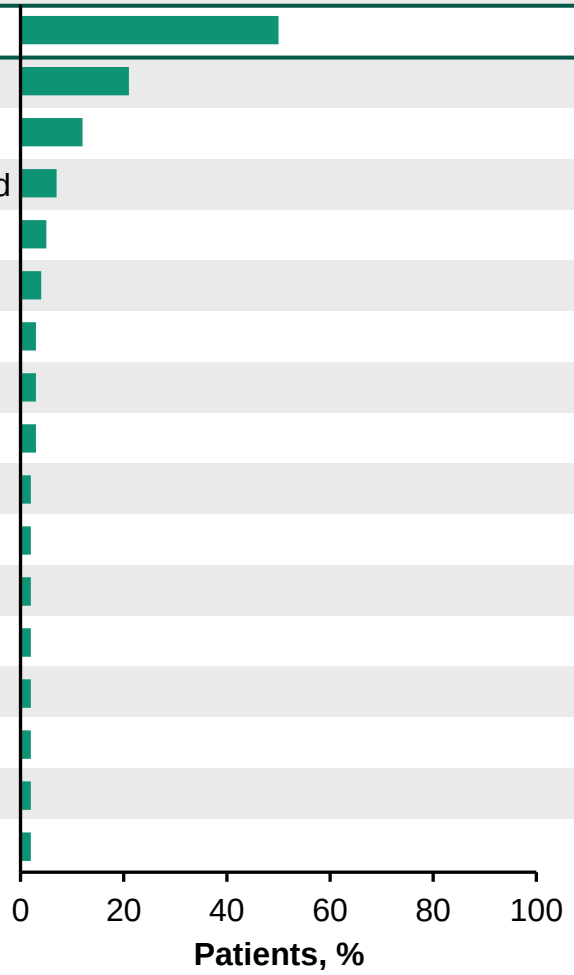


ALT=alanine aminotransferase; AST=aspartate aminotransferase.

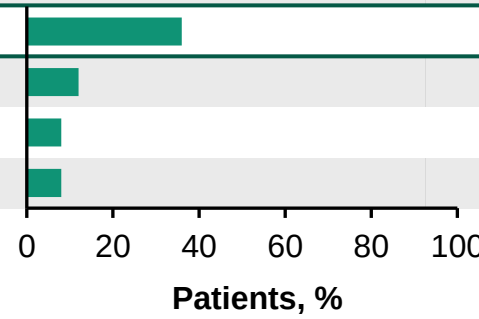
Serious Adverse Events

Trials 03-133 and 101 (>1 Patient)

Trial 03-133 Preferred Term	Patients, n (%) N=109
Patients with any SAE	**54 (50)**
Platelet count decreased	23 (21)
Neutrophil count decreased	13 (12)
White blood cell count decreased	8 (7.3)
Hemoglobin decreased	5 (4.6)
ALT increased	4 (3.7)
Meningitis chemical	3 (2.8)
Vomiting	3 (2.8)
Myelodysplastic syndrome	3 (2.8)
Acute myeloid leukemia	2 (1.8)
AST increased	2 (1.8)
Headache	2 (1.8)
Device-related infection	2 (1.8)
Lymphopenia	2 (1.8)
Nervous system disorder	2 (1.8)
Pyrexia	2 (1.8)
Seizure	2 (1.8)



Trial 101 Preferred Term	Patients, n (%) N=50
Patients with any SAE	**18 (36)**
Platelet count decreased	6 (12)
Lymphocyte count decreased	4 (8.0)
Hemorrhage intracranial	4 (8.0)



SAE=serious adverse event.

Summary of Safety

- Most common TEAEs related to laboratory abnormalities from myelosuppression
- Majority of Grade 3/4 TEAEs were hematologic and manageable with standard measures
- Overall safety profile was acceptable in the context of this serious disease

Clinical Perspective

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Staff Physician, Solid Tumor Program, Hospital for Sick Children
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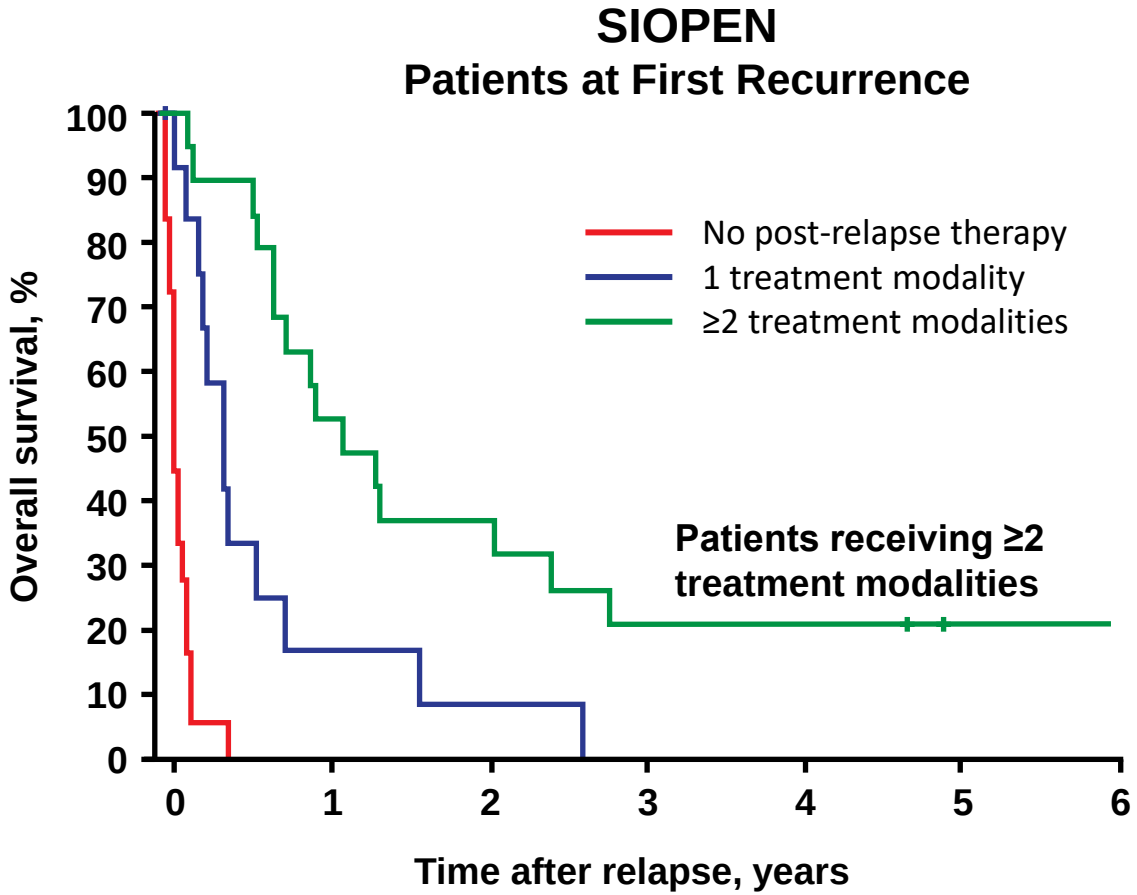
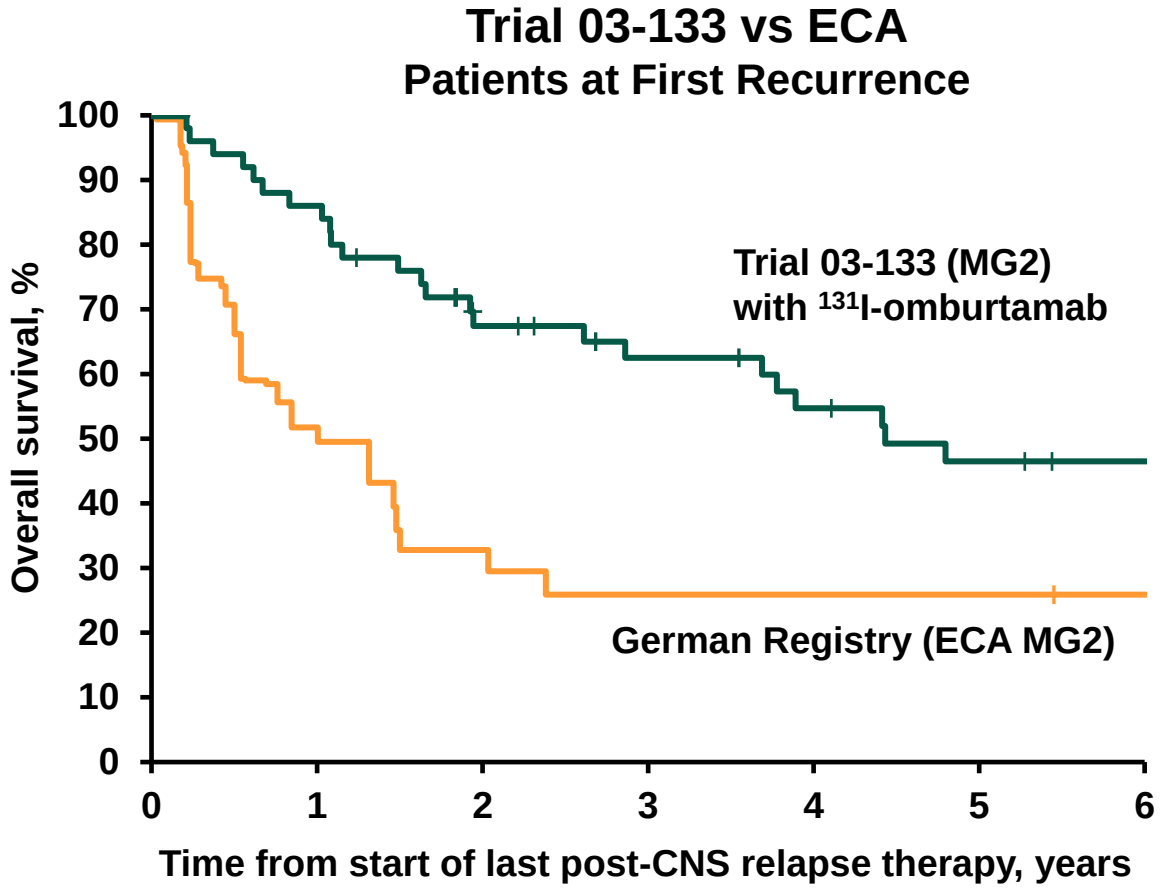
Toronto, Ontario, Canada

CNS-Directed Therapy Is Needed

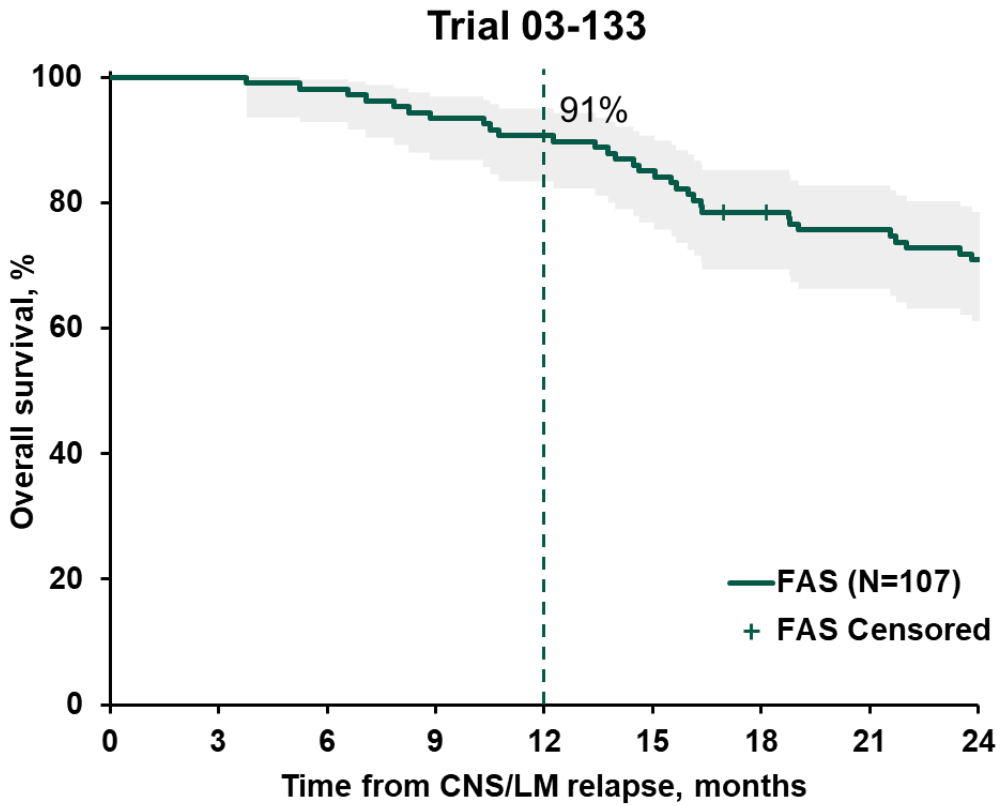


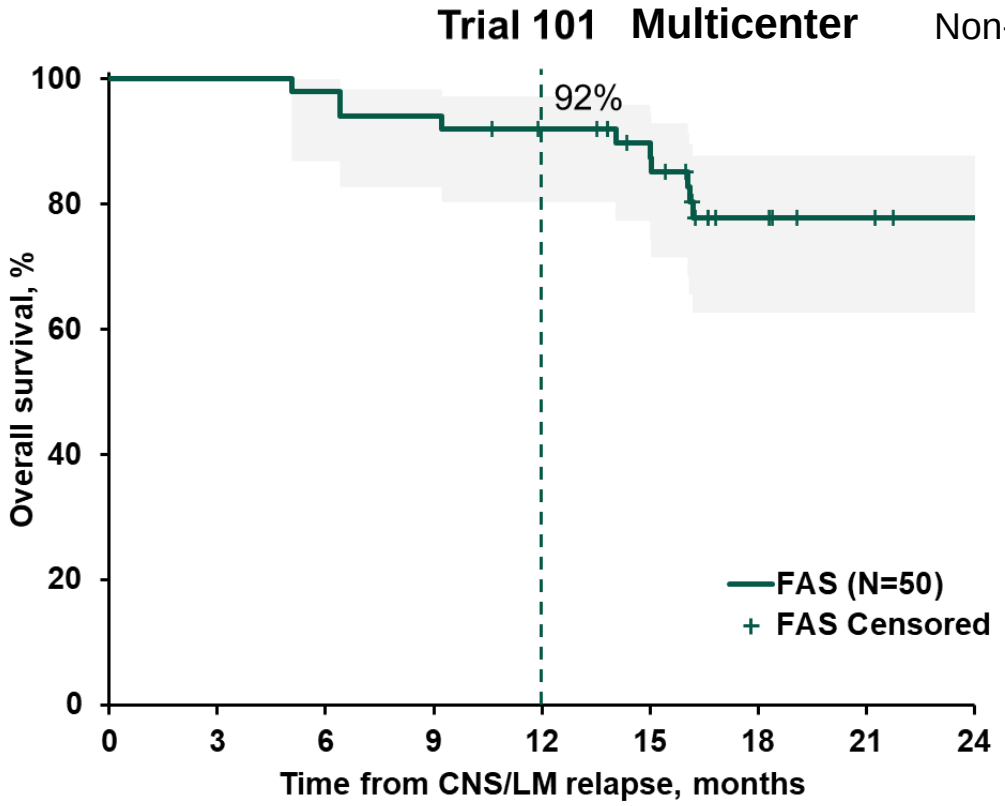


SIOPEN=International Society of Paediatric Oncology Europe Neuroblastoma Group.

Left image reprinted from from *Eur J Cancer*, 144, Berlanga P, et al, Central nervous system relapse in high-risk stage 4 neuroblastoma: the HR-NBL1/SIOPEN trial experience, 1-8, Copyright 2021, with permission from Elsevier.

Are 03-133 Data From a Single Institution Generalizable?





MSKCC n=24
Non-MSKCC n=26

FAS=Full Analysis Set.

Totality of Evidence Supports a Positive Benefit-Risk

- **Trial 03-133 compared to External Control Arm (MG2)**
  - OS rate at 3 years: **54% vs 31%**
  - Median OS: **48 vs 16 months**
  - OS hazard ratio: **0.58** (95% CI: 0.31, 1.09); *P*=0.0544
  - OS hazard ratio for first recurrence subgroup: **0.42** (95% CI: 0.22, 0.82); ***P*=0.007**
- **Trial 101 (N=50)**
  - Confirms OS in Trial 03-133
  - Objective response rate: **35%** (5 CR, 2 PR); stable disease **35%**
- **Adverse events are predictable and manageable**
  - Mainly myelosuppression

CI=confidence interval; CR=complete response; PR=partial response.

A Randomized Trial Would Not Be Feasible

- 9-18 per year with CNS relapse neuroblastoma in the United States
- Randomized trial to detect a minimal clinically relevant effect, corresponding to a HR=0.70 with α=0.05 and 80% power
  - ~250 events/430 patients
  - With 18 patients/year in the US, it would take 27 years to complete

Is a Better Comparison Data Set Available?

- Challenging to identify patients with true CNS relapse
  - Most trial databases for upfront studies don't collect site of relapse
  - Children's Oncology Group data don't capture site of relapse
- SIOPEN retrospective study identified 53 patients with confirmed first CNS recurrence among 1161 with recurrent disease

Summary

- No CNS-directed therapy approved for CNS neuroblastoma
- Totality of evidence supports efficacy of ^{131}I-omburtamab for CNS neuroblastoma in the context of multimodality therapy
- Not feasible to conduct a randomized trial
- No suitable additional external data sources
- Need to make a judgement based on best available data rather than theoretical ideal
- Toxicity is manageable and ^{131}I-omburtamab can be safely administered
- ^{131}I-omburtamab should be made available as an additional option for clinicians to treat their patients with CNS neuroblastoma

Overall Conclusion

- The studies presented for ^{131}I-omburtamab constitute the only prospective data within CNS/LM metastatic neuroblastoma, with more than 14 years of follow-up in Trial 03-133

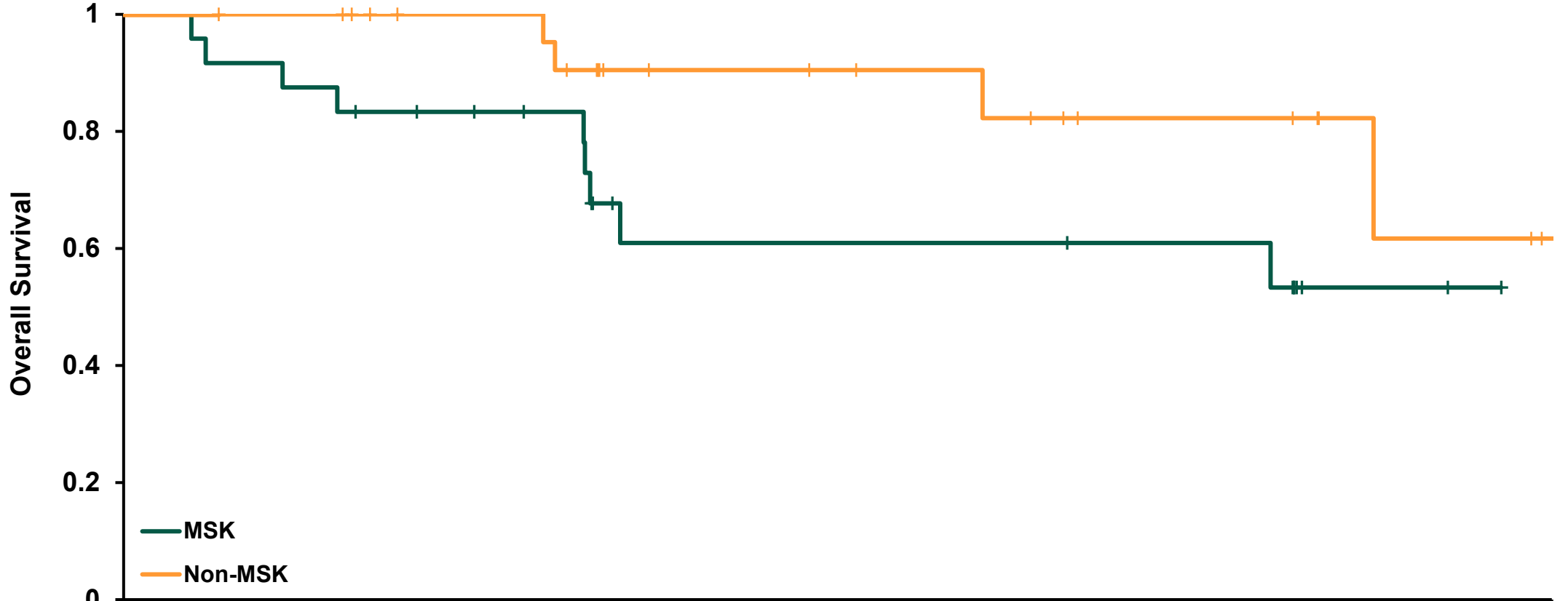
- ^{131}I-Omburtamab showed compelling and clinically meaningful efficacy, with an acceptable and manageable safety profile

- Degree of flexibility in the evaluation is appropriate in the context of the evidence presented and the significant unmet need in this rare and life-threatening disease

Additional Slides Shown

Overall Survival by Site Group

Trial 101 (N=50)

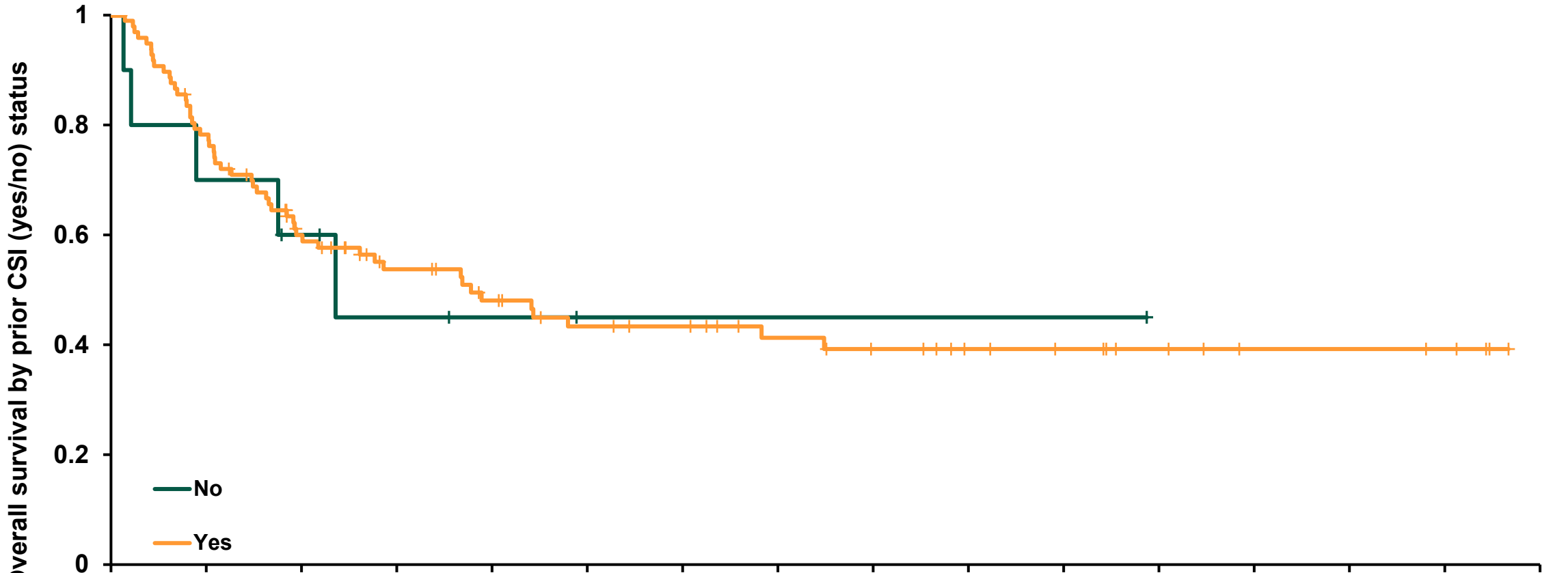


MSK	24	22	19	17	11	9	9	9	8	8	2	2	0
Non-MSK	26	25	23	21	15	13	12	11	8	7	6	3	1

Subjects alive are censored at the date subject was last confirmed alive.

Overall Survival from First Infusion by Prior Craniospinal Irradiation

Trial 03-133, FAS



No	10	7	5	3	2	1	1	1	1	1	1	0			
Yes	97	75	52	40	33	27	25	20	17	13	11	8	5	5	4	0

Total Absorbed Treatment Dose of ^{131}I-omburtamab by Organ

Study 101 (N=22) Excluding Outlier