Y-mAbs Therapeutics Inc.

^{131}I-omburtamab

Neuroblastoma with Central Nervous System/Leptomeningeal Metastases

Oncologic Drugs Advisory Committee
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Y-mAbs Therapeutics, Inc.
230 Park Avenue, Suite 3350
New York, NY 10169
United States

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List of Abbreviations

ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse Event
BLA	Biologics License Application
BTD	Breakthrough Therapy Designation
CD276	Cluster of differentiation 276
CGCCR	Central German Childhood Cancer Registry
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CNS	Central Nervous System
CR	Complete Response
CSF	Cerebrospinal Fluid
CSI	Craniospinal Irradiation
CSR	Clinical Study Report
CT	Chemotherapy
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
EANO	European Association of Neuro-Oncology
ECA	External Control Arm
ESMO	European Society for Medical Oncology
FAS	Full Analysis Set
FDA	Food and Drug Administration
Gy	Gray
HR	Hazard Ratio
IND	Investigational New Drug
INSS	International Neuroblastoma Staging System
INRG	International Neuroblastoma Risk Group
KM	Kaplan-Meier
LM	Leptomeningeal
Max	Maximum
MBq	Mega-becquerel
mCi	Millicurie
MedDRA	Medical Dictionary for Regulatory Activities
MG	Modality Group
Min	Minimum
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum Tolerated Dose
MYCN	v-myc myelocytomatosis viral related oncogene
NB	Neuroblastoma
NE	Not estimable
ODD	Orphan Drug Designation
OLINDA	Organ Level Internal Dose Assessment
OMBLASTYS	^{131}I-omburtamab
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression-Free Survival

PK	Pharmacokinetics
PM	Parenchymal
PNET	Primitive Neuroectodermal Tumor
PR	Partial Response
PT	Preferred Term
RANO	Response Assessment in Neuro-Oncology
RPD	Rare Pediatric Disease Designation
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Standard Deviation
SIOPEN	International Society of Paediatric Oncology Europe Neuroblastoma Group
SMQ	Standardized MedDRA queries
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time to maximum concentration
US	Unites States
V_d	Volume of Distribution
Y-mAbs	Y-mAbs Therapeutics, Inc.

1 Executive Summary

Introduction

Y-mAbs Therapeutics Inc. (Y-mAbs) is developing [131]I-omburtamab (OMBLASTYS) for the treatment of central nervous system (CNS)/leptomeningeal (LM) metastases in pediatric patients with neuroblastoma following standard multimodality treatment for CNS disease. Patients with this ultra-rare disease have a very poor prognosis and there is a high unmet medical need for an efficacious treatment.

Disease Background and Unmet Medical Need

Neuroblastoma - Incidence and Treatment

Neuroblastoma is a rare cancer of neural crest origin with an incidence of approximately 10 per million children per year.[1-7] At time of diagnosis 90% of patients are younger than 5 years with a median age at diagnosis of 19 months.[8]

The prognosis of neuroblastoma correlates closely with biological and clinical factors such as age at diagnosis, tumor stage and histology, and genetic and chromosomal abnormalities.[9] These factors classify neuroblastoma into prognostic risk categories (low, intermediate, or high-risk) that are useful for prediction of outcome and choice of treatment strategies.

At the time of diagnosis about 50% of patients present with metastatic disease (Stage 4) classified as high-risk neuroblastoma.[9] The frontline therapy for Stage 4 high-risk neuroblastoma is multimodal and intensive with standard regimens containing four main components: induction chemotherapy, local control (surgery and radiation) of known tumor residues, consolidation therapy, and maintenance therapy.[10] Similar for all therapy options for systemic neuroblastoma is that they are unsuited for treatment of metastases in the CNS due to low penetration of the blood-brain-barrier. Therefore, the CNS may serve as a sanctuary site for cancer cells.[11, 12]

CNS/LM Metastases in Patients with Neuroblastoma – Incidence, Treatment and Unmet Medical Need

CNS involvement at time of initial neuroblastoma diagnosis is uncommon.[12] In most cases, patients present with either isolated CNS/LM relapse (estimated 50% of all CNS relapses) or CNS/LM relapse concomitant with recurrence in other sites.[12-14] Overall, neuroblastoma with CNS/LM metastases is an ultra-rare disease. Only approximately 3-6% of patients with high-risk Stage 4 neuroblastoma will develop CNS/LM metastases.[6, 12-15] The number of new diagnoses of neuroblastoma with CNS/LM metastases in the US is estimated at 9–18 patients per year.

Treatment of CNS/LM metastases is typically multimodal and may include surgery, radiation, and chemotherapy, although there are no broadly accepted clinical practice guidelines. Irrespective of the treatment combinations used, overall survival (OS) remains poor, which is likely due to persistence of macroscopic and/or microscopic CNS/LM disease.[15] The median OS after detection of the CNS/LM metastases is less than 1 year even with early detection and intervention[11-13, 16], and 3-year OS is <10%.[1, 13, 17, 18] Even among the best prognostic subset of patients who are able to receive intensive multimodal therapy, the available data suggest a

median OS of only approximately 15 months.[13] Therefore, there is a high unmet medical need for additional treatment options to be added to the existing treatment armamentarium and thereby improve the prognosis.

^{131}I-omburtamab – Mode of Action

^{131}I-omburtamab is an iodine-131 radiolabeled murine monoclonal antibody that recognizes and binds selectively to the transmembrane protein B7-H3, which is highly expressed on the surface of neuroblastoma tumor cells, with only minimal expression in normal tissues.[19, 20] Beta-emission from iodine-131 induces cellular damage to the B7-H3-expressing cells resulting in tumor cell death. The specific targeting of B7-H3 allows delivery of radiation to the tumor cells with limited toxic effects on normal tissues.[19] When administered directly into the intraventricular space, and using the cerebrospinal fluid (CSF)-flow as a conduit, ^{131}I-omburtamab will reach and target B7-H3-expressing tumor cells in the entire CSF compartment, including micro-metastatic CNS disease.

Proposed Indication and Dosing Regimen

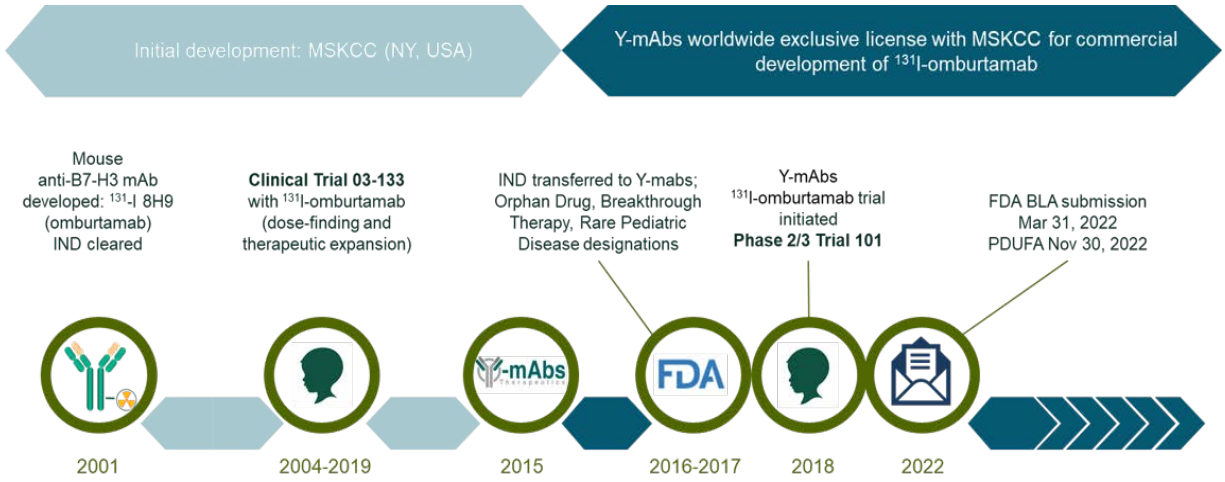
The proposed indication for ^{131}I-omburtamab is treatment of CNS/LM metastases in pediatric patients with neuroblastoma following standard multimodality treatment for CNS disease.

The route of administration of ^{131}I-omburtamab is infusion via an intraventricular access device (e.g., Ommaya catheter). The recommended dose of ^{131}I-omburtamab is 2 age-based doses given 4 weeks apart. For patients less than 1 year the recommended dose is 25.0 mCi; for patients 1 to less than 3 years the recommended dose is 33.5 mCi; and for patients 3 years and older the recommended dose is 50 mC. The age-based dose recommendations are based on differences in CSF volume and follows the clinical practice for intraventricular dosing.[21] ^{131}I-omburtamab can be administered in an outpatient setting, observing standard radiation health and safety measures.

Clinical Development of ^{131}I-omburtamab

^{131}I-omburtamab was initially developed at the Memorial Sloan Kettering Cancer Center (MSKCC; New York, US). The product has been in clinical development since 2001 under the Investigational New Drug application (IND) 009351, which was originally submitted by MSKCC. The rights to commercial development of ^{131}I-omburtamab were licensed to Y-mAbs in 2015, and ownership of the IND was transferred from MSKCC to Y-mAbs in 2017. Rare Pediatric Disease (RPD) Designation and Orphan Drug Designation (ODD) were granted for ^{131}I-omburtamab for the treatment of neuroblastoma in 2016. Breakthrough Therapy Designation (BTD) was granted for the treatment of relapsed neuroblastoma with CNS/LM metastases in 2017. Figure A highlights key milestones in the clinical development history of ^{131}I-omburtamab.

Figure A History of [131]I-omburtamab Clinical Development



BLA=Biologics License Application; IND=Investigational New Drug; mAb=monoclonal antibody; MSKCC=Memorial Sloan Kettering Cancer Center; PDUFA date=Prescription Drug User Fee Act date

Following transfer of the IND to Y-mAbs, clinical development of [131]I-omburtamab continued with frequent regulatory interactions with the FDA. General agreement was reached with the FDA on important aspects of the clinical and manufacturing development of [131]I-omburtamab and on the details of the content and format of a Biologics License Application (BLA).

The BLA is supported by data from two open-label, single-arm clinical trials: Trial 03-133 (Phase 1 dose-finding and therapeutic expansion) and Trial 101 (Phase 2/3); see Table A.

Table A Clinical Trials with [131]I-omburtamab

Trial	Design and Objectives	Number of Neuroblastoma Patients
Trial 03-133 (MSKCC initiated)	• Single-center trial since 2004 at MSKCC • Safety and PK/dosimetry • Efficacy	• Safety: 109 • Efficacy: 107 • PK/dosimetry: 27
Trial 101 (Y-mAbs initiated)	• International, multi-center trial initiated in Dec. 2018 • Ongoing • Safety and PK/dosimetry • Efficacy	• Safety: 50 • Efficacy: 50 • PK/dosimetry: 25

MSKCC=Memorial Sloan Kettering Cancer Center. PK: pharmacokinetics.

Trial 03-133 was investigator-initiated at MSKCC (2004) and was not originally intended for regulatory purposes. Some of the endpoints to support the BLA were therefore added at a late stage of the trial following transfer of the IND to Y-mAbs in 2017. These changes were made in agreement with the FDA; for details, see Summary of Clinical Efficacy below.

Trial 101 was initiated by Y-mAbs in 2018. The trial, which was designed with input from the FDA, is an ongoing international trial that has been conducted at multiple institutions, including

MSKCC. Trial 101 was conducted to support efficacy and safety results in Trial 03-133 and to demonstrate that ^{131}I-omburtamab could be administered consistently in a multicenter set-up.

Results from 159 pediatric neuroblastoma patients with CNS/LM metastases are included in this Briefing Document (109 from Trial 03-133 and 50 from Trial 101).

Trial 03-133 and Trial 101 were conducted at different time periods and there are differences in the trial design and data capturing between the two trials. Therefore, as agreed with the FDA, data from the two trials were not pooled. Trial 03-133 and Trial 101 are the only prospective clinical trials in this indication, and Trial 03-133 represents the largest clinical study of neuroblastoma patients with CNS/LM metastases in the US, enrolling at least one-third of all diagnosed patients in the US from 2004 to 2018. To support the assessment of clinical efficacy of ^{131}I-omburtamab, patient-level data from external controls sources (German Registry and SIOPEN) were included in the BLA. Refer to Section 4.6 for a description of the external controls.

Summary of Clinical Efficacy

Efficacy was assessed in 157 neuroblastoma patients with CNS/LM metastases treated with ^{131}I-omburtamab (107 in Trial 03-133 and 50 in Trial 101). Overall survival outcomes for patients in Trial 03-133 were compared to an external control population (German Registry).

Trials 03-133 and 101

Trial Design

Trial 03-133 (single-center) and Trial 101 (multi-center) are both open-label, non-randomized, single-arm trials in neuroblastoma patients with CNS/LM metastases.

Trial 03-133 had two parts: Part 1 (dose-escalation) designed to evaluate the maximum tolerated dose of intraventricularly infused ^{131}I-omburtamab (10–70 mCi), and a Part 2 in which the selected treatment dose (50 mCi) was administered to additional patients to obtain additional efficacy and safety data. The treatment dose of 50 mCi was selected based on safety (Section 8).

In both trials, a treatment cycle started with a dosimetry dose (2 mCi) of ^{131}I-omburtamab during Week 1, followed by a treatment dose (50 mCi) of ^{131}I-omburtamab during Week 2. The dosimetry dose was used to assess clinical pharmacological parameters, including dosimetry and PK. Patients without objective disease progression 4 weeks after the first treatment dose and without clinically significant Grade 3 or 4 toxicity were eligible for a second dosing cycle with the same dose as administered during the first cycle. Dose adjustments were made for patients under 3 years of age (33% dose reduction), and under 1 year of age (50% dose reduction). Overall, key inclusion and exclusion criteria were similar between the two trials. Details on trial designs are provided in Section 4.4 (Trial 03-133) and Section 4.5 (Trial 101).

Efficacy Endpoints

The efficacy endpoints for Trial 03-133 and 101 are listed in Table B. Following transfer of the IND from MSKCC to Y-mAbs, the endpoints in Trial 03-133 were introduced at a late stage of

the trial to support the BLA. The endpoints were discussed and agreed with the FDA in advance of the protocol amendment.

Table B Efficacy Endpoints for the BLA

Trial	Efficacy endpoints for the BLA
Trial 03-133 (MSKCC initiated)	Primary: • OS at 3 years Secondary: • CNS/LM PFS at 12 months • Duration of follow-up
Trial 101 (Y-mAbs initiated)	Primary: • CNS/LM PFS at 6 months Secondary: • OS at 12 months • ORR at 6 months

CNS=central nervous system; LM=leptomeningeal; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

In Trial 03-133, assessment of CNS/LM PFS by the Investigator was not done at prespecified timepoints, and the analysis is included for supportive purposes. It should also be noted that objective response rate (ORR) was not assessed in Trial 03-133 since firm guidelines for assessment of response were not available when Trial 03-133 was designed (2004). For details, see Section 6.2.1. The efficacy data from Trial 101 are considered supportive of Trial 03-133. Assessment of ORR was included in Trial 101, and an independent review of images (MRI scans) was performed to reduce variability and to ensure interpretability of the neuroimaging assessment. Definition and details on the calculation of the endpoints are provided below.

Patient Baseline Characteristics

The neuroblastoma patients enrolled in Trials 03-133 and 101 had similar baseline characteristics (Table C).

Table C Trial 03-133 and Trial 101: Patient Baseline Characteristics

Characteristics	Trial 03-133 N=107	Trial 101 N=50
Median age, years (range)	4.7 (0.9-13)	4.0 (0-11)
Mean body weight, kg	17.3	17.6
Sex, n (%)		
Male	72 (67)	29 (58)
Female	35 (33)	21 (42)
Race, n (%)		
White	84 (79)	38 (76)
Black or African American	9 (8)	1 (2)
Asian	3 (3)	7 (14)
American Indian or Alaska Native	-	1 (2)
Unknown	11 (10)	-
Other	-	3 (6)

Patient Disease Characteristics

In Trial 03-133, site of CNS/LM disease was assessed at time of relapse. Most patients had unifocal parenchymal (PM) disease (48%), followed by multifocal PM disease (15%) (Table D).

In Trial 101, site of CNS/LM disease was assessed at trial baseline (i.e., after post-CNS relapse multimodal therapy). Consequently, 30 patients (60%) did not have measurable disease at baseline, as assessed by independent review of MRI scans. The remaining 20 patients were assessed to have measurable disease, which were recorded as either PM lesions, LM lesions or both.

In both trials, most patients received radiation therapy, chemotherapy, and/or surgery for their CNS/LM metastases before ^{131}I-omburtamab administration.

Table D Trial 03-133 and Trial 101: Patient Disease Characteristics

Characteristics	Trial 03-133 N=107	Trial 101 N=50
Site of metastases at time of CNS/LM relapse, n (%)		
Unifocal PM	51 (48)	-
Multifocal PM	16 (15)	-
LM	10 (9)	-
PM + LM	9 (8)	-
Not known	11 (10)	-
Not reported	10 (9)	-
Site of metastases at time of trial baseline, n (%)		
PM	-	5 (10)
LM	-	6 (12)
LM + PM	-	8 (16)
LM + PM/LM[a]	-	1 (2)
No measurable LM/PM disease	-	30 (60)
MYCN amplification, n (%)	55 (51)	21 (42)
Prior therapy for CNS/LM metastases, n (%)		
Surgery	83 (78)	37 (74)
Radiotherapy	98 (92)	46 (92)
Chemotherapy	105 (98)	46 (92)

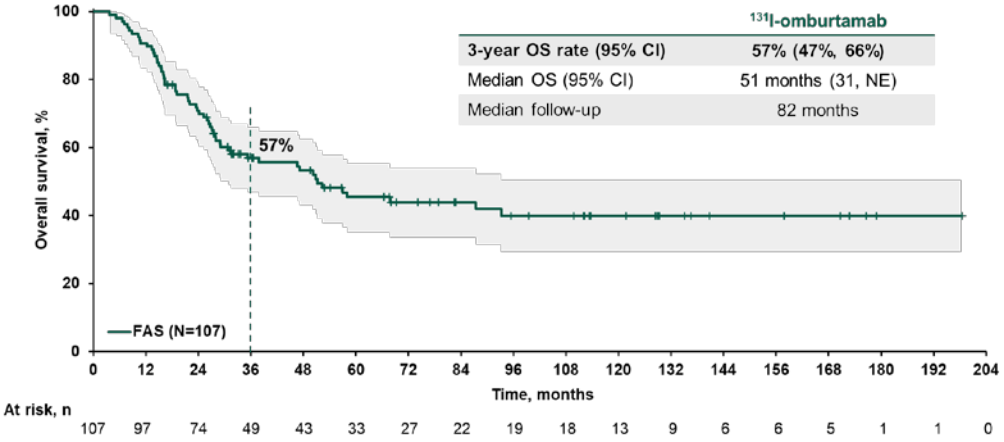
CNS=central nervous system; LM=leptomeningeal; MYCN=v-myc myelocytomatosis viral related oncogene; PM= parenchymal

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

Trial 03-133 Efficacy Results

The primary endpoint, 3-year overall survival (OS), was calculated from date of first diagnosis of CNS/LM relapse until death, or until latest date confirmed alive. The 3-year OS rate was 57% (95% CI: 47%; 66%). The median survival estimate was 51 months (95% CI: 31, not estimable [NE]). The median duration of follow-up time was 82 months (Figure B).

Figure B Trial 03-133: Overall Survival



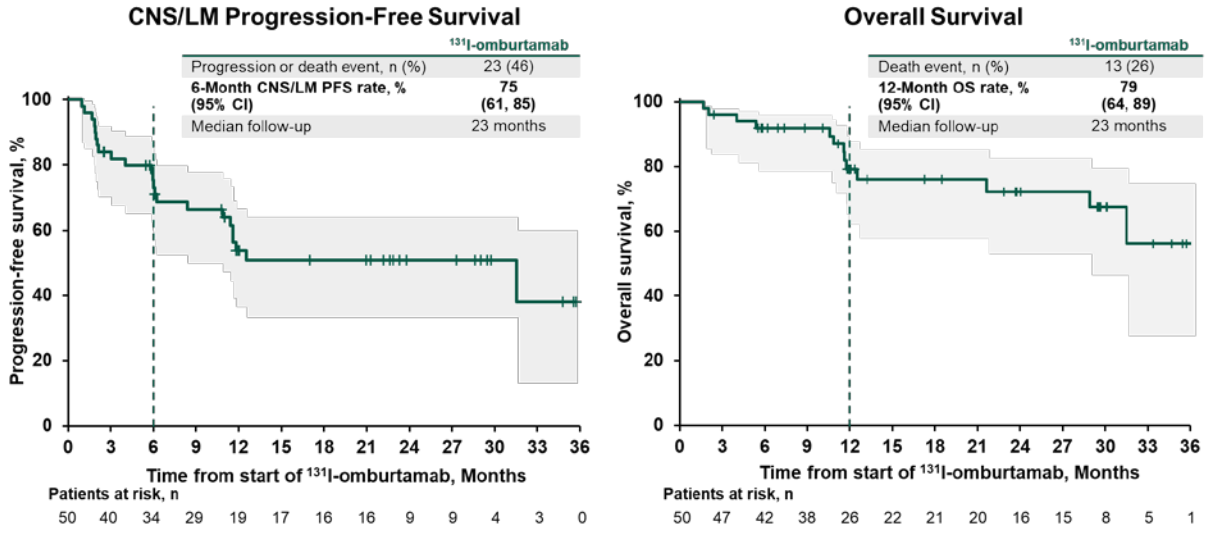
CI = confidence interval; FAS = full analysis set; NE = not estimable; OS = overall survival

The secondary endpoint, CNS/LM progression-free survival (PFS) rate at 12 months, was calculated from the date of first infusion of study drug until the date of CNS/LM progression or death, or until the latest date confirmed to be CNS/LM progression-free. The CNS/LM PFS rate at 12-months was 63% (95% CI: 52%, 71%) (Figure 10).

Trial 101 Efficacy Results

The primary endpoint, CNS/LM PFS at 6 months, was defined as time from the first treatment dose of [131]I-omburtamab to CNS/LM progression, or death from any cause. The CNS/LM PFS rate at 6 months was 75% (95% CI: 61%, 85%). With a median follow-up time of 23 months, 54% of the patients were still alive without progression. In total, 23 patients (46%) had documented CNS/LM progression or died (Figure C).

Figure C Trial 101: CNS/LM PFS and Overall Survival



CI = confidence interval; CNS=central nervous system; LM= leptomeningeal; PFS=progression-free survival

The secondary endpoint, OS at 12 months, was calculated from the first treatment dose of ^{131}I-omburtamab until the date of death from any cause (event). Patients alive at the time of analysis were censored on the date the patient was last confirmed alive. The 12-month survival rate post first treatment dose of ^{131}I-omburtamab was 79% (95% CL: 64%; 89%). The median follow-up time was 23 months; 13 patients (26%) had died, whereas the remaining 37 patients (74%) were censored alive (Figure C).

Comparative analyses of OS between Trial 03-133 and Trial 101 were not originally performed due to the difference in duration of follow-up and start dates for survival calculations. However, a post-hoc analysis of OS aligning the index date (time from first CNS/LM relapse) showed comparable 1-year OS rates between the two trials (Trial 03-133 [91%] and Trial 101 [92%]), demonstrating that the efficacy results of Trial 101 are consistent with, and supportive of Trial 03-133 in a multicenter setting.

For patients with measurable disease at baseline, ORR was assessed at Week 26 according to the RANO criteria for PM brain metastases[22] or EANO-ESMO criteria for LM metastases.[23] Of the 20 patients with measurable disease at baseline, 7 patients achieved an objective response, resulting in an ORR of 35% (95% CI: 15; 59). Five (5) patients had a complete response with a median duration of 280 days, and 2 patients had a partial response. In addition, 7 patients (35%) had stable disease at Week 26 extending up to 2 years. Overall, the disease control rate (defined as a combination of complete and partial response and stable disease) was 70% (Table E).

Table E Trial 101: Objective Response Rate

Up to Week 26	**Patients, n (%)**
Patients with measurable 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	143 days
Duration of response for complete responders (N=5), median	280 days
Disease Control Rate	14 (70)

[a] Objective Response = Complete Response and Partial Response. Central review based on RANO and EANO/ESMO Criteria.

The 7 responders had all received multimodal treatment for their CNS/LM relapse including chemotherapy, radiation therapy and surgery prior to enrollment in the trial. The 7 responders all had a period of at least 4 weeks (mean of 70 days, range: 33 days to 122 days) between their prior anti-cancer therapy and the first ^{131}I-omburtamab administration.

External Control Source

In this rare and life-threatening indication with no approved therapies, a randomized controlled clinical trial of sufficient size is neither considered feasible nor ethically justifiable (i.e., inclusion of a placebo arm). Therefore, within rare diseases, an alternative option for generation of evidence is to utilize data from external control sources to create an external control arm (ECA). There are very few repositories of patient-level data for neuroblastoma patients with CNS/LM metastases available world-wide. An extensive search for external patient-level data was performed, including within US cooperative groups such as the Children's Oncology Group. This led to the identification of two external control sources with sufficient patient-level data: the Study Database for Neuroblastoma at the Neuroblastoma Study Center (Cologne, Germany) and the European International Society of Pediatric Oncology Neuroblastoma Group (SIOPEN) (Section 4.6).

Data from the Study Database for Neuroblastoma (referred to as "German Registry" in this Briefing Document) is the largest and most comprehensive repository for neuroblastoma patients with CNS/LM metastases available and hence the best and most suitable source for an ECA for direct comparison to the clinical efficacy results from Trial 03-133. The registry is comprised of data prospectively collected during three national neuroblastoma clinical trials covering 99% of all neuroblastoma cases in Germany over the period 1990 to 2015. An on-site FDA inspection conducted in September 2022 at the study center in Cologne confirmed that the registry data are verifiable and generally of very high quality suitable for real-world evidence studies.

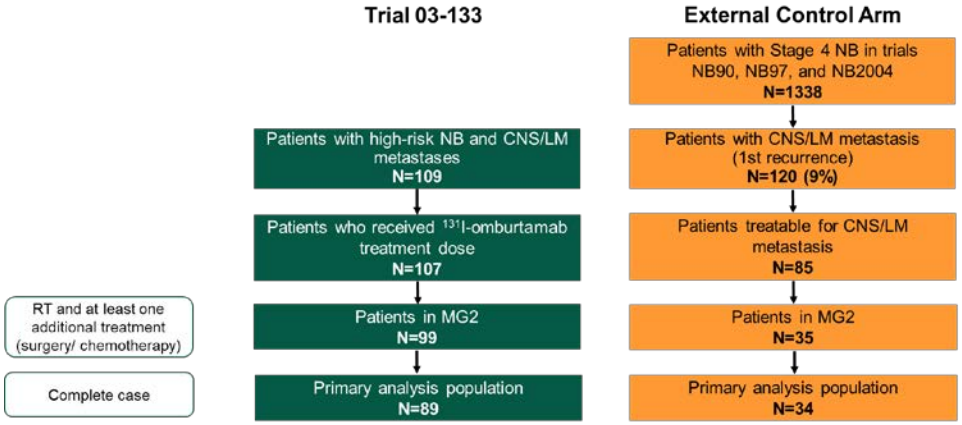
External Control Arm

The key inclusion criteria for patients in Trial 03-133 and patients from the German Registry included in the ECA were similar (see Table 13). The flow chart of the patient selection process for Trial 03-133 and the ECA is shown in Figure D.

In Trial 03-133, most patients received a multimodal treatment regimen of surgery, chemotherapy, and/or radiotherapy before the first ^{131}I-omburtmab administration. A total of 99 patients received radiotherapy and at least one other treatment (surgery or chemotherapy) and were defined as "modality group 2" (MG2). In the German registry, 1338 patients with Stage 4 neuroblastoma were identified from three national clinical trials. A subset of these (N=120) had CNS or LM disease at first recurrence. The population was further limited to those patients who had received treatment for their CNS or LM disease (N=85). Of these, 35 patients had received multimodal treatment and were included in MG2.

To increase the degree of comparability between the two groups, the primary analysis was restricted to MG2 and only included complete cases (89 patients in Trial 03-133 and 34 patients in the ECA).

Figure D Selection of Patients in Trial 03-133 and the External Control Arm



CNS=central nervous system; LM=leptomeningeal; MG2=modality group 2; NB=neuroblastoma; RT=radiotherapy

Propensity Score Model

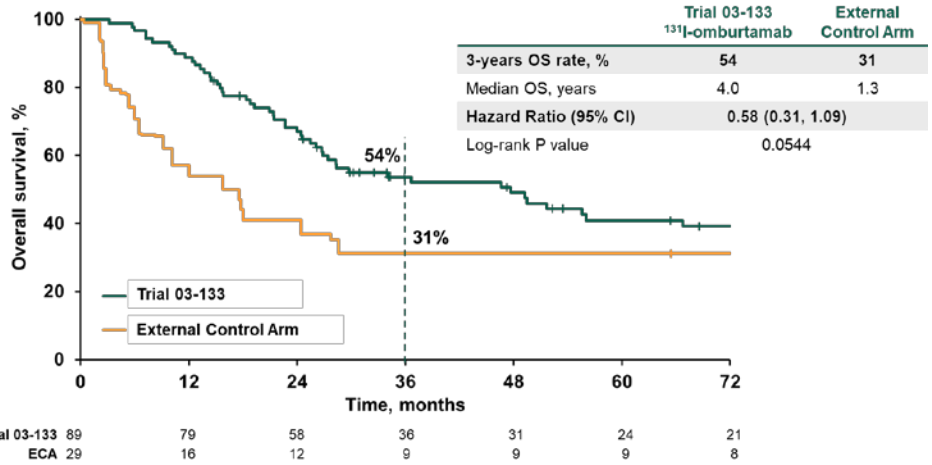
The propensity score method, which was mandated by the FDA, is a well-known and common approach for estimating a treatment effect when random assignment of treatments to patients is not possible. The method was used to balance all available baseline characteristics and prognostic factors between the populations in Trial 03-133 and the ECA. A statistical analysis plan pre-specifying several analyses was developed with input from the FDA. The analyses were conducted by an external statistical contract research organization (CRO). For more details on propensity score methods, please refer to Appendix 1.

The baseline characteristics and prognostic factors included in the propensity score model were age at neuroblastoma diagnosis, MYCN amplification, time from neuroblastoma diagnosis to CNS relapse, other timings e.g., time from CNS/LM relapse to initiation of treatment, and number of post-relapse treatments. The prognostic factors included in the model were all well balanced between patients in Trial 03-133 and the ECA (Table 18). Specific clinically important factors not included in the propensity score model were pattern of relapse (i.e., isolated CNS/LM metastases or combined CNS and systemic disease) and type of CNS/LM disease. However, for reasons described in detail in Section 6.4.3, these factors are not expected to materially change the outcome of the analysis. A post-hoc sensitivity analysis including pattern of relapse under additional assumptions was performed (Figure F).

Overall Survival in Trial 03-133 vs. External Control Arm

The complete case comparison of survival between Trial 03-133 and the ECA within MG2 is shown in Figure E. A clinically meaningful 42% relative reduction in the risk of death with [131]I-omburtamab (hazard ratio of 0.58 [95% CI: 0.31, 1.09], log-rank p-value = 0.0544) was obtained. The 3-year OS rate was notably higher in Trial 03-133 (54%) than in the ECA (31%), and an improved median OS exceeding 2 years was observed with [131]I-omburtamab (4 years vs. 1.3 years).

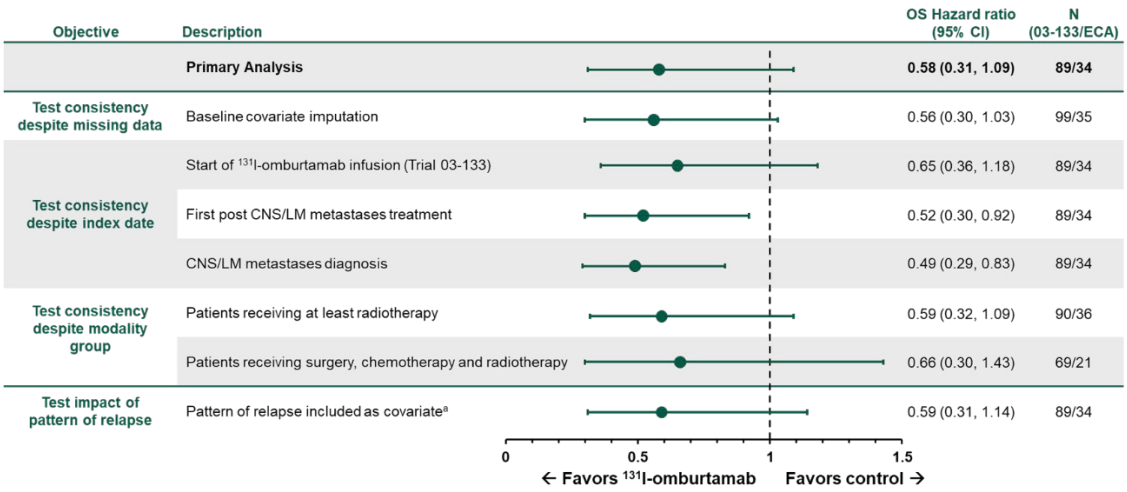
Figure E Overall Survival by Treatment Group – Primary Analysis



Note: The comparison of OS between Trial 03-133 and the External Control Arm is restricted to MG2 and index date A (start date of last type of post-CNS treatment). Subjects with missing values for the pre-specified baseline characteristics were excluded from the primary analysis (complete case analysis).

Six pre-specified sensitivity analyses were performed to assess the robustness of the primary analysis by examining the impact on the treatment effect of using imputation of missing data, different definitions of index dates (start date for the calculation of survival time), and choice of treatment modality groups. The magnitude of the effect seen in the primary analysis was maintained throughout the array of sensitivity analyses, with hazard ratios ranging from 0.49 to 0.66 in favor of [131]I-omburtamab, thus confirming the robustness of the results from the primary analysis (Figure F).

Figure F Overall Survival by Treatment Group – Sensitivity Analysis



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

Note: See Table 19 for a description of the sensitivity analyses.

CNS=central nervous system; ECA= external control arm; LM=leptomeningeal; OS=overall survival

Presence of isolated CNS/LM metastases versus combined CNS and systemic disease is an important prognostic factor. In Trial 03-133, presence of systemic disease was reported at time of first ^{131}I-omburtamab infusion. In the ECA, systemic disease was reported at time of CNS/LM relapse. The data suggests a similar distribution of systemic disease at time of CNS/LM relapse (Trial 03-133 [25%] and ECA [20%]), assuming that patients in Trial 03-133 also had systemic disease at time of CNS/LM relapse. A post-hoc sensitivity analysis examining the impact of pattern of relapse on the treatment effect was performed (Figure F), and the magnitude of the effect was in line with the results of the primary analysis.

Efficacy Conclusions

The rarity and severity of the indication necessitates non-standard trial design and analysis approaches. Under these circumstances, a conclusion of effectiveness cannot rely on one single analysis, but rather on the totality of evidence.

The results from Trial 03-133 demonstrate a 3-year OS rate of 57% and a median OS estimate of 51 months. The results of the supportive Trial 101 were consistent with Trial 03-133, demonstrating similar results in a multicenter setting. Moreover, in Trial 101, a clinically meaningful ORR of 35% with 5 complete and 2 partial responders was observed among the 20 patients with measurable disease at baseline. Additionally, stable disease was observed in 7 patients resulting in an overall disease control rate of 70%, which may contribute to the observed delay in disease progression.

The ECA selected for comparison to Trial 03-133 was derived from the largest population-based registry of high-quality patient-level data in this indication and represents an appropriate comparator. A clinically meaningful 42% relative reduction in the risk of death (hazard ratio of 0.58; 95% CI: 0.31, 1.09) was observed with the addition of ^{131}I-omburtamab to a multimodal treatment strategy compared with the ECA. An improved median OS exceeding 2 years (Trial 03-133 [4 years] and ECA [1.3 years] and an improved 3-year OS rate by 23% (Trial 03-133 [54%] and ECA [31%]) was also observed with ^{131}I-omburtamab. An array of sensitivity analyses consistently demonstrated the treatment effect in favor of ^{131}I-omburtamab.

The totality of the data provides substantial evidence of the efficacy of ^{131}I-omburtamab as addition to multimodal treatment for the treatment of neuroblastoma CNS/LM metastases.

Summary of Clinical Pharmacology

Following the intraventricular administration, ^{131}I-omburtamab that did not bind to tumor B7-H3 was rapidly removed from the CSF with a mean clearance half-life of 2 hours. The tumor bound fraction was cleared more slowly from the brain with a mean clearance half-life of 24 hours. Upon entering the blood, the median time to maximum concentration (T_{max}) was 24 hours. Clearance half-life from the whole body was 48 hours. The absorbed dose to the CSF was much higher than to the blood in both trials, reflecting the intraventricular administration of ^{131}I-omburtamab. Imaging dosimetry demonstrated that no organ absorbed radiation doses that were higher than generally accepted tissue tolerance levels.

Summary of Clinical Safety

The safety evaluation of ^{131}I-omburtamab is based on data from 159 patients with neuroblastoma with CNS/LM metastases (109 patients in Trial 03-133 and 50 patients in Trial 101).

Exposure

Across the two trials, 53% of the patients received two treatment doses (50% in Trial 03-133 and 60% in Trial 101), and 44% received one treatment dose (46% in Trial 03-133 and 40% in Trial 101). In Trial 03-133, two patients received no treatment doses (only dosimetry doses of 2 mCi), and two patients received more than two treatment doses. Overall, 144 patients received the proposed labeled treatment dose (50 mCi): 94 patients in Trial 03-133 and 50 patients in Trial 101. A total of 10 patients in Trial 03-133 received treatment doses ranging from 10 to <50 mCi and 5 patients received treatment doses ranging from >50 to 70 mCi during the dose-escalation part of the trial.

Adverse Events and Potential Risks

An overview of treatment emergent adverse events (TEAEs) is provided in Table F.

Table F Overview of Treatment Emergent Adverse Events

	Patients, n (%)	
	Trial 03-133 N (%)	Trial 101 N (%)
Safety Analysis Set	**109**	**50**
Patients with at least one TEAE	**102 (93.6)**	**49 (98.0)**
Grade ≥3 TEAEs	93 (85.3)	33 (66.0)
SAEs	54 (49.5)	18 (36.0)
TEAEs leading to discontinuation of ^{131}I-omburtamab	11 (10.1)	7 (14.0)
TEAEs leading to death	0	1 (2.0)

SAE = serious adverse event; TEAE = treatment-emergent adverse event.

As expected in a heavily pretreated population, and known from other radiolabeled antibody products, the most common TEAEs were consistent with myelosuppression.[24, 25] The most common TEAEs were decreased lymphocyte count/lymphopenia, decreased platelet count and decreased white blood cell count. Overall, 83% (Trial 03-133) and 72% (Trial 101) of the patients had at least one event relating to hematopoietic cytopenia. The most common severe TEAEs (CTCAE Grade 3 or higher) were also related to myelosuppression, with decreased platelet count as the most common event (55% and 32% of patients in Trial 03-133 and Trial 101, respectively); see Figure G and Figure H.

Note, in Trial 03-133, all abnormal laboratory results were recorded as adverse events (without Investigator's assessment of clinical significance). Thus, many of the TEAEs related to myelosuppression had only minimal clinical impact.

Figure G Trial 03-133: TEAEs consistent with myelosuppression

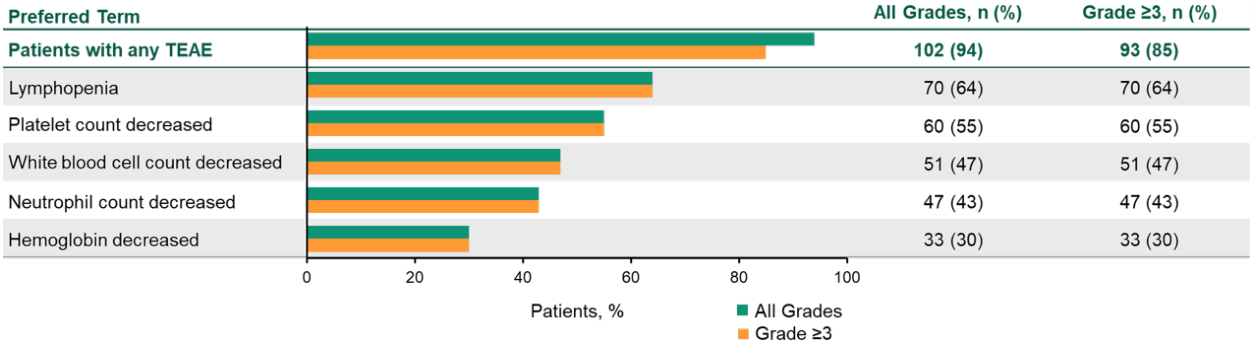
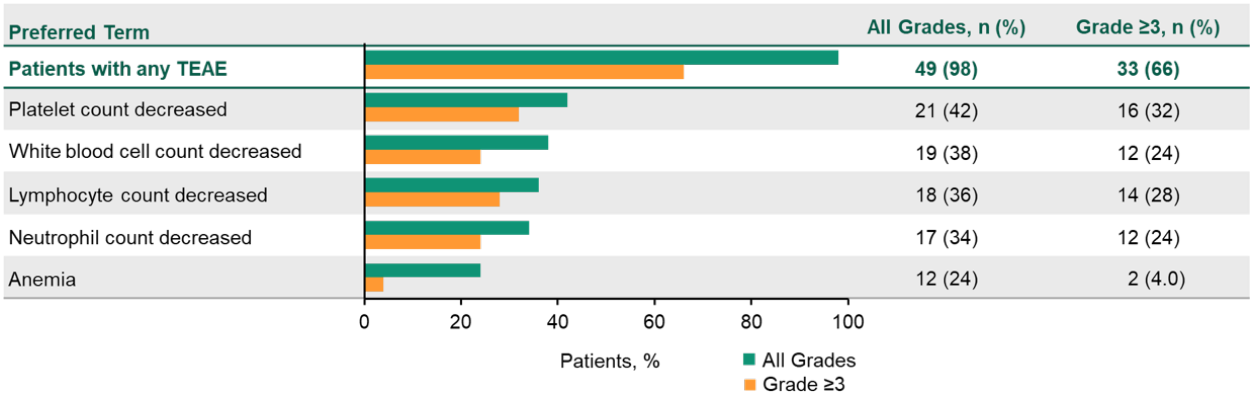


Figure H Trial 101: TEAEs consistent with myelosuppression



Decreased platelet count was the most common cause of treatment discontinuation (8 of 11 TEAE discontinuations in Trial 03-133 and 5 of 7 TEAE discontinuations in Trial 101), hindering patients from receiving a second treatment dose of [131]I-omburtamab.

Myelosuppression is considered the key risk with [131]I-omburtamab treatment and is discussed below, together with other potential risks. Rare TEAEs considered medically important include intracranial hemorrhage, secondary malignancies and chemical meningitis (Table G).

Table G Rare Medically Important Adverse Events

System Organ Class Preferred Term	Patients, n (%) Trial 03-133 N=109	Patients, n (%) Trial 101 N=50
Nervous system disorders		
Hemorrhage intracranial	0	4 (8)
Secondary malignancies		
Myelodysplastic syndrome	3 (3)	0
Acute myeloid leukemia	2 (2)	0
Papillary thyroid cancer	0	1 (2)
Procedural complications		
Chemical meningitis	3 (3)	2 (3)

Potential clinical risks with myelosuppression are severe bleedings and increased susceptibility to infections. One possibly related fatal event of intracranial hemorrhage was reported for a patient with multiple CNS metastases in Trial 101 (see further details on events of intracranial hemorrhage below). Two cases of febrile neutropenia were reported, and one serious infectious event (sepsis) was found to be associated with severely reduced (CTCAE grade 3 or higher) neutrophil levels (Trial 101). The risks related to myelosuppression are mitigated by withholding or delaying treatment for patients with insufficient hematological status and by closely monitoring blood counts during treatment. Severe myelosuppression may be treated with transfusions or growth factors in accordance with local medical practice.

Four events of intracranial hemorrhage were reported in Trial 101 (Table G). One event was fatal. Two of the patients were reported to have neurological sequelae, in the form of limb weakness. The last patient had no sequalae. Out of the 4 patients with intracranial hemorrhage, 3 patients had Grade 3 or 4 thrombocytopenia and 1 patient had Grade 1 thrombocytopenia at time of the event. In all 4 cases, CNS disease progression was observed, and considered to be the most likely cause of the intracranial hemorrhage. It is well documented that hemorrhage is a common manifestation of disease progression in neuroblastoma patients with CNS metastases, based on the natural history of this disease.[12, 26]

Secondary malignancies such as myelodysplastic syndrome or acute leukemia are potential risks with the use of ^{131}I-omburtamab, especially in patients who have received significant amounts of chemotherapy and radiation therapy prior to treatment with ^{131}I-omburtamab. In Trial 03-133, isolated cases of myelodysplastic syndrome (3 cases) and acute leukemia (2 cases) diagnosed between 7 months and 5 years after the last dose of ^{131}I-omburtamab were reported. One patient in Trial 101 was diagnosed with a thyroid malignancy (papillary thyroid cancer) approximately one year after the first exposure to ^{131}I-omburtamab.

Chemical meningitis is a non-infectious inflammation of the meninges caused by exposure to the radiolabeled antibody and is considered to be infusion related. Five patients had chemical meningitis (3 in Trial 03-133 and 2 in Trial 101). Four events were SAEs and led to discontinuation of trial treatment. All 5 events resolved with supportive treatment and without any sequalae. Chemical meningitis can be mitigated with dexamethasone treatment. Since the dose of the required dexamethasone pre-treatment in Trial 101 was increased in 2019, 33 additional patients have been treated. No new events of chemical meningitis have been reported among the additional patients, and Y-mAbs considers the risk of chemical meningitis to be successfully mitigated.

Other risks related to radiation exposure were assessed and did not give rise to any safety concern. These included thyroid suppression, neurotoxicity, and infusion-related reactions; for details, please refer to Section 7.8.5.

Safety Conclusions: In both clinical trials, adverse reactions were generally manageable. The most common severe (Grade 3 or higher) TEAEs were related to myelosuppression, which was expected and known from other radiolabeled antibody products. Other medically important TEAEs included intracranial hemorrhage, secondary malignancies, and chemical meningitis.

Benefit-Risk Evaluation

There is a high unmet medical need for an efficacious treatment of CNS/LM metastases in pediatric patients with neuroblastoma. Considering the extreme rarity of neuroblastoma with CNS/LM metastases, the number of patients treated with ^{131}I-omburtamab in the clinical trial program and the duration of follow-up provide an extraordinary and unprecedented amount of data and a solid basis to evaluate ^{131}I-omburtamab in this patient population.

Survival results from Trial 101 were consistent with Trial 03-133, supporting the efficacy of ^{131}I-omburtamab in a multicenter setting. Following multimodal treatment with addition of ^{131}I-omburtamab, a disease control rate of 70% (Trial 101), and CNS/LM PFS rate at 6 months of 75% (Trial 101) and at 12 months of 63% (Trial 03-133) underline that a delay in CNS/LM disease progression was achieved. In today's treatment landscape for neuroblastoma, the overall survival benefit for patients comes from their ability to receive and tolerate a sequence of therapies or multimodal treatments. The addition of ^{131}I-omburtamab to this sequence of treatments, contributes to the overall delay in disease progression.

Meaningfully prolonged survival was observed following treatment with ^{131}I-omburtamab after multimodal treatment in Trial 03-133 compared to an ECA with an estimated hazard ratio of 0.58 (95% CI: 0.31, 1.09). In addition, an improved 3-year OS rate by 23% and a clinically relevant median OS benefit exceeding 2 years was observed with ^{131}I-omburtamab treatment.

In both clinical trials, adverse reactions were generally manageable. The most common TEAEs were consistent with myelosuppression. As expected in a heavily pretreated population, and known from other radiolabeled antibody products, the main risk was myelosuppression.[24, 25] The risk is mitigated by withholding or delaying treatment for patients with insufficient hematological status and by closely monitoring blood counts during treatment. Severe myelosuppression may be treated with transfusions or growth factors in accordance with local medical practice. Other medically important events reported in the trials were intracranial hemorrhage (all reported in association with CNS disease progression), secondary malignancies, and chemical meningitis. Overall, the safety profile of ^{131}I-omburtamab is acceptable given the seriousness of the disease being treated.

Conclusion

In the context of a rare life-threatening disease with no approved therapies and a clear unmet medical need, the benefit-risk profile of ^{131}I-omburtamab is favorable. This assessment is based on the totality of the efficacy data, which showed consistent evidence of clinically meaningful efficacy of ^{131}I-omburtamab in the treatment of CNS/LM metastases in neuroblastoma patients, as well as an acceptable and manageable safety profile.

2 Background and Scientific Rationale

2.1 Introduction

Y-mAbs Therapeutics Inc. (Y-mAbs) is developing ^{131}I-omburtamab (OMBLASTYS) for the treatment of CNS/LM metastases in pediatric patients with neuroblastoma. Patients with this ultra-rare disease have a very poor prognosis and there is a high unmet medical need for an efficacious treatment.

^{131}I-omburtamab is an iodine-131 radiolabeled murine monoclonal antibody that recognizes and binds selectively to the B7-H3 (cluster of differentiation 276 [CD276]) antigen expressed on the surface on neuroblastoma tumor cells. ^{131}I-omburtamab emits radiation in the form of beta particles and gamma rays. The beta-emission from iodine-131 induces cellular damage to B7-H3-expressing and neighboring cells resulting in deoxyribonucleic acid (DNA) damage and tumor cell death. For further information on ^{131}I-omburtamab and the mode of action, see Section 3.1.

^{131}I-omburtamab was initially developed at the Memorial Sloan Kettering Cancer Center (MSKCC; New York, US). The product has been in clinical development since September 2001 under the Investigational New Drug application (IND) 009351, which was originally submitted by MSKCC. The rights to the commercial development of omburtamab were licensed to Y-mAbs, and ownership of the IND was transferred from MSKCC to Y-mAbs in October 2017. For further information on the development and regulatory history of ^{131}I-omburtamab, see Section 4.1.

2.2 Disease Background and Unmet Medical Need

Neuroblastoma – Incidence and Treatment

Neuroblastoma is a rare cancer of neural crest origin with an incidence of approximately 10 per million children per year.[1-7] It is the most common extracranial solid tumor cancer in children and occurs most frequently in one of the adrenal glands, or in the para- and pre-vertebral sympathetic ganglia. At time of diagnosis 90% of patients are younger than 5 years with a median age at diagnosis of 19 months.[8]

The prognosis of neuroblastoma correlates closely with biological and clinical factors such as age at diagnosis, tumor stage and histology, and genetic and chromosomal abnormalities[9] These factors classify neuroblastoma into prognostic risk categories (low, intermediate, or high-risk) that are useful for prediction of outcome and choice of treatment strategies.

At the time of diagnosis about 50% of patients present with metastatic disease (Stage 4) classified as high-risk neuroblastoma.[9] The most frequent metastatic sites are the bone marrow, bone, liver, and skin.[27] The frontline therapy for Stage 4 high-risk neuroblastoma is multimodal and intensive with standard regimens containing four main components; induction chemotherapy, local control (surgery and radiation) of known tumor residues, consolidation therapy, and maintenance therapy.[10] Similar for all therapy options for systemic neuroblastoma is that they are unsuited for treatment of metastases in the CNS system and as a consequence the

CNS can act as a "sanctuary site" for cancer cells because the blood-brain barrier may impede the penetration of most chemotherapeutic agents. Additionally, antibodies used in systemic immunotherapy do not penetrate the blood-brain barrier.

CNS/LM Metastases in Patients with Neuroblastoma – Incidence, Treatment and Unmet Medical Need

CNS involvement at time of initial diagnosis is uncommon.[12] In most cases, patients present with either isolated CNS/LM relapse (estimated 50% of all CNS relapses) or CNS/LM relapse concomitant with recurrence in other sites.[12-14]

An estimated total of 3-6% of patients with Stage 4 high-risk neuroblastoma will develop CNS/LM metastases.[6, 12-15] Based on the incidence of neuroblastoma, the frequency of patients with CNS/LM metastases, and the size of US population, the number of patients with Stage 4 neuroblastoma and CNS/LM metastases in the US is estimated at 9–18 new patients per year (Table 1).

Table 1 Number of Neuroblastoma Patients with Stage 4 Disease and CNS/LM Metastases per Year in the US

	US
Population <15 years	~60 million
Incidence of neuroblastoma (10 per million per year)[1-6]	600
Number of patients with Stage 4 neuroblastoma per year[3-5]	300
Number of patients with Stage 4 neuroblastoma and CNS/LM metastases per year (frequency 3-6%)[6, 12-15]	**9-18**

CNS=central nervous system; LM=leptomeningeal; US=United States

The diagnosis of CNS/LM metastases in neuroblastoma is based on clinical symptoms, imaging, and CSF cytology. Magnetic resonance imaging (MRI) is the imaging modality of choice.[12]

Treatment of CNS/LM metastases in neuroblastoma is typically multimodal and may include one or more of the following options, although there are no broadly accepted clinical practice guidelines:

- Surgical debulking of tumor when feasible prior to irradiation, to reduce symptoms, oedema, and hemorrhage, or to correct CSF flow.
- Maximum feasible focal irradiation, whole brain irradiation, or craniospinal irradiation to alleviate symptoms, obtain disease control, and correct CSF flow in cases of obstruction.
- Systemically administered combination of blood-brain barrier crossing chemotherapies (e.g., irinotecan and temozolomide).

Irrespective of the treatment combinations used, OS remains poor, which is likely due to persistence of macroscopic and/or microscopic CNS/LM disease.[15] The median OS after

detection of the CNS/LM metastases is less than 1 year even with early detection and intervention[11-13, 16], and 3-year OS is <10%.[1, 13, 17, 18] Even among the best prognostic subset of patients who are able to receive intensive multimodal therapy, the available data suggest a median OS of only approximately 15 months.[13]

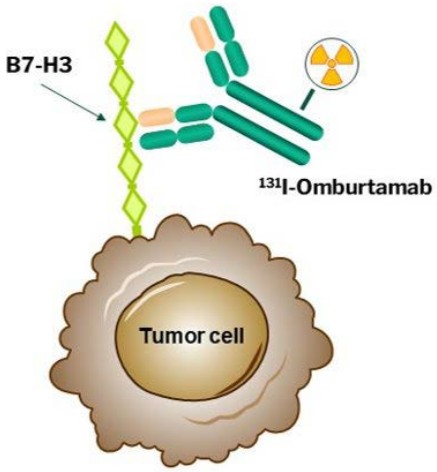
Therefore, there is a high unmet medical need for additional treatment options to be added to the existing treatment armamentarium and thereby improve the prognosis.

3 Product Overview

3.1 Drug Description and Mechanism of Action

^{131}I-omburtamab is an iodine-131 radiolabeled murine monoclonal antibody that recognizes and binds selectively to the transmembrane protein B7-H3 (Figure 1). B7-H3 is highly overexpressed in a wide range of human solid tumors, including neuroblastoma, and with only minimal expression in normal tissues.[19, 20] B7-H3-positive tumors are often correlated with a poor prognosis.

Figure 1 ^{131}I-omburtamab: an Iodine-131 Radiolabeled Anti-B7H3 Monoclonal Antibody



^{131}I-omburtamab emits radiation in the form of beta particles and gamma rays. The beta-emission from iodine-131 induces cellular damage to B7-H3-expressing and neighboring cells resulting in DNA damage and tumor cell death. The specific targeting of B7-H3-positive solid tumors allows delivery of radiation with limited toxic effects on normal tissues.[19]

^{131}I-omburtamab is delivered directly to the CSF via an intraventricular access device (e.g., Ommaya catheter); for details, see Section 3.2.2. Using the CSF-flow as a conduit, ^{131}I-omburtamab will reach and target B7-H3 expressing tumors or single tumor cells in the entire CSF compartment, including micro-metastatic CNS disease.

Omburtamab can be radiolabeled with iodine-131 up to a specific activity of 100 mCi/mg and still retain its immunoreactive properties.

The mass of antibody has been fixed (approximately 1 mg) in the clinical trial program with ^{131}I-omburtamab, both in the dosimetry and therapeutic dose setting.

Omburtamab was initially developed by MSKCC as a murine monoclonal antibody produced from a hybridoma derived from the fusion of mouse myeloma cells, Sp2/0-g14, and splenic lymphocytes from BALB/c mice immunized with human neuroblastoma cells (NMB 7).

Y-mAbs has since changed the manufacturing process to an *in vitro* cell culture-based process using the same hybridoma cell line as the MSKCC product.

3.2 Proposed Indication and Dosing Regimen

3.2.1 Proposed Indication

The proposed indication for ^{131}I-omburtamab is treatment of CNS/LM metastases in pediatric patients with neuroblastoma following standard multimodality treatment for CNS disease.

3.2.2 Proposed Dosing Regimen

^{131}I-omburtamab (OMBLASTYS) is formulated as a solution for intraventricular infusion. The proposed dosing regimen of ^{131}I-omburtamab is 2 age-based doses given 4 weeks apart (Table 2).

Table 2 ^{131}I-omburtamab (OMBLASTYS) Recommended Doses by Age

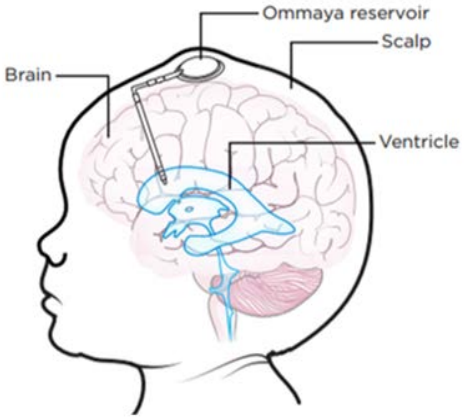
Age (years)	Dose (mCi)[a]
Less than 1	25.0 (22.5 – 27.5)
1 to less than 3	33.5 (30.2 – 36.9)
3 or older	50.0 (45.0 – 55.0)

a Doses should be adjusted to an accuracy of ± 10% prior to administration.

The rationale for the proposed dosing regimen is provided in Section 8.

^{131}I-omburtamab is administered via an intraventricular access device (e.g., Ommaya catheter); see Figure 2. Prior to starting treatment, adequate CSF flow and patency of the intraventricular access device must be confirmed. ^{131}I-omburtamab can be administered in an outpatient setting, observing standard radiation health and safety measures.

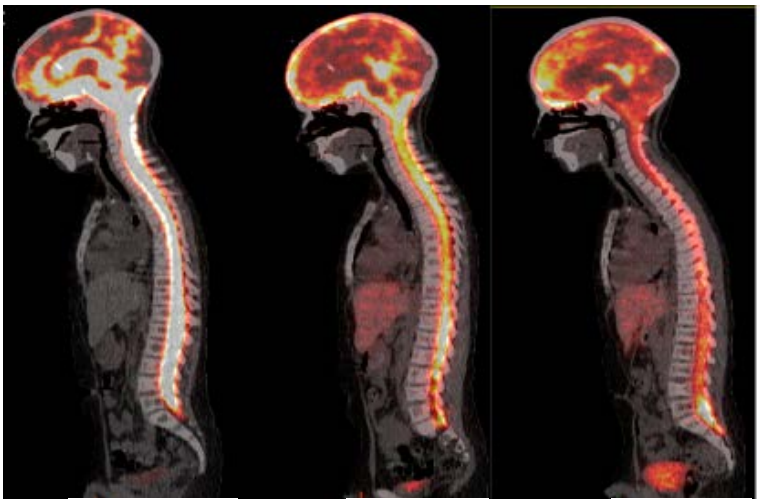
Figure 2 Administration of ^{131}I-omburtamab via an Ommaya Reservoir



Source: Memorial Sloan Kettering Cancer Center. 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.

As ^{131}I-omburtamab is delivered directly to the CSF via the intraventricular access device, distribution within the entire CSF and localization to tumor cells is ensured. Given the limited volume of CSF, even a low mass dose of antibody will result in a high concentration of radiolabeled omburtamab in the targeted compartment (Figure 3).

Figure 3 Distribution of Radiolabeled Omburtamab: 2–4, 24 and 48 Hours after Administration



2 to 4 hours 24 hours 48 hours

^{124}I-omburtamab administered to patients with neuroblastoma with LM metastases (Pandit-Taskar et al. 2019).[28]

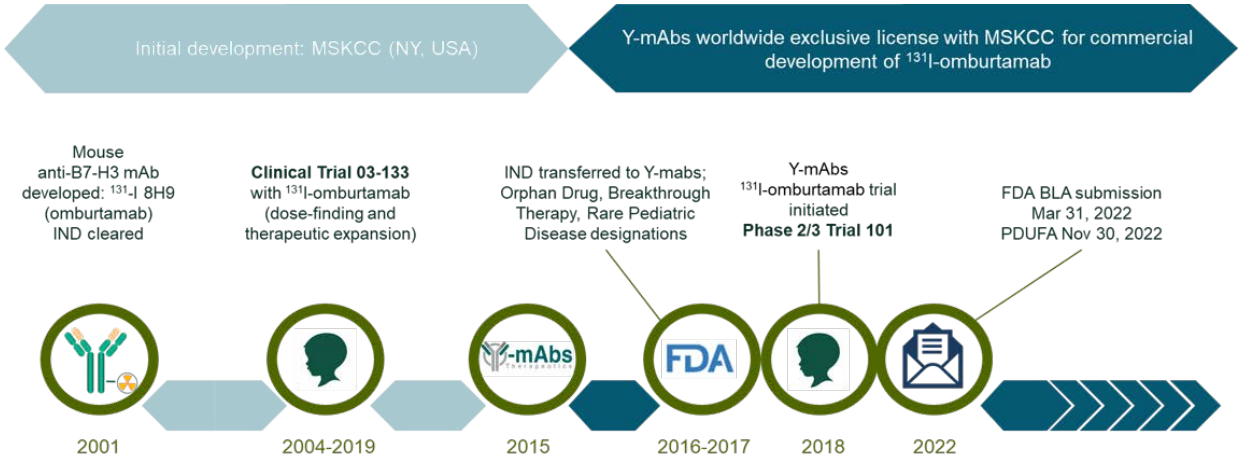
Intracerebroventricular administration has been used for decades in the clinic to circumvent the blood-brain barrier and provide treatment for adult and pediatric populations suffering from a variety of conditions, including varying cancer types.[29, 30] Kramer et al. assessed the safety and complication rate associated with ventricular access devices in patients receiving compartmental intraventricular radioimmunotherapy and concluded that minimal acute complications are observed and that long-term complications are rare.[29] In addition, a literature review conducted by Cohen-Pfeffer and colleagues concluded that the intracerebroventricular route of administration appears to be a safe and well-tolerated method of repeated long-term drug delivery in both pediatric and adult patients.[30]

4 Development Program

4.1 History of [131]I-omburtamab Development and Regulatory Interactions

[131]I-omburtamab was initially developed at the MSKCC; New York, US. The product has been in clinical development since 2001 under the IND 009351, which was originally submitted by MSKCC. The rights to the commercial development of [131]I-omburtamab were licensed to Y-mAbs in 2015, and ownership of the IND was transferred from MSKCC to Y-mAbs in 2017. Figure 4 highlights key milestones in the history of clinical development of [131]I-omburtamab. Details on regulatory interactions are summarized below.

Figure 4 History of [131]I-omburtamab Clinical Development



BLA=Biologics License Application; IND=Investigational New Drug; mAb=monoclonal antibody; MSKCC=Memorial Sloan Kettering Cancer Center; PDUFA date=Prescription Drug User Fee Act date

Clinical investigation of [131]I-omburtamab for the treatment of neuroblastoma with CNS/LM metastases was initiated with submission of Protocol 03-133 on 16 January 2004. Trial 03-133 was investigator-initiated at MSKCC. Rare Pediatric Disease (RPD) Designation and Orphan Drug Designation (ODD) were granted for the treatment of neuroblastoma on 20 July 2016 and 29 August 2016, respectively. Based on preliminary clinical evidence of efficacy in Trial 03-133, Breakthrough Therapy Designation (BTD) was granted to [131]I-omburtamab for the treatment of relapsed neuroblastoma with CNS/LM metastases on 18 May 2017. After partnering with Y-mAbs to pursue commercialization of [131]I-omburtamab, ownership of IND 009351 was transferred from MSKCC to Y-mAbs, effective 01 October 2017. The Y-mAbs sponsored Protocol 101 was submitted to the IND on 16 October 2017 and the trial was initiated (first drug administration) in December 2018.

Following transfer of the IND to Y-mAbs, clinical development of [131]I-omburtamab continued with frequent meetings and other regulatory interactions with the FDA. Important aspects of the clinical and manufacturing development of [131]I-omburtamab were determined, and general agreement was reached with the FDA on the details of the content and format of a BLA for [131]I-omburtamab.

The key regulatory interactions are summarized below:

- *09-Dec-2016 Type B meeting and 14-Jun-2017 Pre-IND/End of Phase 2 meeting*
  Essential design elements of the multicenter clinical trial (Trial 101) were discussed to ensure that the trial design could provide substantial evidence of safety and effectiveness in support of a future BLA. Important elements discussed included non-randomized design and conduct of the trial at sites outside of MSKCC.
- *26-Mar-2019 Type B multidisciplinary meeting*
  The proposed dosing regimen, including the rationale for not utilizing individualized doses was discussed. Further discussion included the low number of patients in clinical trials with measurable disease at baseline, the number of patients eligible for one versus two treatment cycles, and the rationale for age-based dose modifications implemented in the dosing regimen.
- *1-Sep-2019 Type B CMC meeting*
  Y-mAbs and FDA discussed product comparability data and additional information needed to ensure that differences noted in Drug Substance would not impact clinical safety or efficacy; process validation activities and timing with respect to BLA submission and Pre-License Inspection were discussed.
- *19-Nov-2019 Type B and 25-Feb-2020 Pre-BLA meetings*
  Y-mAbs and FDA agreed on clinical endpoints to support a BLA for accelerated approval of ^{131}I-omburtamab, including 3-year OS data and 12-month CNS/LM PFS from Trial 03-133 and 12-month OS and 6-month CNS/LM PFS from 101. Plans to assess ^{131}I-omburtamab immunogenicity as post-marketing requirement were also discussed.
- *05-Aug-2020 Initial BLA submission completed*
  Y-mAbs initially completed the submission of BLA 761176 for rolling review. However, after a preliminary review, the FDA determined that the application was not sufficiently complete to permit a substantive review based on the comparisons of survival data from Trial 03-133 with external controls, as communicated in the Refusal to File letter received on 02-Oct-2020.
- *November 2020 to September 2021 – Type A meeting and a series of Type B guidance meetings*
  Discussions centered around assessing the suitability of the external control data (German Registry and SIOPEN) for comparisons with survival data from Trial 03-133. This included plans for statistical analyses of the data to adequately establish the treatment effect of ^{131}I-omburtamab and support an approvable application for the use of ^{131}I-omburtamab in the indicated population. In these discussions, Y-mAbs and FDA agreed that a resubmission of BLA 761176 would incorporate new efficacy analyses, including multiple sensitivity analyses, performed using a propensity score weighting approach for external control comparisons. FDA stated that the determination of efficacy of ^{131}I-omburtamab would be based on the totality of evidence, and not rely on a single analysis.

- *13-Jan-2022 Type B pre-BLA meeting*
  Plans for a resubmission of BLA 761176, based on the efficacy analyses using a propensity score model to evaluate OS in Trial 03-133 compared with the external control group were discussed. FDA confirmed that the application would be considered for a regular approval pathway based on the OS primary endpoint. FDA indicated that additional information regarding radiation treatment of patients in the external control arm, as well as plan for an audit of the external control database was needed before agreement on the content of a complete application could be reached.
- *21-Mar-2022 Informal teleconference*
  Discussion of outstanding issues identified during the pre-BLA meeting. Y-mAbs followed up with a proposal for FDA to validate the data in the German Registry dataset based on a potential audit of de-identified records at the Neuroblastoma Study Center in Cologne, Germany.
- 31-Mar-2022 BLA resubmission completed.

4.2 Early Development Supporting Development of ^{131}I-omburtamab

Pharmacological and toxicological studies provided nonclinical evidence of the potential effectiveness of ^{131}I-omburtamab as an anti-tumor agent which was unlikely to have significant adverse effects on unintended target tissues. *In vitro* pharmacology studies have shown that omburtamab specifically targets the membrane of B7-H3 expressing cancer cells, that it has preferential affinity for a spectrum of cancerous tissues with marginal binding to normal tissues, and that it does not cross-react with normal human brain tissue. The *in vivo* effectiveness of ^{131}I-omburtamab as an anti-tumor agent was observed in a xenograft mouse model bearing omburtamab-reactive human tumor cells. In early nonclinical studies evaluating the safety and feasibility of dosing with omburtamab in animals, administration of either the unlabeled or radiolabeled form of the antibody was well tolerated in mice, rats, and monkeys. These characteristics supported ^{131}I-omburtamab as a viable clinical candidate for radioimmunotherapy.

4.3 Clinical Development Overview

An overview of the clinical trials that comprise the clinical development program for ^{131}I-omburtamab (Trials 03-133 and 101) is provided in Table 3.

Trials 03-133 and 101 are conducted in patients with neuroblastoma with CNS/LM metastases. Trial 03-133 also included adult and pediatric non-neuroblastoma patients with a histologically confirmed diagnosis of an omburtamab-reactive (i.e., B7-H3 positive) malignancy with CNS/LM metastases; however, only SAE data from those patients are included in the BLA.

Both trials are open-label, single-arm trials. Open-label trials are appropriate in this rare and life-threatening indication with currently no approved treatment options. A randomized controlled clinical trial of sufficient size is neither considered feasible nor ethically justifiable (i.e., inclusion of a placebo arm).

Trial 03-133 was investigator-initiated at MSKCC (2004) and was not originally intended for regulatory purposes. Some of the endpoints to support the BLA (Table 3) were therefore added at a late stage of the trial following transfer of the IND to Y-mAbs in 2017. These changes were made in agreement with the FDA (Section 4.1).

Trial 101 was initiated at Y-mAbs (2018) after transfer of the IND. Trial 101 is an ongoing supportive international multicenter trial. Historically, most of ^{131}I-omburtamab development has occurred at MSKCC where Trial 03-133 has been conducted. Trial 101 was conducted to support efficacy and safety results in Trial 03-133 and to demonstrate that ^{131}I-omburtamab could be prepared and administered consistently in a multicenter set-up.

Trial 03-133 and Trial 101 have been initiated and conducted at different time periods and there are differences in the trial design and data capturing between the two trials. Therefore, data from the two trials were not pooled.

Trial 03-133 and Trial 101 are the only prospective clinical trials in patients with neuroblastoma with CNS/LM metastases, and Trial 03-133 represents the largest clinical study of neuroblastoma patients with CNS/LM metastases in the US, enrolling at least one-third of all diagnosed patients in the US from 2004 to 2018.

To support the assessment of clinical efficacy of ^{131}I-omburtamab appropriate external control sources were used for comparison with data from Trial 03-133 (Section 4.6).

Table 3 Overview of Clinical Trials in ^{131}I-omburtamab Development Program

Trial ID	Objectives of the Trial[a]	Efficacy Endpoints for the BLA	Full Trial Population	No. of Neuroblastoma Patients	^{131}I-omburtamab Treatment Dose[b]	Status
03-133[c] Single-center	Primary: • Define clinical toxicities of intrathecal ^{131}I-omburtamab Main secondary: • OS at 3 years • CNS/LM progression at 6 months	Primary: • OS at 3 years Secondary: • CNS/LM PFS at 12 months • Duration of follow-up	Patients with a histologically confirmed diagnosis of an omburtamab-reactive malignancy[d] with CNS/LM disease	Safety: 146 (109 neuroblastoma, 68 non-neuroblastoma) Efficacy: 107 PK/dosimetry: 27	Dose escalation: 10–80[e] mCi Expansion phase: 50 mCi/treatment dose	Initiated: February 2004; Enrolment closed July 2019
101[f] Multi-center	Primary: • OS at 3 years Main secondary: • Estimated OS at 12 months • CNS/LM PFS at 6 and 12 months • ORR at 6 months • PK and dosimetry • Assess safety • Evaluate immunogenicity	Primary: • CNS/LM PFS at 6 months Secondary: • OS at 12 months • ORR at 6 months	Pediatric neuroblastoma patients with CNS/LM metastases	Safety: 50 Efficacy: 50 PK/dosimetry: 26[g]	50 mCi/treatment dose	Initiated: December 2018 (first drug administration) Ongoing

CNS = central nervous system; LM = leptomeningeal; MBq = mega-becquerel; mCi = millicurie; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics.

a: Except for the primary objectives for Trial 03-133 and Trial 101, and the secondary objective of CNS/LM progression at 6 months in Trial 03-133, the objectives listed are addressed in the BLA.

b: Treatment dose reductions were made in both trials for patients less than 3 years old per protocol instructions. Route of administration: intraventricular. Patients were also exposed to a 2 mCi dosimetry dose in Trials 03-133 and 101 (Trial 101: only patients enrolled on protocol versions 1-7) (Trial 03-133: dosimetry dose was ^{124}I-omburtamab for patients enrolled on protocol versions 7-13).

c: Trial 03-133: The efficacy data cut-off date for neuroblastoma patients was 30 June 2019 with follow-up survival data collected through 12 March 2020. The safety data cut-off date was 01 February 2022 (neuroblastoma and non-neuroblastoma patients).

d: Trial 03-133: Testing of omburtamab reactivity by immunohistochemical staining or immunofluorescence was not necessary for the enrolment of neuroblastoma patients in Trial 03-133 per Inclusion Criterion 1.

e: Trial 03-133: The highest dose level administered to any patient in Trial 03-133 was 80 mCi; the highest dose level administered to a neuroblastoma patient was 70 mCi.

f: Trial 101: Enrolment cut-off was 01 February 2022; data cut-off was 31 March 2022.

g: Trial 101: 26 patients were dosed with a dosimetry dose, but one of the patients did not contribute to the PK and dosimetry evaluations.

4.4 Trial 03-133

Trial Design

Trial 03-133 was an open-label, non-randomized, single-arm, single-center trial in patients with CNS/LM relapse from a histologically confirmed diagnosis of an omburtamab-reactive (i.e., B7-H3 positive) malignancy, such as neuroblastoma, medulloblastoma, retinoblastoma, rhabdomyosarcoma, and desmoplastic small round cell tumor. The BLA is based on data from neuroblastoma patients. Non-neuroblastoma patients contribute with supportive data on SAEs.

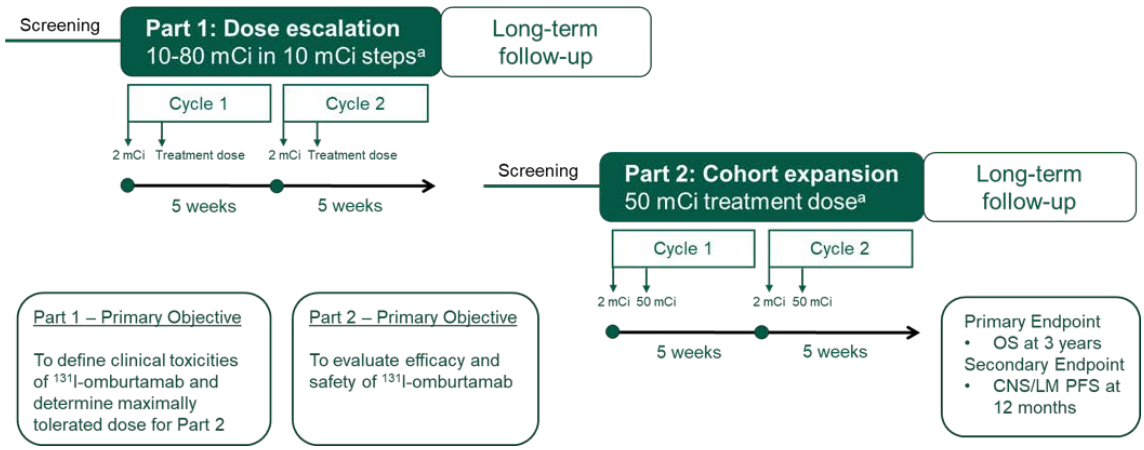
Trial 03-133 had two parts:

Part 1 was an open-label, 3+3 dose escalation part, designed to evaluate the maximum tolerated dose (MTD) of intraventricularly infused [131]I-omburtamab. To identify the MTD, a dose escalation scheme was employed with patients entering the trial in cohorts of three patients to receive treatment doses from 10 mCi to 60 mCi, and cohorts of six patients to receive treatment doses planned from 70 to 100 mCi. Note that dose in this context describes an activity and not a mass dose.

Part 2 was a single-arm, open-label design, in which the selected treatment dose of 50 mCi (based on the dose escalation part) was administered intraventricularly to additional patients to obtain additional efficacy and safety data.

In both parts of the trial, patients received a dosimetry dose (2 mCi) in Week 1, followed by administration of a treatment dose in Week 2 (Figure 5). Patients without objective disease progression (as determined by neurologic and/or radiographic examination) 4 weeks after the last treatment dose and without unexpected Grade 3 or 4 toxicity were eligible for a second cycle of treatment (including a dosimetry and a treatment dose). Patients underwent the same treatment plan and post-treatment evaluation after the second infusion series.

Figure 5 Trial 03-133: Trial Design



[a] Treatment dose was reduced depending on age

CNS=central nervous system; LM=leptomeningeal metastases; PFS=progression-free survival; OS=overall survival

As per Trial 03-133 protocol, dose adjustments were made for patients under 3 years of age (33% dose reduction), and under 1 year of age (50% dose reduction). The rationale for dose reduction is provided in Section 8.

Procedures and schedule

Pre- and post-treatment evaluation included a detailed history, physical examination, neurological examination, Ommaya patency/CSF flow study (pre-treatment), vital signs, hematology, biochemistry, urinalysis, comprehensive metabolic profile, thyroid function tests and CSF cytology. Blood and CSF for dosimetry and PK was sampled after the dosimetry dose. Adverse events (AEs) were recorded continuously and up to 30 days after the last treatment. Further details on recording/reporting of AEs are provided in Section 7.4. Magnetic resonance imaging (MRI) studies of the brain and spine and CSF cytology were performed <3 weeks before initiation of the first ^{131}I-omburtamab treatment cycle.

Trial Location

The trial is a single-center trial conducted at MSKCC, New York, United States.

Inclusion/Exclusion Criteria

Key inclusion criteria:

- Historically confirmed omburtamab reactive malignancy.
- CNS/LM disease that is refractory to conventional therapies or for which no conventional therapy exists.
- Eligible patients may have active malignancy outside the CNS.

Key exclusion criteria:

- Obstructive or symptomatic communicating hydrocephalus.
- Uncontrolled life-threatening infection.
- Rapidly progressing or deteriorating neurologic examination.
- Prior cranial or spinal irradiation or chemotherapy < 3 weeks prior to the start of the trial.
- Severe major organ toxicity greater than Grade 1. Specifically, renal, cardiac, hepatic, pulmonary, and gastrointestinal system toxicity.

Dose Selection

The decision to escalate the dose to a higher level or stop escalation in Part 1 of Trial 03-133 was based on the occurrence of dose-limiting toxicities. A dose-limiting toxicity was defined as a Common Terminology Criteria for Adverse Event (CTCAE) Grade 3 or 4 toxicity assessed as clearly related to ^{131}I-omburtamab (excluding headache, fever, vomiting, hyperglycemia, lymphopenia, and anemia). In Part 1, neuroblastoma and non-neuroblastoma patients received treatment doses ranging from 10 to 80 mCi administered by intraventricular infusion. The highest treatment dose administered to a neuroblastoma patient was 70 mCi, and the highest dose level administered to a non-neuroblastoma patient was 80 mCi.

Although a maximum tolerated dose was not attained in Part 1, a dosing regimen of 2 treatment doses of 50 mCi given 4 weeks apart was selected for further development and implemented in Part 2 of the trial. The 50 mCi dose level was selected because the overall safety and tolerability and specifically the level of myelosuppression observed at this dose was found to be manageable.

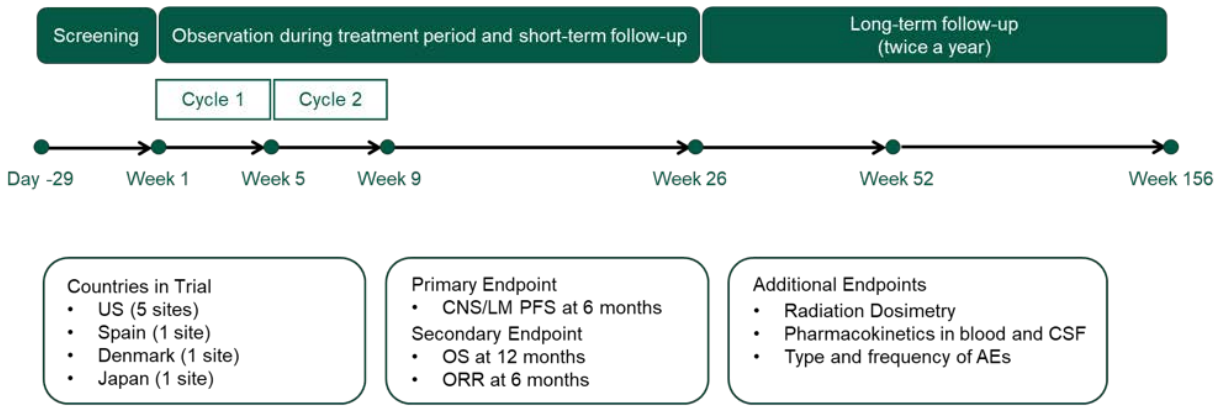
4.5 Trial 101

Trial Design

The supportive Trial 101 was an open-label, single-arm, non-randomized international multicenter trial including patients with histologically confirmed neuroblastoma with progression or relapse in the CNS or LM. Patients must have progressed in CNS/LM through induction therapy or have relapsed in CNS/LM following induction.

A treatment cycle started with a dosimetry dose (2 mCi) of ^{131}I-omburtamab during Week 1, followed by a treatment dose (50 mCi) of ^{131}I-omburtamab during Week 2. The treatment dose was followed by a 3-week observation period, which was followed by MRI, CSF cytology, and safety monitoring. Patients without objective disease progression (as determined by radiographic examination) 4 weeks after the treatment dose and without clinically significant Grade 3 or 4 toxicity were eligible for a second dosing cycle at the same dose administered during the first cycle (Figure 6). After Version 7 of Protocol 101 the dosimetry dose was removed from the dosing cycles since sufficient information on PK and dosimetry had been obtained. The same dose reduction as in Trial 03-133 for children below 3 years of age was applied.

Figure 6 Trial 101: Trial Design



CNS=central nervous system; LM=leptomeningeal metastases; PFS=progression-free survival; ORR=objective response rate; OS=overall survival

Procedures and schedule

Screening evaluations (including medical history, physical and neurologic examination, hematology, clinical chemistry) were completed within 30 days before the ^{131}I-omburtamab treatment period. MRI, CSF cytology, and baseline performance testing were completed before

the first ^{131}I-omburtamab administration. Adequate CSF flow for ^{131}I-omburtamab intraventricular therapy was determined by Ommaya patency/CSF flow study.

MRI scans of the brain and spine was carried out at end of Cycle 1, end of Cycle 2 and at Week 26. Investigation for neurotoxicity was carried out at baseline, end of Cycle 1, start of Cycle 2, end of Cycle 2 and Week 26. CSF sampling for cytology, total protein, glucose, and cell count took place at end of Cycle 1, end of Cycle 2 and Week 26. Blood and CSF for dosimetry and PK was sampled at Week 1 and 3.

Clinical response assessment for CNS/LM metastases was carried out during screening and at end of Cycle 1, end of Cycle 2 and Week 26. Systemic disease progression was assessed weekly from Week 1 to end of Cycle 2, at Week 26 and twice a year during long-term follow up. CNS/LM disease progression was assessed at Week 26 and twice a year during long-term follow up.

Trial Location

Trial 101 is a multicenter trial conducted at eight sites: five sites in the United States (36 patients), one site in Spain (12 patients), one site in Denmark (1 patient), and one site in Japan (1 patient).

Inclusion/Exclusion Criteria

Key inclusion criteria:

- Patients aged 0-18 years
- Historically confirmed neuroblastoma with CNS/LM metastases
- Life expectancy of ≥ 3 months
- Adequate CSF flow via an indwelling ventricular catheter (e.g., Ommaya catheter)
- Progressive disease in the CNS/LM through induction therapy or CNS/LM relapse following induction
- Stable systemic disease not requiring chemo/immunotherapy

Key exclusion criteria:

- Obstructive or symptomatic communicating hydrocephalus
- Worsening neurological function within 3 weeks of first dose of study treatment
- Cranial or spinal irradiation within 3 weeks before the first dose of ^{131}I-omburtamab
- Previous anti-B7-H3 treatment
- Severe major nonhematologic organ toxicity greater than Grade 2; specifically, any renal, cardiac, hepatic, pulmonary, and gastrointestinal system toxicity

Dose selection

The dosing regimen of two treatment doses of 50 mCi given 4 weeks apart was selected on the basis of Trial 03-133.

4.6 Selection of External Controls for Comparison of Efficacy

Given the rare and serious nature of neuroblastoma with CNS/LM metastases, randomized controlled trials in this patient population are operationally infeasible within a reasonable timeframe. Thus, there are inherent challenges with conducting studies that meet regulatory standards for demonstrating effectiveness in this disease. Therefore, as discussed in the draft FDA guidance Demonstrating Substantial Evidence of Effectiveness for Human Drugs and Biological Products (December 2019)[31] flexibility in approval standards may be warranted under these circumstances (i.e., rare and serious condition) in order for patients to gain access to life-prolonging treatment in diseases with a high unmet medical need. In this situation, use of an external control population to establish the effectiveness, in accordance with the ICH E10 guidance Choice of Control Group and Related Issues in Clinical Trials (20 July 2000) and the FDA Guidance for Industry Rare Diseases: Common Issues in Drug Development (January 2019), is considered appropriate.

To support the assessment of clinical efficacy of ^{131}I-omburtamab two external patient-level data sources were used:

- Data from the Study Database for Neuroblastoma maintained at the Neuroblastoma Study Center (Cologne, Germany). The database is regularly aligned with data from the Central German Childhood Cancer Registry (CGCCR). Data from the Study Database for Neuroblastoma is referred to as “German Registry” in this Briefing Document (Section 4.6.1).
- Data from the International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) (Section 4.6.2).

Due to differences in the granularity of data in these two sources, pooling for the purpose of formal analyses was not possible. The German registry was more comprehensive and was chosen as source for the external control arm. The SIOPEN data were used for supportive purposes only.

4.6.1 German Registry

The source data in the German registry are clinical data from patients included in the national clinical trials NB90, NB97, and NB2004 from 1990 to 2015; 98.8% of all neuroblastoma patients diagnosed in Germany were included in the national trials, with continuous update of clinical data. The survival information in the German Registry is aligned yearly with the national CGCCR collecting data from all pediatric oncology units affiliated with the German Society for Pediatric Oncology and Hematology, and the Neuroblastoma Study Center in Cologne.

In the German Registry, 1338 patients with Stage 4 neuroblastoma were identified from the 3 clinical trials. A subset of these (N=120) had CNS or LM disease at first recurrence. This group of patients is of adequate size to support a comparison with the Trial 03-133 population. Furthermore, an on-site FDA inspection conducted in September 2022 at the study center in Cologne confirmed that the registry data were verifiable and generally of very high quality suitable for real-world evidence studies.

4.6.2 SIOPEN

European International Society of Pediatric Oncology Neuroblastoma Group (SIOPEN) was formed in 1998 with the goal of being a pan European neuroblastoma clinical trial group for all stages of neuroblastoma. The purpose of the organization is to perform and facilitate clinical, translational, and basic research for children and adolescents with neuroblastoma in European countries and worldwide to improve the outcome of these patients. SIOPEN coordinates neuroblastoma trials across European countries.

SIOPEN initiated a multicenter, international, randomized Phase 3 trial (HR NBL1/SIOPEN, NCT00030719) that recruited high-risk neuroblastoma patients beginning in 2002. Patients were randomized to receive high-dose chemotherapy and from 2002 to 2010, the patients received either busulfan-melphalan (Bu-Mel) or carboplatin/etoposide/melphalan. After 2010, Bu-Mel became the SIOPEN standard of care. Data from the recent SIOPEN publication (Berlanga et al, 2021)[13] were presented in the BLA (N=53 patients with confirmed CNS relapse). Due to the limited granularity of the available data, it was not technically possible to pool the SIOPEN and the data from the German Registry. Thus, the SIOPEN data were included as supportive only on a summary level.

5 Clinical Pharmacology

5.1 Methods

Background

The clinical pharmacology of ^{131}I-omburtamab was investigated in Trials 03-133 and 101 in pediatric patients with neuroblastoma with CNS/LM metastases. The clinical pharmacology investigations included radiation dosimetry, based on imaging (whole body gamma scans) and samples (CSF and blood), and PK based on radioactivity counts data from CSF and blood samples.

The assessment of the dosimetry and PK properties of ^{131}I-omburtamab is primarily based on Trial 101 as a central dosimetry vendor was employed to standardize the collection, processing, and analysis of dosimetry data in this trial. Additionally, the PK and dosimetry sampling schedule employed in Trial 101 was more elaborate than that of Trial 03-133 and is thus considered to provide a more precise PK and dosimetry evaluation. Data from Trial 03-133 are restricted to PK and sample-based dosimetry from a subset of patients and are considered supportive in the overall assessment of dosimetry and PK properties of ^{131}I-omburtamab.

In Trial 101, 25 patients (16 patients at MSKCC and 9 patients at sites outside of MSKCC) were included in the dosimetry and PK analysis. The PK and dosimetry analysis for Trial 03-133 is based on the unselected sample of neuroblastoma patients consecutively enrolled over 3 years (2016-2018). A total of 27 patients were enrolled in this period.

Differences in the sampling schedule for dosimetry and PK analyses employed in Trial 101 and Trial 03-133 made pooling of data or a formal comparison between the trials not feasible.

Pharmacokinetic Methods

No formal ADME studies have been performed for ^{131}I-omburtamab. Radioactivity measurements in the CSF and blood were used instead of protein-quantification-based PK analysis in the ^{131}I-omburtamab clinical development program. Radioactivity counts were measured in the CSF and blood collected after administration of ^{131}I-omburtamab during the first cycle.

CSF and blood samples were collected prior to and after the dosimetry dose (2 mCi) at multiple time points in both trials (up to 72 hours and 48 hours in Trial 101 and Trial 03-133, respectively). There was a more frequent sampling in Trial 101 as compared to Trial 03-133. In addition, sampling was done following the treatment dose (50 mCi) in Trial 101.

PK parameters were estimated following the dosimetry dose. The PK parameters were evaluated for all patients and by age and weight subgroups.

Dosimetry Methods

Dosimetry assessment of ^{131}I-omburtamab included quantitative analyses based on imaging (only Trial 101) and on samples of CSF and blood collected during the first cycle.

Organ dosimetry estimates were calculated on the basis of nuclear imaging by whole body planar gamma camera scans in Trial 101. Target organ absorbed dose estimates were computed using established, industry standard software (organ level internal dose assessment [OLINDA/EXM 2.0]). Whole body gamma scans were performed at 3 timepoints (4, 24, and 48 hours) after the dosimetry dose. An additional scan was performed 48 hours after the treatment dose.

Sample-based dosimetry was conducted in Trial 101 and Trial 03-133 using the same samples of CSF and blood as used for the PK analysis (see above). Absorbed doses in the CSF and blood were presented to characterize the distribution and absorption for ^{131}I-omburtamab. The sample-based dosimetry parameters were evaluated for all patients and by age and weight subgroups.

5.2 Results

The PK and dosimetry results from Trial 03-133 were in line with the results from Trial 101. There were some differences in the results that could be explained by the different CSF and blood sampling schedule in the two trials. Given the more rigorous sampling protocol employed in Trial 101, the assumption is that the PK and dosimetry results were most accurately determined in Trial 101. Therefore, the below presentation of PK and dosimetry is based on Trial 101.

5.2.1 Pharmacokinetic Results

Trial 101

PK parameters are summarized in Table 4. The geometric mean volume of distribution (V_d) in the CSF compartment was 27 mL. The unbound ^{131}I-omburtamab left the CSF compartment with a geometric mean clearance half-life of 120 min (2 hours). Upon entering the blood, the C_{max} of ^{131}I-omburtamab was orders of magnitude lower than in the CSF and occurred later with a median T_{max} of ^{131}I-omburtamab in the blood of approximately 24 hours.

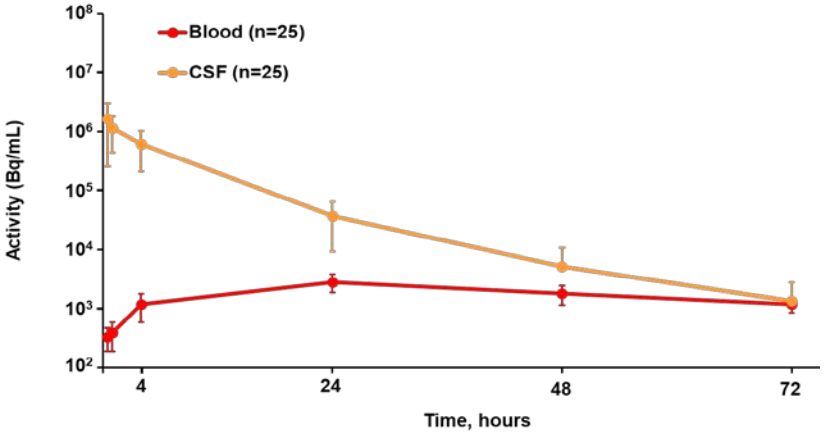
Table 4 Trial 101: Summary of Pharmacokinetic Parameters – Dosimetry Dose

T_{max}[a]		C_{max}[b]		V_d[b]	Clearance Half-life[b]		Half-life[b]
CSF (h)	Blood (h)	CSF (Bq/mL)	Blood (Bq/mL)	CSF (mL)	CSF (h)	Brain (h)	Whole body (h)
0.5 (0.4-1.1)	24.0 (22.7-47.4)	1308195 (84.4)	2683 (38.1)	27.1 (237)	2.0 (2.7)	23.7 (38.7)	47.7 (39.9)

N = 25 patients
C_{max} = maximum concentration (activity); CSF = cerebrospinal fluid; h = hour; T_{max} = time of maximum concentration (activity); V_d = volume of distribution.
[a] Median (minimum-maximum) values.
[b] Geometric mean (geometric coefficient of variation) values.

Mean time-activity profiles in CSF and blood following a dosimetry dose of ^{131}I-omburtamab are displayed in Figure 7.

Figure 7 Trial 101: Mean Time-Activity Profiles in CSF and Blood (Log Scaled) – Dosimetry Dose



Activity and timepoint means with SD error bars. CSF = cerebrospinal fluid.

5.2.2 Dosimetry Results

Trial 101

The CSF absorbed a much higher dose than the blood. Following the treatment dose, the CSF to blood absorbed dose mean ratio was 25.45:0.36 or 71 times higher in the CSF compared to the blood (Table 5). This greater CSF to blood ratio trend remained constant across the age and weight groups.

Table 5 Trial 101: Summary of Absorbed Doses (CSF, Blood and Brain Surface)

Parameter	Dosimetry dose	Treatment dose
CSF Absorbed Dose (Gy)		
N	25	23
Mean (SD)	1.22 (0.67)	25.45 (15.74)
Median	1.07	18.79
Min – Max	0.29 – 2.67	6.70 – 60.31
Blood Absorbed Dose (Gy)		
N	25	23
Mean (SD)	0.02 (0.01)	0.36 (0.12)
Median	0.02	0.31
Min – Max	0.01 – 0.02	0.16 – 0.57
Brain Surface Absorbed Dose (Gy)		
N	25	23
Mean (SD)	0.61 (0.35)	12.72 (7.87)
Median	0.54	9.39
Min – Max	0.14 – 1.34	3.35 – 30.15

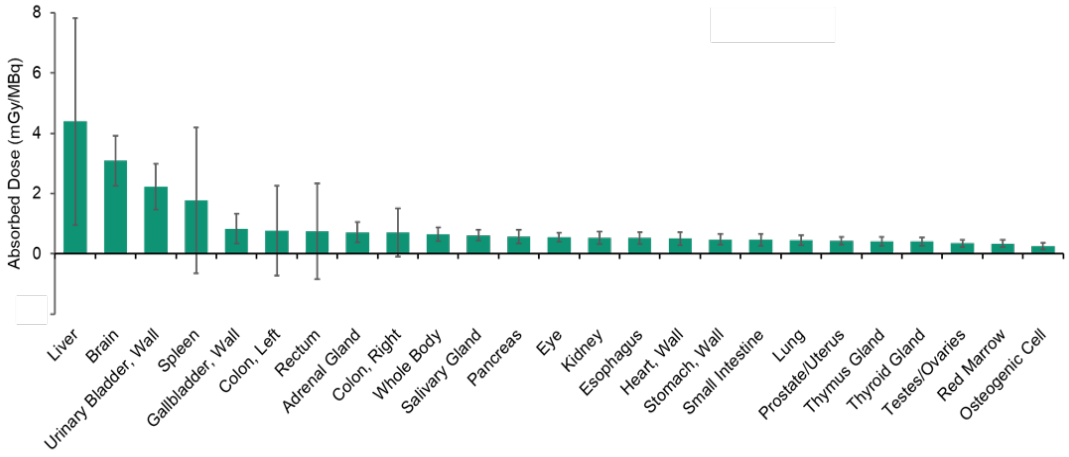
CSF = cerebrospinal fluid; Gy = Gray; Max = maximum; Min = minimum; N = number of patients; SD = standard deviation

The estimated blood absorbed dose per mCi was 0.008 Gy/mCi ~0.22 mGy/MBq (Table 5), equaling a blood absorbed dose of 0.40 Gy after a treatment dose of 50 mCi (1850 MBq).

Organ dosimetry data showed the brain and the liver as the regions with the highest absorbed dose; see Figure 8. Thereafter followed the urinary bladder wall and the spleen albeit with

relatively limited radiation absorption. Across the patient cohort, the absorbed radiation in the above organs was not accompanied by adverse reactions that would indicate organ damage.

Figure 8 Trial 101: Total Absorbed Dose by Organ – Treatment Dose



Absorbed doses in units of mGy/MBq in all OLINDA target organs, estimated for treatment administration (50 mCi [1850 MBq]). Bar height shows mean dose and error bars show standard deviation.
NOTE: One subject with a very high thyroid uptake has been excluded in this figure. Per the investigator, this subject may have complied poorly to the mandatory thyroid protection pre-dosing schedule.

The dosimetry data from Trial 101 were assessed by trial site (MSKCC [N=16 patients] versus all other sites [N=9 patients]). The PK and dosimetry data demonstrated that [131]I-omburtamab could be reproducibly and consistently administered, including at institutions other than MSKCC.

5.3 Clinical Pharmacology Conclusion

Following the intraventricular administration, unbound [131]I-omburtamab (measured as radioactive counts) was rapidly cleared from the CSF and brain, with a mean clearance half-life of 2 hours and 24 hours, respectively. Upon entering the blood, the median time to maximum concentration (T_{max}) was approximately 24 hours after administration. Clearance half-life from the whole body was 48 hours.

The absorbed dose to the CSF was much higher than to the blood in both trials, reflecting the intraventricular administration of [131]I-omburtamab.

Imaging dosimetry showed the brain and the liver as the regions with the highest absorbed radiation dose. No organ absorbed radiation doses that were higher than generally accepted tissue tolerance levels.

The PK and dosimetry data demonstrated that [131]I-omburtamab can be reproducibly and consistently administered at institutions other than MSKCC, in a manner that targets the tumor, with limited systemic risk.

6 Clinical Efficacy

6.1 Efficacy Data

Evidence for the efficacy of ^{131}I-omburtamab is derived from 107 patients in Trial 03-133 (Phase 1 dose-finding and therapeutic expansion) and 50 patients in the supportive Trial 101 (Phase 2/3).

To support the assessment of clinical efficacy of ^{131}I-omburtamab, the survival outcome in Trial 03-133 was compared with that of an external control source (German Registry population). The data from the German Registry was used to create an external control arm (ECA) using a propensity score model. The outcome of all analyses comparing survival data collected in Trial 03-133 with that of the ECA is provided in Section 6.4.

6.2 Trial 03-133

6.2.1 Trial Endpoints and Statistical Methods

Trial Endpoints

The primary efficacy endpoint for the interim analysis of Trial 03-133 was:

- Overall survival (OS) at 3 years.

The secondary efficacy endpoints for the interim analysis of Trial 03-133 were:

- CNS/LM progression-free survival (PFS) at 12 months.
- Duration of follow-up.

All endpoints were agreed with the FDA. Following transfer of the IND from MSKCC to Y-mAbs, the efficacy endpoints in Trial 03-133 were introduced at a late stage of the trial to support the BLA (i.e., were not part of the original protocol). Assessment of CNS/LM PFS by the Investigator was not done at prespecified timepoints, and the analysis is included for supportive purposes in the BLA. It should also be noted that ORR was not assessed in Trial 03-133 since firm guidelines for assessment of response were not available when Trial 03-133 was designed (2004). Although the Trial 03-133 protocol did include a rudimentary effort to assess tumor response by MRI and CSF cytology, the collection of data required for assessing tumor response was not structured to allow for an analysis based on current validated response criteria.

Statistical Methods

The efficacy analyses for Trial 03-133 were based on an interim analysis including all neuroblastoma patients who were enrolled in the trial by 31 December 2018. All efficacy analyses were conducted on the Full Analysis Set (FAS), which included all neuroblastoma patients who received an infusion of the treatment dose of ^{131}I-omburtamab (N=107).

OS: The survival time in Trial 03-133 was calculated from the date of first diagnosis of CNS/LM relapse until the date of death (event) or until the latest date confirmed alive (censored

observation). This time point was selected to facilitate the crude comparison to external controls. Kaplan-Meier methods were used to analyze OS data, to produce a Kaplan-Meier plot, to estimate the 3-year survival probability and 95% CIs, and to estimate median OS and 95% CIs.

CNS/LM PFS: The CNS/LM PFS was calculated from the date of first infusion of study drug until the date of CNS/LM progression or death (event) or until the latest date confirmed to be CNS/LM progression-free (censored observation). PFS was estimated (both 12-month PFS with 95% CI and median PFS with 95% CI) using similar methods as OS.

Duration of follow-up: The duration of follow-up was estimated from the first dose of radiolabeled omburtamab (either ^{124}I-omuburtamab or ^{131}I-omburtamab) by the reverse Kaplan-Meier method, and the median follow-up time with 95% CI was calculated.

6.2.2 Patient Disposition

The interim efficacy analyses in Trial 03-133 were based on the FAS. Two patients did not receive a treatment dose of ^{131}I-omburtamab and were thus excluded from the FAS; one patient discontinued treatment because of excessive toxicity and the other patient discontinued treatment because of progressive disease. The majority of pediatric neuroblastoma patients (94 patients [87.8%]) were in the 50 mCi dose group.

6.2.3 Demographics and Baseline Characteristics

Median age at consent was 4.7 years with a range of 0.9 to 13 years. Males accounted for 67.3% of the study population. Race was mainly 'White' (78.5%). Based on MSKCC medical records, 84% of patients included in the FAS were US residents (Table 6).

Table 6 Trial 03-133: Patient Demographics and Baseline Characteristics

	Statistic/ Category	50 mCi (N=94) [n (%)]	All Patients (N=107) [n (%)]
Age at Consent (years)	N	94	107
	Mean	5.167	5.149
	SD	2.6978	2.6451
	Median	4.784	4.709
	Min, Max	0.85,13.03	0.85,13.03
Weight (kg)	Mean	17.30	17.3
	SD	6.8	6.6
Sex	Female	29 (30.9)	35 (32.7)
	Male	65 (69.1)	72 (67.3)
Race	Asian/ Far East/ Indian Subcontinent	3 (3.2)	3 (2.8)
	Black / African American	9 (9.6)	9 (8.4)
	White	73 (77.7)	84 (78.5)
	Unknown	4 (4.3)	11 (10)
Residency	US	78 (83.0)	90 (84.1)
	Non-US	16 (17.0)	17 (15.9)

Max = maximum; Min = minimum; SD = standard deviation.

The patient population in Trial 03-133 is considered representative for the population of patients with neuroblastoma with CNS/LM metastases refractory to conventional therapies or for which

no conventional therapy exists, thereby providing reassurance regarding the evaluation of the treatment and validity of the efficacy conclusions.

6.2.4 Patient Disease Characteristics

The majority of patients had unifocal PM disease (48%), followed by multifocal PM disease (15%) (Table 7), assessed at CNS/LM relapse.

At initial neuroblastoma disease diagnosis, most patients (73%) were at INSS disease Stage 4. MYCN amplification was reported for 51% of the patients.

Table 7 Trial 03-133: Patient Disease Characteristics

	Statistic/ Category	50 mCi (N=94) [n (%)]	All Patients (N=107) [n (%)]
Site of metastases at CNS/LM relapse	Unifocal PM	46 (48.9)	51 (47.7)
	Multifocal PM	13 (13.8)	16 (15.0)
	LM	8 (8.5)	10 (9.3)
	PM and LM	7 (7.4)	9 (8.4)
	Not known	10 (10.6)	11 (10.3)
	Not reported	10 (10.6)	10 (9.3)
INSS Disease Stage	Stage 3	2 (2.1)	2 (1.9)
	Stage 4	69 (73.4)	78 (72.9)
	Stage 4S	2 (2.1)	3 (2.8)
	Not reported	21 (22.3)	24 (22.4)
MYCN amplification	Neither gain nor amplification	1 (1.1)	1 (0.9)
	Gain	2 (2.1)	2 (1.9)
	Amplification	49 (52.1)	55 (51.4)
	Non-amplified	30 (31.9)	36 (33.6)
	Not reported	12 (12.8)	13 (12.1)
Prognostic Group	Favorable histology	10 (10.6)	12 (11.2)
	Unfavorable histology	45 (47.9)	50 (46.7)
	Not reported	39 (41.5)	45 (42.1)

CNS=central nervous system; INSS = International Neuroblastoma Staging System; LM=leptomeningeal; MYCN=v-myc myelocytomatosis viral related oncogene; PM=parenchymal

6.2.5 Prior Treatment

Most patients in Trial 03-133 received multiple types of anti-cancer treatments for neuroblastoma in the period between CNS/LM relapse and ^{131}I-omburtamab. Overall, 83 patients (77.6%) had surgery performed, 98 patients (91.6%) received external beam radiation therapy, and 102 patients (95.3%) received chemotherapy during this period.

6.2.6 Concomitant Anti-Cancer Therapy

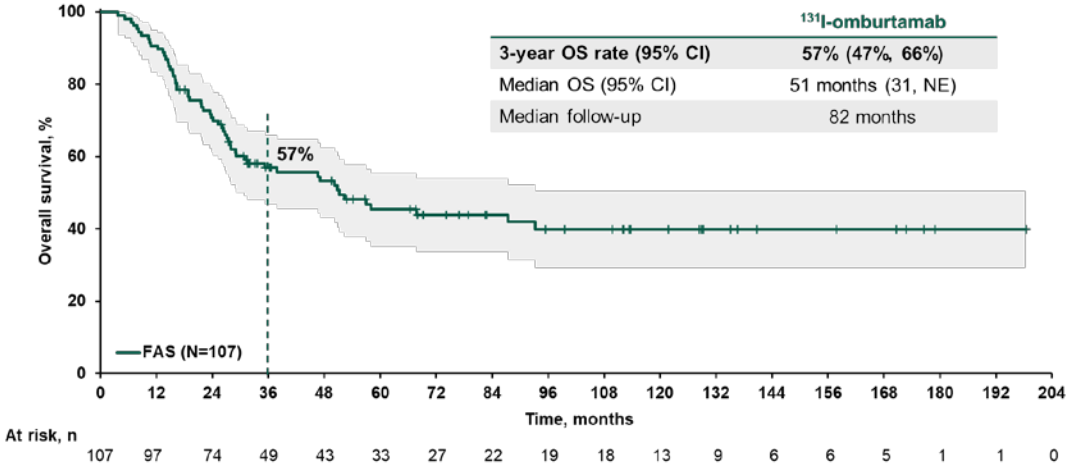
In Trial 03-133, data on concomitant anti-cancer treatment administered after ^{131}I-omburtamab therapy was not collected systematically as part of the protocol.

6.2.7 Efficacy Results

6.2.7.1 Overall survival (OS) at 3 years

The 3-year OS rate and median time of survival is presented in Figure 9. Overall, death was recorded for 57 patients (53.3%); the other 50 patients were censored in the Kaplan-Meier survival analysis. The 3-year OS rate was 57% (95% CI: 47%, 66%), and the median survival estimate was 51 months (95% CI: 31, not estimable [NE]).

Figure 9 Trial 03-133: Overall Survival



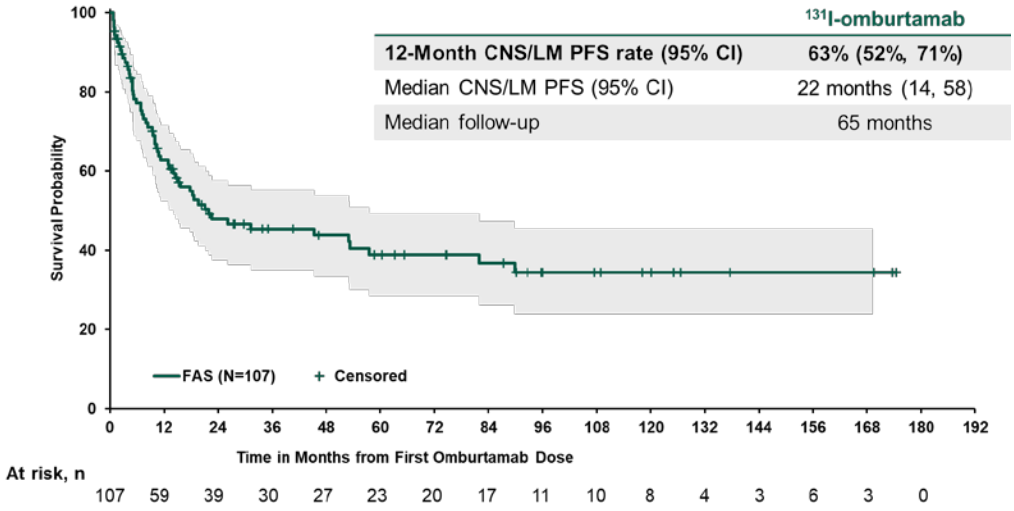
CI = confidence interval; FAS = full analysis set; NE = not estimable; OS = overall survival

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

The CNS/LM PFS rate at 12 months and median CNS/LM PFS estimates is presented in Figure 10. Overall, 49 patients (45.8%) were censored in the Kaplan-Meier CNS/LM PFS analysis (confirmed CNS/LM progression-free at last contact).

Of the 58 patients (54.2%) who failed in the Kaplan-Meier CNS/LM PFS analysis (i.e., died or had CNS/LM progression), 30 patients (51.7%) failed due to CNS/LM progression and 28 patients (48.3%) failed due to death. The CNS/LM PFS rate at 12 months was 63% (95% CI: 52%, 71%), and the median CNS/LM PFS estimate was 22 months (95% CI: 14, 58).

Figure 10 Trial 03-133: CNS/LM Progression-Free Survival



CI = confidence interval; CNS=central nervous system; FAS=Full Analysis Set; LM=leptomeningeal; PFS = progression-free survival

6.2.7.3 Duration of follow-up

For all 107 patients, the median duration of follow-up was 76 months (95% CI: 54, 106), with a minimum and maximum duration of follow-up of 1.6 months and 176 months, respectively.

6.2.8 Trial 03-133: Efficacy Conclusions

Trial 03-133, initiated in 2004, is the largest study of its kind in CNS/LM neuroblastoma. Considering the extreme rarity of CNS/LM neuroblastoma, the number of patients receiving a treatment dose in the trial (107 patients) and the duration of follow-up (median of 76 months) provide an unprecedented amount of data and a solid basis to evaluate [131]I-omburtamab in this patient population. A 3-year OS of 57% (95% CI: 47%, 66%), and a median survival estimate of 51 months (95% CI: 31, NE) was observed with [131]I-omburtamab treatment, which is considered clinically meaningful and support the overall benefit of [131]I-omburtamab for treatment of neuroblastoma with CNS/LM metastases.

6.3 Trial 101

6.3.1 Trial Endpoints and Statistical Methods

Trial Endpoints

The primary efficacy endpoint for the interim analysis in Trial 101 was:

- CNS/LM PFS at 6 months.

The secondary efficacy endpoints for the interim analysis of Trial 101 were:

- OS at 12 months.
- Objective Response Rate (ORR) at 6 months.

All endpoints were agreed with the FDA.

Statistical methods

The efficacy analyses for Trial 101 were based on an interim analysis including patients enrolled in the trial as of the enrollment cut-off date (01 February 2022). All efficacy analyses were conducted on the FAS (N=50), which included patients who began an infusion of ^{131}I-omburtamab. There was no control group, comparison to external control groups or subgroup analyses in the interim analysis for Trial 101.

CNS/LM PFS: The CNS/LM PFS rate was estimated based on the time from first treatment dose of ^{131}I-omburtamab to CNS/LM progression or death from any cause. Kaplan-Meier methods was used to estimate CNS/LM PFS, and Kaplan-Meier plots were used to present CNS/LM PFS rate estimates from first treatment dose to end of trial, together with the corresponding 95% CIs.

OS: The survival time was calculated from the first treatment dose of ^{131}I-omburtamab until the date of death from any cause (event). Patients alive at the time of analysis were censored on the date the patient was last confirmed alive. Kaplan-Meier methods were used to analyze OS data, produce a Kaplan-Meier plot, and to estimate the 12-month survival rate.

ORR: ORR was assessed at 6 months (26 weeks) after the first treatment dose of ^{131}I-omburtamab as a combination of best overall Complete Response or Partial Response. The ORR at Week 26 was defined as the proportion of patients with response (Complete Response or Partial Response) from the total population of patients with radiographically evaluable disease at baseline. The evaluation followed the response assessment in the Neuro-Oncology (RANO) group criteria for brain metastases[22] or in the guideline by European Association of Neuro-Oncology – European Society for Medical Oncology (EANO-ESMO) for LM metastases.[23] The evaluation comprised MRI scans (independent review performed centrally), CSF cytology or use of corticosteroids, and clinical assessments at screening and end of Cycle 1, end of Cycle 2 and Week 26.

6.3.2 Patient Disposition

A total of 50 patients were enrolled in Trial 101 up until the enrollment cut-off date of 01 February 2022. At the time of data cutoff (31 March 2022), 23 patients (71.9%) were continuing in the trial, and 9 patients (28.1%) had ended participation. Of these, 8 patients had died, and 1 patient was withdrawn by parent/guardian.

6.3.3 Demographic and Baseline Characteristics

The neuroblastoma patients enrolled in Trial 101 had similar baseline characteristics as Trial 03-133. Median age at baseline was 4 years with a range of 0 to 11 years. Males accounted for 58% of the study population. Most patients were ‘White’ (76%). Of the 50 eligible patients included in Trial 101, 36 patients (72%) were recruited in the US (Table 8).

Table 8 Trial 101: Patient Demographics and Baseline Characteristic

Patient Demographics and Baseline Characteristics	^{131}I-omburtamab N (%)
Full analysis set (N)	50
Sex (N, %)	
Male	29 (58)
Female	21 (42)
Age (years)	
Mean (SD)	4.7 (2.49)
Median	4.0
Minimum–maximum	0 – 11
Weight	
Mean (SD)	17.6 (5.92)
Median	16.1
Minimum–maximum	6.0 - 36.3
Race	
White	38 (76.)
Asian	7 (14)
Other	3 (6)
American Indian or Alaska Native	1 (2)
Black or African-American	1 (2)
Country	
United States	36 (72)
Spain	12 (24)
Denmark	1 (2)
Japan	1 (2)

The patient population in Trial 101 is considered representative for the population of patients with neuroblastoma with CNS/LM metastases refractory to conventional therapies or for which no conventional therapy exists population, thereby providing relevant support to the results of Trial 03-133.

6.3.4 Patient Disease Characteristics

The lesion at baseline was recorded either as LM, parenchymal metastases (PM) or both LM and PM. A total of 20 patients had measurable disease at baseline (assessed by independent review of MRI scans). Six patients had LM disease, 5 patients had PM disease and 8 patients had a combination of both lesion types. In addition, 1 patient had LM disease or a combination of both lesion types (discrepancy between the reviewers). The remaining 30 patients had no measurable disease at baseline (Table 9).

At initial neuroblastoma disease diagnosis, most patients (82%) were at INSS disease Stage 4. MYCN amplification was reported in 21 patients (42%) and MYCN neither gain nor amplification was reported in 23 patients (46%).

Table 9 Trial 101: Patient Disease Characteristics

Disease Characteristics	^{131}I-omburtamab N (%)
Full Analysis Set (N)	50
Site of metastases at baseline	
PM	5 (10)
LM	6 (12)
LM + PM	8 (16)
LM + PM/LM[a]	1 (2)
No measurable LM/PM disease	30 (60)
INSS Disease Stage	
Stage 2B	1 (2)
Stage 3	2 (4)
Stage 4	41 (82)
Stage 4S	1 (2)
Not reported	5 (10)
MYCN Status	
Amplification	21 (42)
Gain	3 (6)
Neither gain nor amplification	23 (46)
Not reported	3 (6)
Prognostic group	
Unfavorable histology	35 (70)
Not reported	15 (30)

N = Number of patients; % = Percentage of patients; SD = Standard deviation; LM = Leptomeningeal metastases; PM = Parenchymal metastases; INSS = International Neuroblastoma Staging System; MYCN = v-myc myelocytomatosis viral related oncogene

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

6.3.5 Prior Treatment

A summary of prior anti-cancer treatment for neuroblastoma in the period between CNS/LM relapse and first ^{131}I-omburtamab administration is presented in Table 10.

Most patients (98%) received radiation, chemotherapy, and surgery in the period between CNS/LM relapse and ^{131}I-omburtamab administration. A total of 46 patients (92%) received CNS-directed radiation therapy during this period, and of these, 28 patients received craniospinal irradiation (CSI). Chemotherapy was administered to 46 patients (92%), and surgery was performed in 37 patients (74%). Of the 37 patients who had CNS-directed surgeries performed during this period, 26 patients had surgeries recorded as curative and 2 patients had surgeries recorded as palliative. For the remaining 9 patients the purpose of the surgery was not recorded.

Table 10 Trial 101: Prior Treatments for Neuroblastoma – between CNS/LM Relapse and ^{131}I-omburtamab

Prior Treatment	^{131}I-omburtamab N (%)
Full Analysis Set (N)	50
Irradiation between CNS/LM relapse and ^{131}I-omburtamab administration	
No	4 (8.0)
Yes	46 (92.0)
Surgery between CNS/LM relapse and ^{131}I-omburtamab administration	
No	13 (26.0)
Yes	37 (74.0)
Prior chemotherapy between CNS/LM relapse and ^{131}I-omburtamab administration	
No	4 (8.0)
Yes	46 (92.0)

6.3.6 Concomitant Anti-Cancer Therapy

In Trial 101, concomitant anticancer therapy was not allowed from Week -3 and through the treatment cycles with ^{131}I-omburtamab. The post ^{131}I-omburtamab cancer-related medication/treatments are summarized in Table 11.

A total of 34 patients received concomitant anti-cancer therapy (consolidation treatment for systemic disease or CNS/LM disease and treatment of systemic or CNS/LM progression) after ^{131}I-omburtamab treatment, as part of their treatment regimens at investigational sites.

Table 11 Trial 101: Concomitant Anti-Cancer Therapy

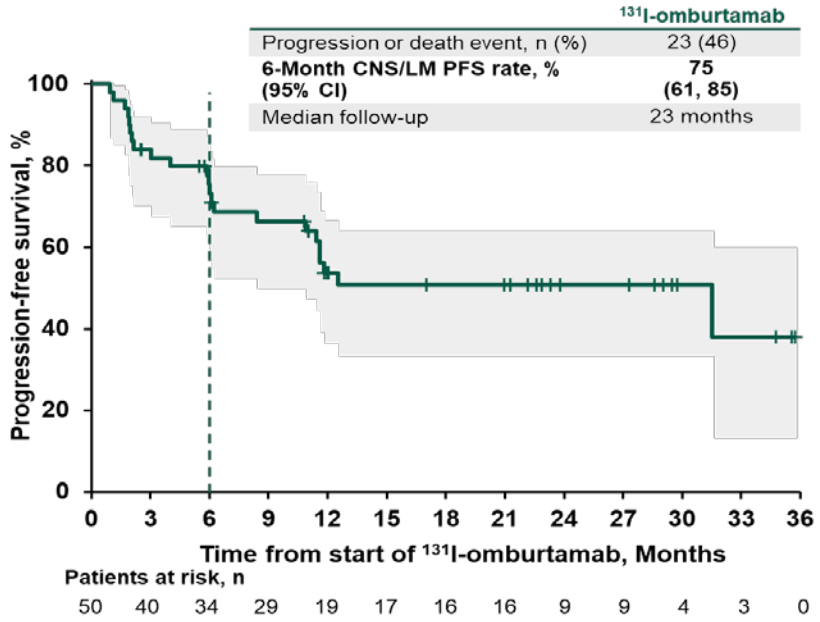
Treatment	Total, n (%) N=50
Patients treated	34 (68)
Chemotherapy	27 (54)
Immunotherapy	25 (50)
Chemotherapy and Immunotherapy	7 (14)
Radiotherapy	10 (20)
Surgery	3 (6)
Other	10 (20)

6.3.7 Efficacy Results

6.3.7.1 CNS/LM Progression Free Survival

The CNS/LM PFS rate at 6 months was 75% (95% CI: 61%, 85%). With a median follow-up time of 23 months, 54% of the patients were still alive without progression. A total of 23 patients (46%) had documented CNS/LM progression or died (Figure 11).

Figure 11 Trial 101: CNS/LM Progression-Free Survival

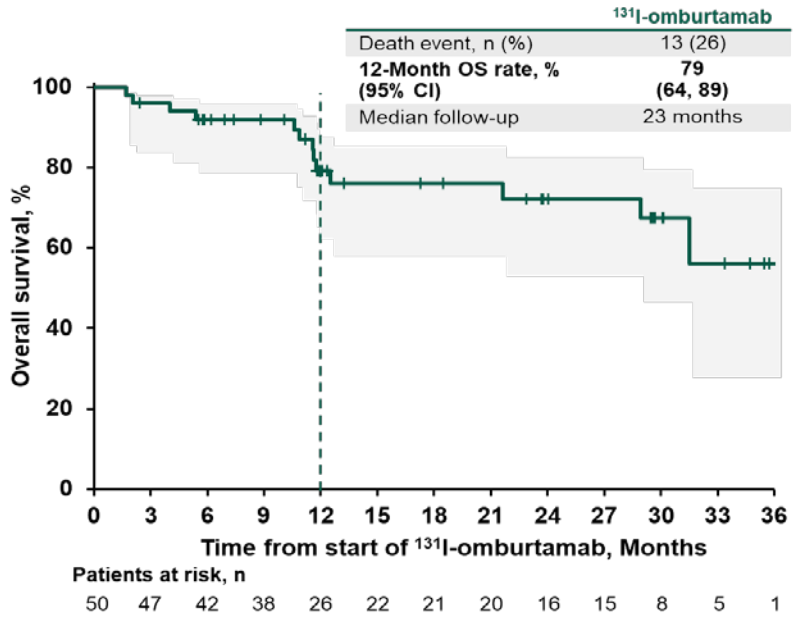


CI = confidence interval; CNS=central nervous system; LM=leptomeningeal; PFS = progression-free survival

6.3.7.2 Overall Survival

In Trial 101, the 12-month survival rate post first [131]I-omburtamab administration was 79% (95% CI: 64%; 89%). The median follow-up time was 23 months. 13 patients (26%) had died, whereas the remaining 37 patients (74%) were censored alive.

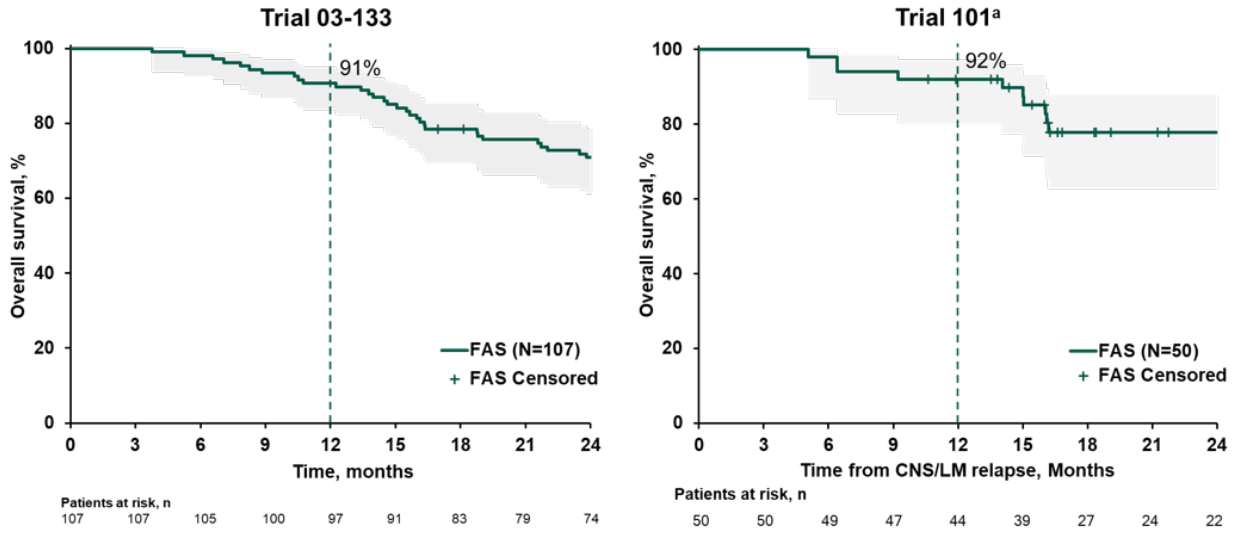
Figure 12 Trial 101: Overall Survival



CI = confidence interval; OS = overall survival

Comparative analyses of OS between Trial 03-133 and Trial 101 were not originally performed due to the difference in duration of follow-up and index dates. However, a post-hoc analysis of OS aligning the index date (time from first CNS/LM relapse) showed comparable 1-year OS rates between the two trials (Trial 03-133 [91%] and Trial 101 [92%] (Figure 13), demonstrating that the efficacy results of Trial 101 are consistent with Trial 03-133 in a multicenter setting.

Figure 13 Trial 101 vs. Trial 03-133: Overall Survival



FAS = full analysis set. Note: Not a pre-specified analysis

6.3.7.3 Objective Response Rate at 6 months

Of 20 patients with measurable disease at baseline, 7 patients achieved an objective response, resulting in an ORR of 35.0% (95% CI: 15; 59). A total of 5 patients had Complete Response and 2 patients had Partial Response as Best Overall Response. The median duration of response for the complete responders were 280 days. For the remaining 13 patients with measurable disease at baseline, 7 patients had Stable Disease as Best Overall Response, 5 patients had Progressive Disease and 1 patient was Not Evaluable.

It is noteworthy that in six out of the seven patients with Stable Disease at Week 26 there were no signs of CNS/LM progression at the follow-up visits conducted from 293 to 718 days after [131]I-omburtamab treatment, according to local clinical and radiological assessments. These data indicate that an image-based categorization as ‘Stable Disease’ at Week 26 may reflect a longer-term beneficial outcome of [131]I-omburtamab and provides the possibility for consolidation of systemic and CNS/LM disease with additional anti-cancer therapies.

Of the 20 patients with measurable disease at baseline, 14 patients achieved disease control, i.e., complete or partial response or stable disease, resulting in a disease control rate of 70% (Table 12).

Table 12 Trial 101: Objective Response Rate at 6 months

Up to Week 26	Patients, n (%)
Patients with measurable 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	143 days
Duration of response for complete responders (N=5), median	280 days
Disease Control Rate	14 (70)

[a] Objective Response = Complete Response + Partial Response. Central review based on RANO and EANO/ESMO Criteria

6.3.8 Trial 101: Efficacy Conclusions

Collectively, the efficacy findings of Trial 101 support the effectiveness of [131]I-omburtamab in a multicenter setting with a 1-year survival rate like the one shown for Trial 03-133.

Tumor response data from Trial 101 provides a significant contribution to the overall assessment of [131]I-omburtamab efficacy. The observation of an ORR of 35% combined with the beneficial outcome in patients with Stable Disease at Week 26 demonstrate that sustained disease control is achieved following multimodal treatment with addition of [131]I-omburtamab.

6.4 Comparative analyses between Trial 03-133 and the External Control Arm

The survival outcome in Trial 03-133 was compared to that of German Registry (Patient-level data from the German Registry were used to construct a comparable external control arm (ECA) using a propensity score weighting approach to balance the patients between the two groups based on important baseline characteristics and prognostic factors.

6.4.1 Key Inclusion Criteria

A query to the German Registry was issued to select patients matching the key inclusion criteria of Trial 03-133 (Table 13). In Trial 03-133 patients were not included if they had rapidly progressing disease or were deteriorating neurologically. This information was not available in the German Registry, but the difference in selection was mitigating by focusing on patients able to receive comprehensive therapy.

Table 13 Key Inclusion Criteria for Patients Included in the Comparative Analyses (Trial 03-133 and German Registry)

Trial 03-133	German Registry
Patients must have a histologically confirmed diagnosis of a malignancy known to be omburtamab reactive. Antigen expression must be confirmed by immunohistochemical staining of tumor and assessed by the Department of Pathology or by immunofluorescence of bone marrow except for patients confirmed to have neuroblastoma.	Stage 4 neuroblastoma
Patients must have CNS/leptomeningeal disease which is refractory to conventional therapies or for which no conventional therapy exists OR a recurrent brain tumor with a predilection for leptomeningeal dissemination (medulloblastoma, PNET, rhabdoid tumor).	CNS disease at first recurrence or with initial CNS involvement
Patients must have no rapidly progressing or deteriorating neurologic examination.	Mitigated by excluding patients without post relapse treatment from analyses.
Both pediatric and adult patients of any age are eligible.	0-20 years
Exclusion Conditions: Patients who have received CSI less than 3 weeks prior to the start of this protocol. Patients who have received systemic chemotherapy (corticosteroids not included) less than 3 weeks prior to the start of this protocol.	In Germany, CSI is not used for treatment in children.

CNS = central nervous system; CSI = cranial or spinal irradiation; PNET = primitive neuroectodermal tumor.

6.4.2 Flow chart

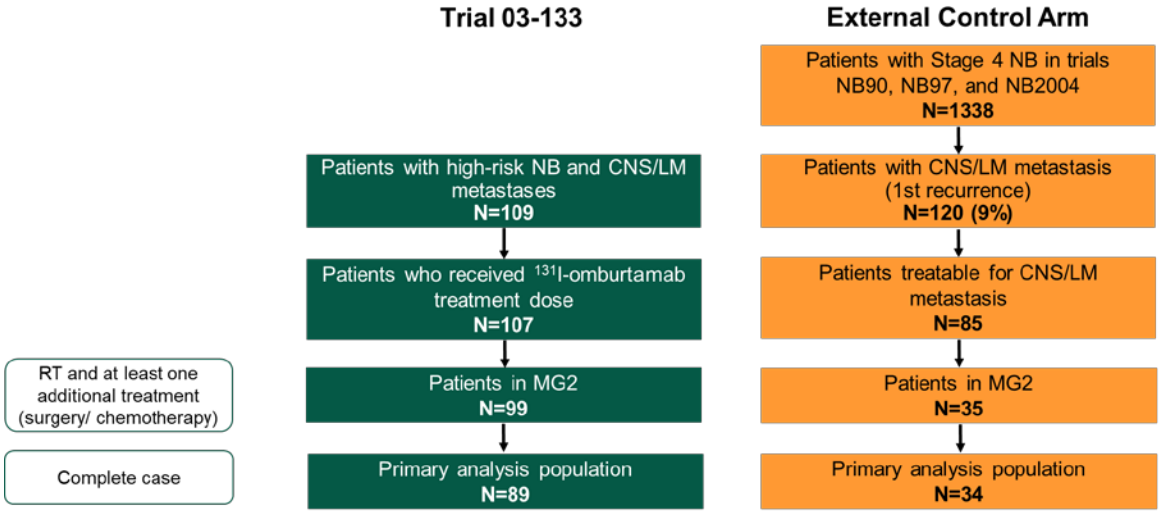
The flow chart of the patient selection process for Trial 03-133 and the ECA is shown in Figure 14.

In Trial 03-133, patients received a multimodal treatment regimen of surgery, chemotherapy, and/or radiotherapy before first ^{131}I-omburtmab administration. A total of 99 patients had received radiotherapy and at least one other treatment (surgery or chemotherapy) and were defined as “modality group 2” (MG2). For definitions on modality groups, refer to Section 6.4.4.

In the German registry, 1338 patients with Stage 4 neuroblastoma were identified from 3 clinical trials (NB90, NB97, and NB2004). A subset (9%) of these (N=120) had CNS or LM disease at first recurrence. The population was further limited to those patients who had received treatment for their CNS or LM disease (N=85) to minimize the inclusion of the frailest patients. The German patients who did not receive treatment had an extremely poor prognosis with a median survival of approximately 1 month. Of the 85 patients who received treatment, 35 patients had received multimodal treatment and were included in MG2.

To increase the degree of comparability between the two groups, the primary analysis was restricted to MG2, index date A (start date of the last post CNS/LM metastases treatment) was aligned, and imputation of missing values was not included (complete case analysis). Ultimately, after propensity score weighting, the overall survival of 89 patients in Trial 03-133 was compared with 34 patients in the ECA, for whom we had complete case data.

Figure 14 Selection of Patients in Trial 03-133 and the External Control Arm



CNS=central nervous system; LM=leptomeningeal; MG2=modality group 2; NB=neuroblastoma; RT=radiotherapy

6.4.3 Clinically Relevant Covariates for Propensity Score Model

Propensity score weighting was used to balance all available prognostic factors between the populations.

Clinically important prognostic factors and baseline characteristics included in the propensity score model were:

- Age at NB diagnosis
- MYCN status
- Time from NB diagnosis to CNS relapse
- Time from the CNS relapse date to the start of post-relapse treatments
- Post-CNS relapse radiotherapy
- Post-CNS relapse chemotherapy
- Post-CNS relapse surgery
- Number of post-CNS relapse treatments (radiotherapy, chemotherapy, and surgery)

6.4.3.1 Limitations of the Propensity Score Model

A limitation of the propensity score model was the inability to include the two variables ‘type of CNS/LM disease’ and ‘pattern of relapse’. These factors could not be directly included due to differences in recording of the information in the two data sources. The type of CNS/LM disease was only recorded in Trial 03-133, whereas information on surgery results were captured in the ECA database. In Trial 03-133, pattern of relapse was assessed at the time of first [131]I-omburtamab, and in the ECA at time of CNS/LM relapse.

Type of CNS/LM disease

In Trial 03-133 (MG2), 51% of the patients had unifocal PM disease at CNS/LM relapse, which are likely to be completely resected. In the ECA (MG2), 43% of patients achieved macroscopic complete resection and 29% of the surgeries were macro- and microscopic complete (Table 14).

Type of CNS disease mainly influences the likelihood of achieving a complete surgical resection; although it was not possible to include this variable directly in a statistical analysis, the available data indicate a similar high degree of complete resection of approximately 50% in both populations. Taking this into consideration, inclusion of the type of CNS/LM disease in the model would not be expected to change the outcome of the analysis materially.

Table 14 Type of CNS/LM Disease (Modality Group 2)

Surgery result	External Control Arm (N=35)
Macro- and microscopic complete	10 (28.6)
Macroscopic complete and microscopic unclear	5 (14.3)
Macroscopic incomplete	7 (20)
Microscopic incomplete	3 (8.6)
None	10 (28.6)

Pattern of Relapse

The variable 'pattern of relapse' is defined as combined (systemic disease and CNS/LM relapse) or isolated (only CNS/LM relapse). In Trial 03-133, presence of systemic disease was reported at time of first ^{131}I-omburtamab infusion. In the ECA, systemic disease was reported at time of CNS/LM relapse. The reported data suggests a similar distribution of systemic disease at time of CNS/LM relapse (Trial 03-133 [25%] and ECA [20%]), assuming that patients in Trial 03-133 also had systemic disease at time of CNS/LM relapse (Table 15). Based on this assumption, a post-hoc sensitivity analysis examining the impact of pattern of relapse on the treatment effect was performed (Figure 16).

Table 15 Pattern of Relapse (Modality Group 2)

Pattern of Relapse	Trial 03-133 (N=99)	External Control Arm (N=35)
Isolated CNS disease, n (%)	72 (72.7)	28 (80)
Combined CNS and systemic disease, n (%)	25 (25.3)	7 (20)
Unknown, n (%)	2 (2.0)	0 (0)

Note: In Trial 03-133, presence of systemic disease was reported at time of first ^{131}I-omburtamab infusion. In the ECA, systemic disease was reported at time of CNS/LM.

6.4.4 Modality Groups and Index Dates

To ensure that patients from Trial 03-133 were appropriately compared with the German Registry population in a manner that would decrease bias, treatment modality groups and different index dates were introduced. Applying multiple treatment modalities may be associated with a better survival outcome.[13] The population from the German Registry generally received fewer treatment modalities compared to the Trial 03-133 population. Therefore, to avoid confounding, patients were divided into modality subgroups according to the type and number of post-CNS relapse treatments that they received (Table 16).

Table 16 Description of Post-CNS Relapse Treatment Modality Groups

Modality Group	Description of Group	Number of Patients
2 (MG2)	Patients who received radiotherapy and at least 1 other treatment modality (chemotherapy or surgery)	Trial 03-133 = 99 patients German Registry = 35 patients
3 (MG3)	Patients who received 3 treatment modalities (radiotherapy, chemotherapy, and surgery)	Trial 03-133 = 78 patients German Registry = 21 patients
4 (MG4)	Patients who received at least 1 CNS-directed radiotherapy[a]	Trial 03-133 = 100 patients German Registry = 40 patients

CNS = central nervous system; MG = modality group.
[a] For the German Registry population specifically, radiotherapy was restricted to CNS directed radiotherapy and surgery to intracranial or CNS directed.

Different index dates (start date for the calculation of survival time) were chosen to align the offset of survival between the two populations (Table 17).

Table 17 Index Dates

Event	Index Date	Description
CNS relapse	Index Date C	Date of first CNS relapse occurrence; used for the sensitivity analyses
First post-CNS relapse treatment	Index Date B	Treatment start date for first type of post-CNS relapse treatment (RT, CT, surgery); used for sensitivity analyses
Last post-CNS relapse treatment	Index Date A	Treatment start date of the last type of post-CNS relapse treatment (RT, CT, surgery); will be primary index date for Trial 03-133 and German Registry
IP start date	Index Date D	Start date of infusion of treatment dose of ^{131}I-omburtamab; only defined for Trial 03-133 and will be used for sensitivity analyses

CNS = central nervous system; CT = chemotherapy; IP = investigational product; RT = radiotherapy
Note: Index dates varied across the sensitivity analyses, see overview in Table 19.

6.4.5 Primary Analysis

The primary analysis included patients who received radiotherapy and at least one other treatment modality (chemotherapy or surgery) as post-CNS relapse treatment for neuroblastoma with CNS/LM relapse (MG2). Patients with missing values for the pre-specified baseline characteristics were excluded from the primary analysis (complete case analysis). The start date of the last post-CNS relapse treatment (Index Date A) was used as index date for the calculation of survival. This date was chosen, as it was the last comparable and common date between the German Registry population and patients in Trial 03-133.

6.4.5.1 Baseline Characteristics and Prognostic Factors

A summary of baseline characteristics and prognostic factors by treatment group for the primary analysis is shown in Table 18. The prognostic factors included in the model were all well balanced between patients in Trial 03-133 and the ECA.

Table 18 Baseline Demographics and Disease Characteristics - Primary Analysis

Parameter	Statistic	Primary Analysis (Index date A, MG2, complete case)	
		Trial 03-133 (N=89)	ECA (N=34[a])
Age at neuroblastoma diagnosis (years)	Mean (SD)	2.9 (2.0)	2.8 (2.8)
MYCN Status, n (%)	Amplified	54 (60.7)	16.6 (56.9)
	Not amplified	35 (39.3)	12.5 (43.1)
Time from NB diagnosis to CNS relapse (months)	Mean (SD)	21.3 (14.2)	21.90 (8.1)
Time from CNS relapse to the start of post-CNS relapse treatments (days)	Mean (SD)	9.6 (12.4)	9.4 (11.1)
Post-CNS relapse chemotherapy, n (%)	Yes	88 (98.9)	28.8 (98.8)
Post-CNS relapse surgery, n (%)	Yes	70 (78.7)	22.2 (76.3)
No. of post-CNS relapse treatments, n (%)	2	20 (22.5)	7.2 (24.9)
	3	69 (77.5)	21.9 (75.1)

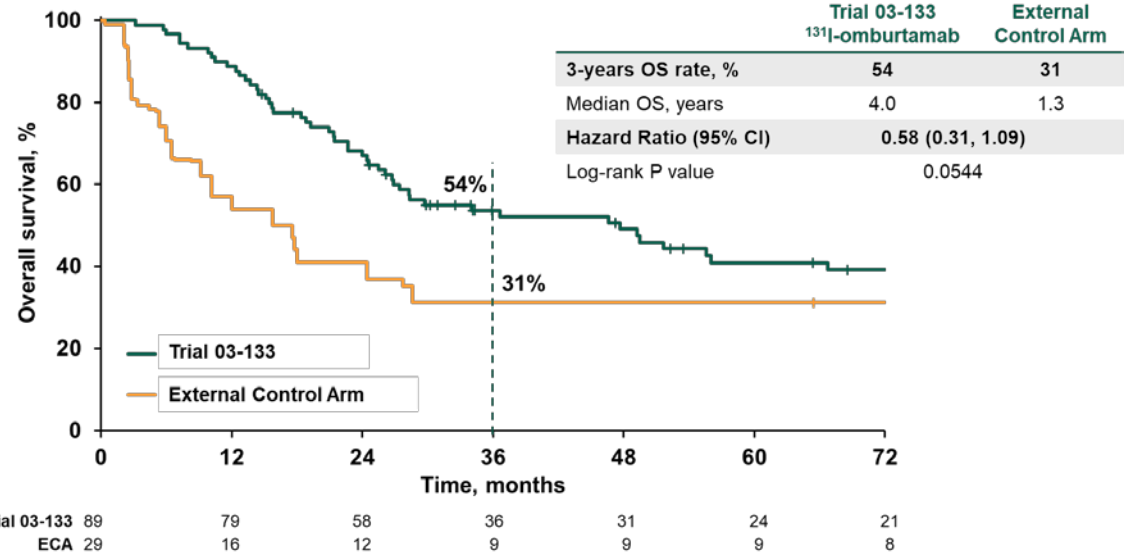
CNS = central nervous system; ECA = external control arm; MYCN = v-myc myelocytomatosis viral related oncogene; MG = modality group NB = neuroblastoma; SD = standard deviation

[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.

6.4.5.2 Overall Survival in Primary Analysis

The comparison of OS in Trial 03-133 with the ECA demonstrated a clinically meaningful 42% relative reduction in the risk of death with [131]I-omburtamab (hazard ratio of 0.58 [95% CI: 0.31, 1.09], log-rank test p-value = 0.0544) (Figure 15). The 3-year OS rate was notably higher in Trial 03-133 (54%) than in the ECA (31%), and an improved median OS exceeding 2 years was observed with [131]I-omburtamab (4 years vs. 1.3 years).

Figure 15 Overall Survival by Treatment Group – Primary Analysis



Note: The comparison of OS between Trial 03-133 and the External Control Arm is restricted to MG2 (patients who received radiotherapy and at least one other treatment modality (chemotherapy or surgery)) and index date A (start date of last type of post-CNS treatment). Subjects with missing values for the pre-specified baseline characteristics were excluded from the primary analysis (complete case analysis).

6.4.6 Sensitivity Analyses

To assess the robustness of the finding from the primary analysis, six pre-specified sensitivity analyses were performed. The sensitivity analyses were designed to examine the impact on the treatment effect of using imputation of missing data, different definitions of index dates, and choice of modality group (Table 19).

Table 19 Description of Pre-specified Sensitivity Analysis

Objective	Sensitivity Analysis	Modality Group	Index Date	Imputation of missing data (Y/N)
Test consistency despite missing data	1	MG2	Index Date A	Y
Test consistency despite index date	2	MG2	Index Date A (German Registry population) and Index D (Trial 03-133)	N
	3	MG2	Index Date B	N
	4	MG2	Index Date C	N
Test consistency despite modality group	5	MG4	Index Date A	N
	6	MG3	Index Date A	N

Refer to Table 16 and Table 17 for definitions of modality groups and index dates, respectively.

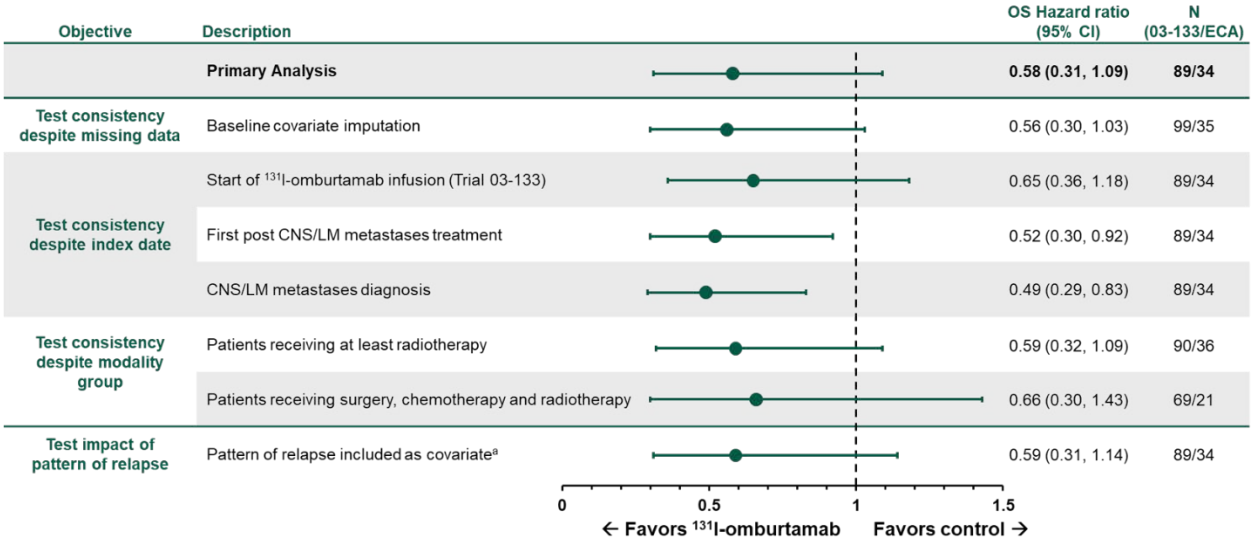
The results from the six pre-specified sensitivity analyses showed:

- Repeating the primary analysis in a sensitivity analysis designed to address the use of complete cases by imputation of missing values, a hazard ratio of 0.56 (95% CI: 0.30, 1.03), log-rank test p-value=0.0346 was found (Figure 16). This underlines the power issue inherent in the rare indication setting.
- In the sensitivity analyses designed to address the different definitions of index dates, the hazard ratios ranged from 0.49 (95% CI: 0.29, 0.83) to 0.65 (95% CI: 0.36, 1.18). These sensitivity analyses all point in the same direction as the primary analysis, confirming that the choice of index date in the primary is conservative.
- The different choice of modality group showed consistent magnitude of the effect with hazard ratios of 0.59 (95% CI: 0.32, 1.09) and 0.66 (95% CI: 0.30, 1.43) (Figure 16).

A post-hoc sensitivity analysis examining the impact of pattern of relapse on the treatment effect was performed (Figure 16), and the magnitude of the effect was in line with the results of the primary analysis.

Overall, the array of sensitivity analysis supports a consistent, robust, and clinically meaningful effect of adding ^{131}I-omburtamab to a multimodal treatment strategy.

Figure 16 Overall Survival by Treatment Group – Sensitivity Analyses



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

CNS=central nervous system; ECA= external control arm; LM=leptomeningeal; OS=overall survival

6.4.7 External Control Arm vs. SIOPEN

A comparison of OS outcomes in the ECA [N=35] and SIOPEN data [N=18], restricted to MG2, demonstrated a 3-year OS rate of 26% and 22%, with a median OS of 16 months and 14.5 months for the ECA and SIOPEN population, respectively (Table 20). This analysis provide reassurance that the OS observed in the ECA is consistent with other data sources and representative of high-risk neuroblastoma patients with CNS/LM metastases able to receive multimodal therapy.

Table 20 External Control Arm vs. SIOPEN: Overall Survival

Parameter	Statistic/Category	External Control Groups	
		ECA (MG2) (N=35)	SIOPEN (MG2) (N=18)
Patient Status, N (%)	Dead	26 (74.3)	15 (83.3)
	Censored	9 (25.7)	3 (16.7)
3-year Survival Proportion	KM estimate	0.26	0.22
	95% CI	0.13, 0.41	0.07, 0.43
	Median (95% CI), months	16.0 (10.0, 29.8)	14.5 (8.0, 24.0)
	At Risk	35	18
	Censored	9	3

The Kaplan-Meier method was used to analyze overall survival.

CI = confidence interval; ECA = external control arm; KM = Kaplan Meier; MG2 = modality group; SIOPEN = International Society of Paediatric Oncology Europe Neuroblastoma Group

6.4.8 External Control Arm: Conclusions

The data from the German Registry was an appropriate external control source for comparative analyses to Trial 03-133. Although comparisons to ECA have limitations due to data availability,

the limitations were manageable, and the clinical outcomes in the ECA are consistent with all available historical data sources.

A clinically meaningful 42% relative reduction in the risk of death with ^{131}I-omburtamab (hazard ratio of 0.58 [95% CI: 0.31, 1.09], log-rank p-value = 0.0544) was obtained. The 3-year OS rate was notably higher in Trial 03-133 (54%) than in the ECA (31%), and an improved median OS exceeding 2 years was observed with ^{131}I-omburtamab (4 years vs. 1.3 years).

An array of sensitivity analyses supported a consistent, robust, and clinically meaningful effect of adding ^{131}I-omburtamab to a multimodal treatment strategy.

6.4.9 Overall Efficacy Conclusion

The rarity and severity of the indication necessitates non-standard trial design and analysis approaches. Under these circumstances, a conclusion of effectiveness cannot rely on one single analysis, but rather on the totality of evidence. The external control arm selected for comparison to Trial 03-133 is the largest patient-level control group in this indication and represent an appropriate control arm.

The results from Trial 03-133 demonstrate a 3-year OS rate of 57% and a median OS estimate of 51 months. The results of the supportive Trial 101 were consistent with Trial 03-133, demonstrating similar results in a multicenter setting. Moreover, in Trial 101, a clinically meaningful ORR of 35% with 5 complete and 2 partial responders was observed among the 20 patients with measurable disease at baseline. Additionally, stable disease was observed in 7 patients resulting in an overall disease control rate of 70%, which may contribute to the observed delay in disease progression.

A clinically meaningful 42% relative reduction in the risk of death (hazard ratio of 0.58; 95% CI: 0.31, 1.09) was observed with the addition of ^{131}I-omburtamab to a multimodal treatment strategy compared with the ECA. An improved median OS exceeding 2 years (Trial 03-133 [4 years] and ECA [1.3 years] and an improved 3-year OS rate by 23% (Trial 03-133 [54%] and ECA [31%]) was also observed with ^{131}I-omburtamab. An array of sensitivity analyses consistently demonstrated the treatment effect in favor of ^{131}I-omburtamab.

The totality of the data provides substantial evidence of the efficacy of ^{131}I-omburtamab as addition to multimodal treatment for the treatment of neuroblastoma CNS/LM metastases.

7 Clinical Safety

7.1 Safety Data

The safety evaluation of ^{131}I-omburtamab is based on data from the two open-label, single-arm trials: Trial 03-133 and Trial 101. The evaluation is based on data from 159 patients with neuroblastoma with CNS/LM metastases (109 patients in Trial 03-133 and 50 patients in Trial 101).

An additional 68 non neuroblastoma patients in Trial 03-133 provided supplemental SAE data on ^{131}I-omburtamab in the BLA. This Briefing Document only includes an overall conclusion of the SAEs from these non-neuroblastoma patients. All other results are based on neuroblastoma patients.

Because the two trials were initiated and conducted during different time periods and there are differences in the trial design and data capturing, data from the two trials were not pooled but presented in separate tables or in side-by-side tables.

Table 21 provides a definition of the analysis sets and the total number of patients within each analysis set used in the safety assessment of ^{131}I-omburtamab.

Table 21 Definitions of Analysis Sets Used in the ^{131}I-omburtamab Safety Assessment

Trial	Analysis Set	Population Definition
Trial 03-133	Safety Analysis Set (SAF)	Includes all neuroblastoma patients enrolled in the trial who began an infusion of radiolabeled omburtamab (N=109).
Trial 101	Safety Analysis Set (SAF)	Includes all enrolled patients who received at least one dose of ^{131}I-omburtamab (N=50).

Safety data in this document are based on the safety analysis sets (SAFs), unless otherwise stated, and includes all patients with neuroblastoma with CNS/LM metastases exposed to ^{131}I-omburtamab.

7.2 Safety Assessments

Safety was evaluated by assessment of treatment emergent adverse events (TEAEs), clinical laboratory data, vital signs, radiographic evaluation, neurotoxicity assessments, and physical examinations.

7.3 Safety Population and Exposure

7.3.1 Patient Disposition

Patient disposition is presented in Section 6.2.2 (Trial 03-133) and Section 6.3.2 (Trial 101).

7.3.2 Patient Demographics

Patient demographics and other baseline characteristics are presented in Section 6.2.3 (Trial 03-133) and Section 6.3.3 (Trial 101). Note, that for Trial 03-133, demographics and other baseline characteristics are presented for the 107 patients included in the efficacy analysis (FAS).

7.3.3 Extent of Exposure

The majority of patients were exposed to one or two treatment doses of [131]I-omburtamab. In accordance with the protocol, patients in Trial 03-133 could receive more than two treatment doses of [131]I-omburtamab; one patient received three and one patient received four treatment doses. The majority (144 of 159 patients) were treated at the 50 mCi dose level (with dose reductions according to age), see Table 22. A total of 10 patients in Trial 03-133 received treatment doses ranging from 10 to <50 mCi and 5 patients received treatment doses ranging from >50 to 70 mCi during the dose escalation part of the trial. Furthermore, most patients received one or two dosimetry doses (2 mCi) (not summarized in Table 22).

Table 22 Exposure of [131]I-omburtamab by Trial

	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 (2)[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)	0	2 (2)	0

[a] Received dosimetry dose only.

In Trial 03-133, the mean total actual dose (including dosimetry dosage) for all patients in the safety analysis set was 71.99 mCi (range: 1.87 to 218.33 mCi). In Trial 101, the mean total actual treatment dose was 75.4 mCi (range: 31.7–110 mCi).

7.4 Overview of Treatment-Emergent Adverse Events

An overview of TEAEs in Trial 03-133 and Trial 101 is provided in Table 23. A TEAE is defined as an adverse event with onset at or after the first administration of [131]I-omburtamab. For Trial 03-133, AEs (including SAEs) were reported until 30 days after the last [131]I-omburtamab administration. For Trial 101, AEs (including SAEs) were reported until three weeks after the last [131]I-omburtamab administration. Depending on trial, SAEs occurring later than 30 days or 3 weeks after the last [131]I-omburtamab infusion were only reported if considered related to the trial medication or in case of new onset of cancers regardless of causality.

Severity of TEAEs is presented by CTCAE classification grade and is referred to as “Grade” in the following.

Details on common TEAEs (including presentation by Grade ≥3) are presented in Section 7.5. Details on SAEs, TEAEs leading to discontinuation of [131]I-omburtamab, and TEAEs leading to death are presented in Section 7.6.

Table 23 Overview of Treatment-emergent Adverse Events by Trial

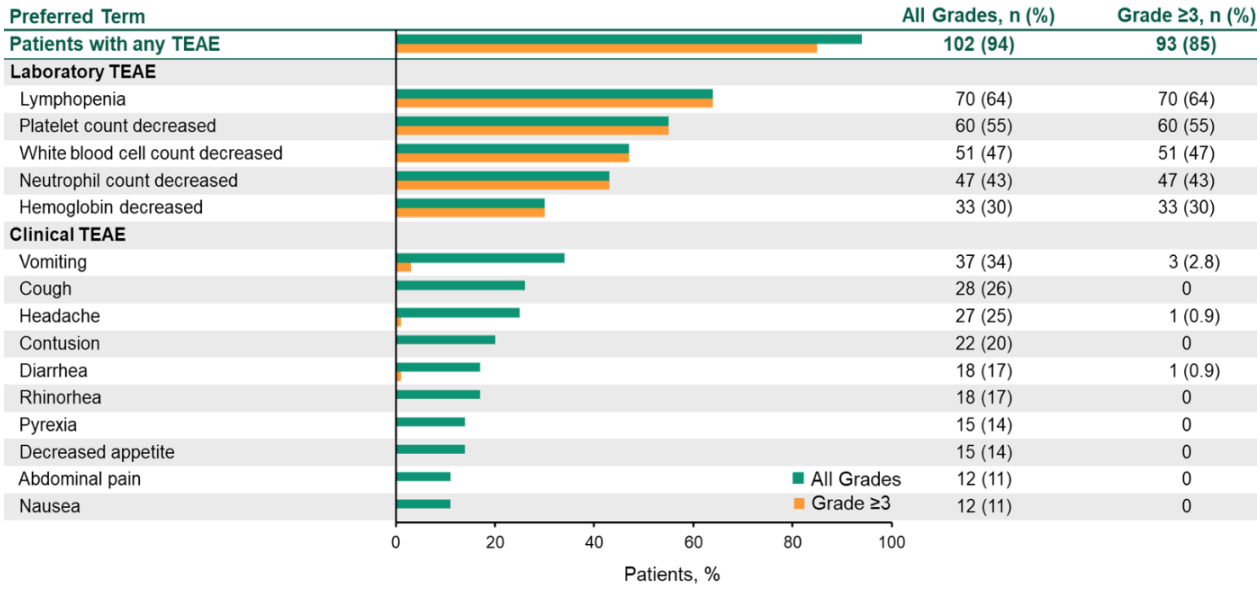
	Patients, n (%)	
	Trial 03-133 N (%)	Trial 101 N (%)
Safety Analysis Set	**109**	**50**
Patients with at least one TEAE	**102 (93.6)**	**49 (98.0)**
Grade ≥3 TEAEs	93 (85.3)	33 (66.0)
SAEs	54 (49.5)	18 (36.0)
TEAEs leading to discontinuation of [131]I-omburtamab	11 (10.1)	7 (14.0)
TEAEs leading to death	0	1 (2.0)

N = number of patients experiencing the event at least once; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

7.5 Most Frequently Reported Adverse Events

A summary of TEAEs by preferred term reported for at least 10% of the patients is presented in Figure 17 (Trial 03-133) and in Figure 18 (Trial 101).

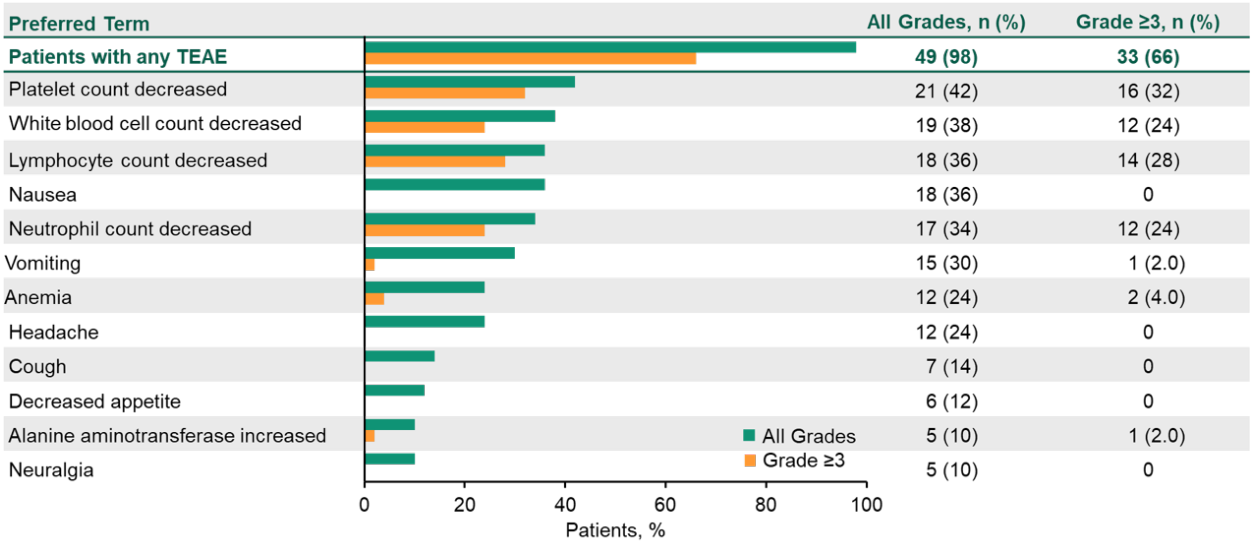
Figure 17 Trial 03-133: Most Frequent TEAEs Occurring in at Least 10% of Patients



% = percentage of patients; n = number of patients; TEAEs=treatment-emergent adverse events.

Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies are numbers of patients who reported at least one AE of that PT. Patients reporting more than one AE in a given PT were counted only once for that particular PT.

Figure 18 Trial 101: Most frequent TEAEs occurring in at Least 10% of Patients



% = percentage of patients; n = number of patients; TEAEs=treatment-emergent adverse events.
Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies are numbers of patients who reported at least one AE of that PT. Patients reporting more than one AE in a given PT were counted only once for that particular PT.

In Trial 03-133, 1756 TEAEs were reported in 102 patients (94%). The most common TEAEs were lymphopenia (64%), decreased platelet count (55%), decreased white blood cell count (47%) and decreased neutrophil count (43%); see Figure 17.

In Trial 101, 365 TEAEs were reported in 49 patients (98%). The most common TEAEs were decreased platelet count (42%), decreased white blood cell count (38%), decreased lymphocyte count (36%), nausea (36%), decreased neutrophil count (34%) and vomiting (30%); see Figure 18.

Numbers of events per patient differ between the two trials due to differences in handling of lab data: In Trial 03-133, all abnormal lab results were recorded as AEs, while in Trial 101 only abnormal lab results that were assessed as clinically significant by the investigator were recorded as AEs.

The events of decreased platelet count, decreased white blood cell count, decreased lymphocyte count, decreased neutrophil count and anemia are consistent with myelosuppression. As expected in a heavily pretreated population, and known from other radiolabeled antibody products, myelosuppression was anticipated to be a significant risk.[24, 25] An analysis of TEAEs included in the standardized MedDRA query (SMQ) 'Haematopoietic cytopenias' showed that most patients, 83% of the patients in Trial 03-133 and 72% of the patients in Trial 101, had at least one event relating to cytopenia; see also Section 7.8.1.

In both trials, the majority of the patients with TEAEs related to myelosuppression had at least one Grade 3 or higher myelosuppression events; see Figure 17 and Figure 18.

7.6 Deaths, Serious Adverse Events, and Other Significant Adverse Events

7.6.1 Deaths

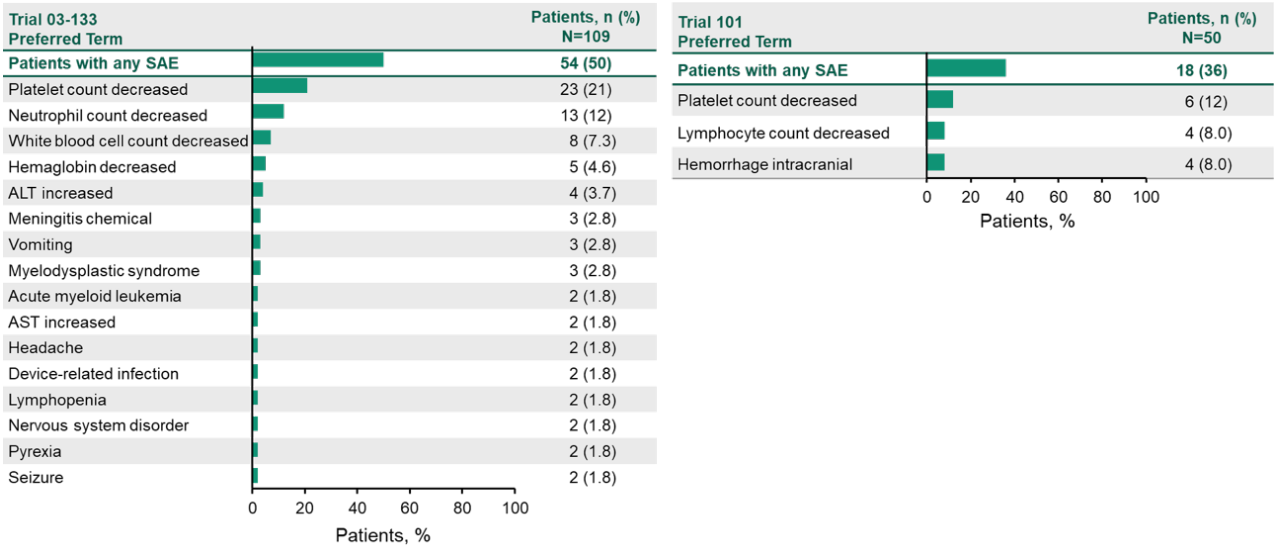
In Trial 03-133 there were no deaths due to TEAEs. It should be noted that two patients with secondary malignancies (acute myeloid leukemia and myelodysplastic syndrome) died 2.5 and 8 years after their last dose of [131]I-omburtamab.

In Trial 101 there was one death due to a TEAE of intracranial hemorrhage. This event was reported as not related to [131]I-omburtamab but related to recurrence of multiple CNS metastases by the investigator. The event was assessed as possibly related by the Sponsor as the patient had concomitant Grade 4 thrombocytopenia which the Sponsor considered may have been a contributing factor to the event of intracranial hemorrhage.

7.6.2 Serious Adverse Events

A summary of SAEs in both trials is provided in Figure 19.

Figure 19 Trial 03-133 and Trial 101: Treatment-Emergent Serious Adverse Events Occurring in More Than One Patient



% = percentage of patients; n = number of patients; SAE = serious adverse event

Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies are numbers of patients who experienced at least one SAE of that PT. Patients who experienced more than one SAE of a given PT were counted only once for that particular PT.

In Trial 03-133, 95 SAEs were reported for 54 of the 109 patients (50%). The following SAEs occurred in more than 5% of the patients and were attributable to myelosuppression: decreased platelet count (21%), decreased neutrophil count (12%) and decreased white blood cell count (7%).

In Trial 101, 24 SAEs were reported for 18 of the 50 patients (36%). Like in Trial 03-133, most SAEs were attributable to myelosuppression. The following SAEs occurred in more than 5% of

the patients: decreased platelet count (12%), decreased lymphocyte count (8%) and intracranial hemorrhage (8%). The remaining SAEs each occurred in a single patient.

SAEs in Non-Neuroblastoma Patients (Trial 03-133)

Patients with a non-neuroblastoma diagnosis provided supplemental SAE data. The SAE data were consistent with SAE data for the patients with neuroblastoma.

7.7 Adverse Events Leading to Discontinuation of Study Medication

TEAEs leading to discontinuation of trial drug is provided in Table 24.

In Trial 03-133, 11 of 109 patients (10%) had a total of 12 TEAEs that led to discontinuation of ^{131}I-omburtamab treatment. These treatment-limiting TEAEs included decreased platelet count in 8 patients (7.3%) and chemical meningitis in 3 patients (2.8%). One patient with decreased platelet count also had immune thrombocytopenic purpura.

In Trial 101, 7 of 50 patients (14%) had a total of 8 TEAEs that led to discontinuation of ^{131}I-omburtamab treatment. Six of these 8 TEAEs were consistent with myelosuppression with 5 patients (10%) discontinuing for decreased platelet count and one patient discontinuing for decreased lymphocyte count. The last two TEAEs were chemical meningitis and intracranial hemorrhage.

Table 24 Trial 03-133 and Trial 101: Treatment Emergent Adverse Events Leading to Discontinuation of Study Treatment

	Trial 03-133 N (%) E	Trial 101 N (%) E
Safety Analysis Set	**109**	**50**
Number of TEAEs leading to discontinuation	12	8
Patients with at least one TEAE leading to discontinuation	11 (10) 12	7 (14) 8
Preferred term		
Platelet count decreased	8 (7.3) 8	5 (10) 5
Meningitis chemical	3 (2.8) 3	1 (2.0) 1
Immune thrombocytopenic purpura	1 (0.9) 1	0
Hemorrhage intracranial	0	1 (2.0) 1
Lymphocyte count decreased	0	1 (2.0) 1

% = percentage of patients; E = number of events; N= number of patients; TEAEs = treatment-emergent adverse events

7.8 Analysis of Potential Risks Associated with ^{131}I-omburtamab Treatment

To better understand the safety profile of ^{131}I-omburtamab, investigations of adverse events by organ systems were undertaken. The following sections outline the potential risks of treatment with ^{131}I-omburtamab and the proposed plan to mitigate these risks.

The following was in focus to identify potential risks: adverse events related to myelosuppression, hemorrhage, infections, infusion-related reactions (including anaphylaxis), secondary malignancies, neurotoxicity, hepatic toxicity and thyroid suppression. Searches for AEs relating to myelosuppression, hemorrhage, anaphylactic reactions, hepatic toxicity, and

thyroid suppression were performed using standardized MedDRA queries (SMQs). Infections, secondary malignancies and neurotoxicity were investigated by summarizing AEs in the associated system organ classes (SOCs) or selected relevant AE Preferred Terms (PTs).

Myelosuppression was expected in a heavily pretreated population and known from other radiolabeled antibody products.[24, 25] Other medically important AEs included intracranial hemorrhage, secondary malignancies, and chemical meningitis.

7.8.1 Myelosuppression

The most common severe (Grade 3 or higher) TEAEs were related to myelosuppression.

A total of 83% and 72% of the patients had at least one event relating to cytopenias in Trials 03-133 and 101, respectively (identified by the SMQ 'Haematopoietic cytopenias').

In Trials 03-133 and 101, 55% and 32% of the patients had decreased platelet count Grade 3 or higher as the most common event related to myelosuppression. Reduced platelet count / thrombocytopenia was also the most common TEAE leading to treatment discontinuation, hindering patients from receiving a second treatment dose of ^{131}I-omburtamab (Table 24).

Potential clinical risks with myelosuppression are severe bleedings and increased susceptibility to infections. Two cases of febrile neutropenia were reported, and one serious infectious event (sepsis) was found to be associated with severely reduced (CTCAE grade 3 or higher) neutrophil levels (Trial 101). One fatal event of intracranial hemorrhage was reported for a patient with multiple CNS metastases in Trial 101, see Section 7.8.2. The risks related to myelosuppression are mitigated by withholding or delaying treatment for patients with insufficient hematological status and by closely monitoring blood counts during treatment. Severe myelosuppression may be treated with transfusions or growth factors in accordance with local medical practice.

7.8.2 Intracranial Hemorrhage

Four events of intracranial hemorrhage were reported in Trial 101, thereof one event was fatal. There were no events of intracranial hemorrhage in Trial 03-133. In all 4 cases in Trial 101, CNS disease progression was observed and considered to be the likeliest cause of the intracranial hemorrhage. It is well documented that hemorrhage is a common manifestation of disease progression in neuroblastoma patients with CNS metastases, based on the natural history of this disease.[12, 26] Out of the 4 patients with intracranial hemorrhage, 3 had Grade 3 to 4 thrombocytopenia and 1 patient had Grade 1 thrombocytopenia at the time of the event. Since all patients had thrombocytopenia to some degree, Y-mAbs assessed the intracranial hemorrhage as possibly related to study drug, despite investigators reporting two of the events as not related or unlikely related. As mentioned above, one event was fatal. Two of the patients were reported to have neurological sequelae in the form of limb weakness. The last patient had no sequalae.

To the degree that myelosuppression is part of the etiology for intracranial hemorrhage, mitigating measures will be the same as for myelosuppression as such, see above.

7.8.3 Secondary Malignancies

Secondary malignancies such as myelodysplastic syndrome or acute leukemia are potential risks with the use of ^{131}I-omburtamab. These hematologic malignancies are known risks in patients who have received significant amounts of chemotherapy and radiation therapy prior to treatment with ^{131}I-omburtamab. Since some of the patients in Trial 101 and Trial 03-133 were heavily pre-treated with a combination of intensive chemo- and radiotherapy, the contribution of ^{131}I-omburtamab to the safety risk is difficult to ascertain.

All TEAEs in the SOC 'Neoplasms benign, malignant, and unspecified' were assessed. In Trial 03-133, a total of 6/109 patients (5.5%) had at least one TEAE belonging to this SOC. Myelodysplastic syndrome was reported for 3 patients, 2 patients had acute myeloid leukemia and 1 patient had skin papilloma (wart). With the exception of the skin papilloma (wart), all TEAEs belonging to this SOC were considered serious and were diagnosed between 7 months and 5 years after the last dose of ^{131}I-omburtamab. One patient in Trial 101 was diagnosed with a thyroid malignancy (papillary thyroid cancer) approximately one year after the first exposure to ^{131}I-omburtamab. The investigator reports the event of papillary thyroid cancer as possibly related to ^{131}I-omburtamab. The investigator's suggested alternative etiology was specified as MIBG scans and prior therapy, and it was stated that "radiation uptake to the thyroid gland could have contributed to diagnosis, however, timing seemed quite short, so it was not completely clear but definitely possible".

7.8.4 Chemical Meningitis

Patients treated with ^{131}I-omburtamab may develop chemical meningitis, which is a non-infectious inflammation of the meninges. Chemical meningitis is considered to be infusion related.

A total of 5 patients had chemical meningitis (3 in Trial 03-133 and 2 in Trial 101). Three events were Grade 3, and 2 events were Grade 2 (one was a non-serious AE). All 4 SAEs led to discontinuation of trial treatment and were assessed as probably related to trial drug by the investigator. A total of 4 of the 5 events were considered infusion-related (onset <1 day after latest infusion). All 5 cases resolved with supportive treatment and/or treatment discontinuation and without sequelae.

Risk mitigation related to chemical meningitis include permanent discontinuation of ^{131}I-omburtamab if a patient experiences Grade 4 neurotoxicity. Furthermore, monitoring of patients for signs of meningitis after ^{131}I-omburtamab administration is advised. Signs include fever, headache, nausea and vomiting. Patients should be pre-treated with dexamethasone to reduce the risk of chemical meningitis. Since the dose of the required dexamethasone pre-treatment in Trial 101 was increased in 2019, 33 additional patients have been treated. No new events of chemical meningitis have been reported among the additional patients, and Y-mAbs considers the risk of chemical meningitis to be successfully mitigated.

7.8.5 Other Risks Related to Ionizing Radiation

Thyroid Suppression

The risk of hypothyroidism is well-known when treating with iodine-131[32], and thyroid suppression is a potential risk with ^{131}I-omburtamab due to the effects of radioactive iodine on the thyroid. A search for all TEAEs in Trials 03-133 and 101 relating to thyroid suppression was performed using the SMQ 'Hypothyroidism'.

No patients in Trial 03-133 had TEAEs related to thyroid suppression. In Trial 101, 3 of 50 patients (6.0%) had at least one TEAE related to thyroid suppression. The events were non-serious and Grade 1 or 2.

The risk is mitigated by ensuring compliance to a thyroid protection regimen which was used with success in both Trial 03-133 and Trial 101. Thyroid protection is ensured by treating all patients with thyroid-blocking stable iodide drops and liothyronine starting one week before ^{131}I-omburtamab treatment until two weeks after the last therapeutic dose.

Neurotoxicity

Intracerebral exposure to therapeutic irradiation carries the risk of neurological injury. The radiation emitted from the radiolabeled antibody bound to the tumor cell may also damage normal neighboring cells since beta-emission penetration-range in tissue can extend over several cell diameters. Chemical meningitis, as discussed above, is a non-infectious inflammation of the meninges caused by exposure to the radiolabeled antibody; it is considered to be infusion related and not a result of neurotoxicity.

All TEAEs in the SOC 'Nervous system disorders' as well as all events of PT chemical meningitis were assessed. Neurotoxicity have not been seen to any clinically relevant extent in the two clinical trials.

A total of 6 of 109 patients (5.5%) and 7 of 50 patients (14%) had at least one TEAE possibly associated with neurotoxicity in Trial 03-133 and Trial 101. Of these, 4 patients had peripheral sensory neuropathy, 2 patients had peripheral motor neuropathy, 2 patients had seizures, 2 patients had dysesthesia, and 1 patient each had hypoesthesia, loss of consciousness, tremor, or depressed level of consciousness. Specific neurotoxicity events considered to be SAEs were as follows: seizure (2 patients) and depressed level of consciousness (1 patient).

In Trial 101, performance testing was conducted and analyzed using the Lansky Play-Performance Scale for children less than 16 years and the Karnovsky Scale for children at least 16 years to evaluate gross neurologic function and measure patients' overall function. In general, patients were high functioning at baseline and had little or no deterioration in follow-up performance scores.

Infusion-Related Reactions

Infusion-related TEAEs were TEAEs with onset <1 day after the latest infusion. Severe infusion-related reactions, including anaphylactic reaction, is a well-known risk associated with systemic administration of monoclonal antibodies,[33, 34] but have not been seen to the same extent with intraventricular or intrathecal drug administration.[35]

Severe (Grade 3 or higher) infusion-related reactions were reported by 3% of the patients across Trial 03-133 and Trial 101 (3 of 109 patients and 1 of 50 patients, respectively). These included three Grade 3 TEAEs of chemical meningitis (see above), headache and vomiting (1 event of each in Trial 03-133). No infusion-related TEAEs met the criteria for anaphylactic reactions (as per MedDRA (v20.1) SMQ Anaphylactic reactions [narrow terms]).

The patients are treated at highly specialized clinics with experience in managing infusion-related reactions. To mitigate the risk, premedication based on dexamethasone (or equivalent), antipyretics and oral antihistamine is to be administered in association with ^{131}I-omburtamab infusion. Furthermore, risk mitigation includes permanent discontinuation of ^{131}I-omburtamab in patients who develop signs and symptoms of severe infusion-related reactions.

Hepatic Toxicity

Organ dosimetry data (Trial 101) showed the liver as the organ with the highest absorbed dose, however, still within acceptable tolerability levels. The absorbed radiation in the liver was not accompanied by adverse reactions that would indicate organ damage.

7.9 Overall Safety Conclusion

In both clinical trials, adverse reactions were generally manageable. The most common severe (Grade 3 or higher) TEAEs were related to myelosuppression, which was expected and known from other radiolabeled antibody products. Other medically important adverse events included intracranial hemorrhage, secondary malignancies, and chemical meningitis. Overall, the safety profile of ^{131}I-omburtamab is acceptable given the seriousness of the disease being treated.

8 Rationale for Proposed Dosing Regimen

The recommended dosing regimen for ^{131}I-omburtamab is 2 age-based doses given 4 weeks apart. For patients less than 1 year the recommended dose is 25.0 mCi; for patients 1 to less than 3 years the recommended dose is 33.5 mCi; and for patients older than 3 years the recommended dose is 50 mC (Table 2).

The decision to use a treatment dose of ^{131}I-omburtamab of 50 mCi, with age-based dose reductions, was based on the safety data obtained from the dose-escalation part of Trial 03-133 that included both neuroblastoma and non-neuroblastoma patients. During the last part of the dose-escalation at the 60 and 70 mCi dose levels, severe and prolonged myelosuppression was observed, whereas a non-myelosuppressive maximum tolerated dose (MTD) was not reached.

The patients administered >50 mCi experienced prolonged thrombocytopenia lasting more than four weeks. Although this did not constitute a dose-limiting toxicity, as defined in the Trial-03-133 protocol, 4 of 6 patients (67%) receiving >50 mCi ^{131}I-omburtamab post-CSI had Grade 4 thrombocytopenia and had not attained platelet-transfusion independence before the second dose would have been due. In contrast, none of the 3 patients who received 50 mCi ^{131}I-omburtamab after CSI, developed prolonged thrombocytopenia. A treatment dose of 50 mCi dose was therefore selected as myelosuppression was manageable at this dose. The treatment dose of 50 mCi ^{131}I-omburtamab was subsequently administered to 94 patients in the dose expansion part of Trial 03-133. In the therapeutic setting of neuroblastoma with CNS/LM metastases where the tumor volume is mostly impossible to establish and where there is no known threshold radioactive dose over which tumor kill is assured, the dose finding approach employed in Trial 03-133 is in alignment with the principle to “dose as high as safely attainable” as described for dosing of other radiopharmaceuticals in cancer patients.[36]

It appears that patients who received <50 mCi had a numerically higher 3-year survival proportion than patients in the other dose groups (0.88 [<50 mCi] versus 0.54 [50 mCi] and 0.60 [>50 mCi]). However, there were notably fewer patients in the <50 mCi dose group (N=8) than the 50 mCi dose group (N=94), and the lower bound of the 95% CI of the median survival estimates were similar between these dose groups (23.5 and 27.8, respectively).

Furthermore, the two 50 mCi doses are supported from comparing the median time of survival and 3-year survival estimates from the time of CNS/LM diagnosis for Trial 03-133 FAS patients by number of cycles initiated. Although Trial 03-133 was not statistically powered for subgroup analysis, some analyses could indicate that efficacy was better for patients who initiated two cycles of ^{131}I-omburtamab than for patients who initiated one cycle: 3-year survival probability (0.40 versus 0.70) and 12-month CNS/LM PFS probability (0.47 versus 0.75). These differences, however, must be interpreted with caution, since they are confounded by the fact that for a proportion of the patients that did not receive the second treatment cycle the reason was progression of the disease. While this result could be potentially confounded by underlying ill-disposing factors for the patients who only received one cycle, Y-mAbs believes that the recommended dosing regimen of ^{131}I-omburtamab should be two doses of 50 mCi.

The age-based dose recommendation is based on differences in CSF volume and follows the clinical practice for intrathecal dosing.[21] Data from the clinical trials with ^{131}I-omburtamab demonstrate that this dosing regimen is clinically appropriate. There are no data to suggest that dosing according to weight is superior to dosing according to age.

The dosimetry dose (2 mCi) which was applied in both clinical trials is not included in the proposed dosing regimen as it has no applicability in directing the treatment dose activity and would only increase the burden of treatment.

9 Benefit/Risk

9.1 Benefits

Administration of ^{131}I-omburtamab by intraventricular infusion ensures distribution within the entire CSF and localization at the tumor sites. This enables targeted delivery of radiation to any tumor cells remaining in the CSF compartment. The sensitivity of current diagnostic tools prevents diagnosis of minimal residual disease, which necessitates treatment with ^{131}I-omburtamab regardless of whether lesions or tumor cells are detectable or not following current multimodality treatment. The benefits of this concept were demonstrated in the clinical development program with ^{131}I-omburtamab.

The PK and dosimetry data showed that ^{131}I-omburtamab can be reproducibly and consistently administered across trial sites in a manner that targets the tumor, with limited systemic risk.

In Trial 03-133, a 3-year OS of 57% (95% CI: 47%, 66%), and a median survival estimate of 51 months (95% CI: 31, NE) was observed with ^{131}I-omburtamab. Results from Trial 101 further supported the clinical benefits of ^{131}I-omburtamab in a multicenter setting.

Of the 20 patients with measurable disease at baseline in Trial 101, 7 patients (35%) responded (complete response or partial response) with complete response seen in 5 patients (25%). The median duration of response in the 5 complete responders was 280 days. Additionally, 7 patients (35%) remained in Stable Disease through Week 26. The disease control rate (i.e., proportion of patients with measurable disease at baseline who achieved complete or partial response or stable disease) was 70% and CNS/LM PFS rate at 6 months was 75%, underlining that a delay in progression was observed.

The combined results from Trial 101 indicate an effect of ^{131}I-omburtamab as part of the post-CNS multimodal treatment that these patients received. In this orphan indication and a patient population with a very poor prognosis, achieving a delay of progression and extending survival is clinically important.

The survival outcome from Trial 03-133 was compared with patient-level data from the German Registry. The data from the German Registry was used to construct an ECA using a propensity score weighting approach to balance the patients in Trial 03-133 based on important baseline characteristics and prognostic factors. Prolongation of survival was demonstrated with ^{131}I--omburtamab treatment in Trial 03-133 as compared to the ECA with an estimated hazard ratio of 0.58 (95% CI: 0.31, 1.09), log-rank test p-value=0.0544. Albeit not statistically significant, the 42% reduction in the risk of death with ^{131}I-omburtamab observed in the primary analysis is considered clinically meaningful. In addition, an improved 3-year OS rate by 23% and a clinically relevant OS benefit exceeding 2 years was observed with ^{131}I-omburtamab treatment.

Conclusion - benefits

The totality of evidence from Trials 03-133 and 101, in the context of an orphan, life threatening and ultra-rare disease with a clear unmet medical need, sufficiently demonstrates a large and

robust effect of ^{131}I-omburtamab as addition to multimodal treatment. The evidence includes data showing prolongation in survival compared to current treatment strategies, disease control rates and CNS/LM PFS underlining that a delay in progression is achieved.

9.2 Risks

The most common severe (Grade 3 or higher) TEAEs were related to myelosuppression. Other medically important TEAEs included intracranial hemorrhage, secondary malignancies, and chemical meningitis.

As expected in a heavily pretreated population, and known from other radiolabeled antibody products, the main adverse reactions were consistent with myelosuppression.[24, 25] A total of 83% (Trial 03-133) and 72% (Trial 101) of the patients had at least one event relating to hematopoietic cytopenias, with Grade 3 or higher decreased platelet count as the overall most common event. Decreased platelet count was also the most common AE leading to treatment discontinuation, hindering patients from receiving an additional treatment cycle. Potential clinical risks with significant myelosuppression are severe bleedings and increased susceptibility to infections. Four cases of intracranial hemorrhage of which one had a fatal outcome were reported in Trial 101. In all four cases, CNS disease progression was observed, and considered to be the likeliest cause of the intracranial hemorrhage. It is well documented that hemorrhage is a common manifestation of disease progression in neuroblastoma patients with CNS metastases, based on the natural history of this disease.[12, 26] However, since all patients had thrombocytopenia to some degree, Y-mAbs could not exclude a causal relationship to ^{131}I-omburtamab. Two cases of febrile neutropenia were reported, and one serious infectious event (sepsis) was found to be associated with severely reduced (CTCAE grade 3 or higher) neutrophil levels (Trial 101). The risks related to myelosuppression are mitigated by closely monitoring blood counts during treatment and withholding or delaying treatment for patients with insufficient hematological status. Severe myelosuppression may be treated with transfusions or growth factors in accordance with local medical practice.

Secondary malignancies such as myelodysplastic syndrome or acute leukemia are potential risks with the use of ^{131}I-omburtamab especially in patients who have received significant amounts of chemotherapy and radiation therapy prior to treatment with ^{131}I-omburtamab. In Trial 03-133, isolated cases of myelodysplastic syndrome (3 cases) and acute leukemia (2 cases) diagnosed between 7 months and 5 years after the last dose of ^{131}I-omburtamab have been reported. One patient in Trial 101 was diagnosed with a thyroid malignancy (papillary thyroid cancer) approximately one year after the first exposure to ^{131}I-omburtamab. Due to the relatively short time from treatment with ^{131}I-omburtamab to onset for most of the events and since some of the patients in Trial 101 and Trial 03-133 were heavily pre-treated with a combination of intensive chemo- and radiotherapy, the causal contribution of ^{131}I-omburtamab to the cases of secondary malignancy is difficult to ascertain.

Chemical meningitis was seen in 5 patients (3 in Trial 03-133 and 2 in Trial 101) and was considered to be infusion related. Four of the events led to discontinuation of trial treatment. All 5 events resolved with supportive treatment and without any sequalae. Infusion-related reactions,

including chemical meningitis can be mitigated by pre-medication with corticosteroids, antipyretics, and antihistamines. Since the dose of the required dexamethasone pre-treatment in Trial 101 was increased in 2019, 33 additional patients have been treated. No new events of chemical meningitis have been reported among the additional patients, and Y-mAbs considers the risk of chemical meningitis to be successfully mitigated.

Conclusion - risks

The observed safety profile of ^{131}I-omburtamab is considered acceptable when assessed in the context of the treatment of a life-threatening disease with an unmet medical need. Although ^{131}I-omburtamab can cause severe/serious adverse reactions, these were generally manageable or could be prevented/mitigated through pre-medication and specific monitoring of patients as addressed by information in the product labeling. Additional risk management measures beyond labeling are not proposed.

9.3 Benefit-Risk Conclusion

In the context of a rare, life-threatening disease with a clear unmet medical need, the benefit-risk profile of ^{131}I-omburtamab is considered favorable. This assessment is based on the totality of the efficacy data, which showed consistent evidence of clinically meaningful efficacy of ^{131}I-omburtamab in the treatment of CNS/LM metastases in neuroblastoma patients, as well as an acceptable and manageable safety profile.

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Appendix 1

External Control Arm Construction

Table of Contents

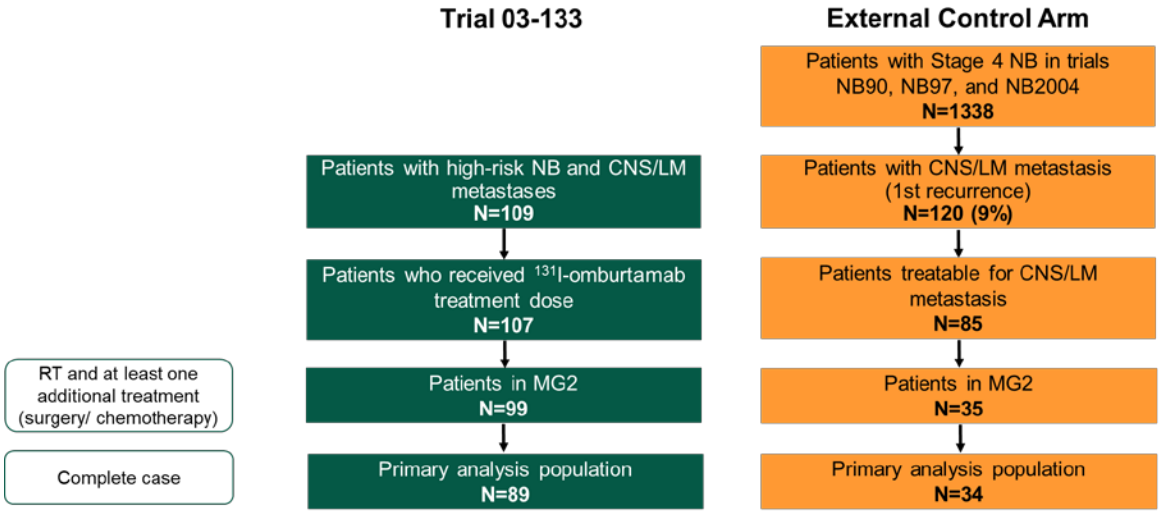
1 External Control Arm Construction

1.1 Data Source

The comparison of Trial 03-133 and the External Control Arm (ECA) is conducted using patient-level data. Trial 03-133 included 109 patients with high-risk neuroblastoma and CNS/LM metastases of which 107 received [131]I-omburtamab treatment. The source of the ECA patients is registry data from the Study Center for Neuroblastoma in Cologne, Germany and included 120 patients with stage 4 neuroblastoma with CNS/LM metastases of which 85 were treatable for CNS/LM metastases.

To further align the comparability of the two data sources and after discussions with FDA, additional eligibility criteria were applied to create modality group 2 (MG2). To be included in modality group 2, patients were required to have received radiotherapy and at least one additional treatment (surgery and/or chemotherapy) as post-CNS relapse treatment. In addition, only patients with complete baseline characteristics were included in the primary analysis, resulting in 89 and 34 patients eligible for the analysis comparing Trial 03-133 and the ECA, respectively (Figure 1). This reduction in the number of eligible patients available for analysis enhances the internal validity of the comparison between Trial 03-133 and the ECA even though it is associated with a loss in power due to the reduction in sample size.

Figure 1: Selection of Patients in Trial 03-133 and the External Control Arm



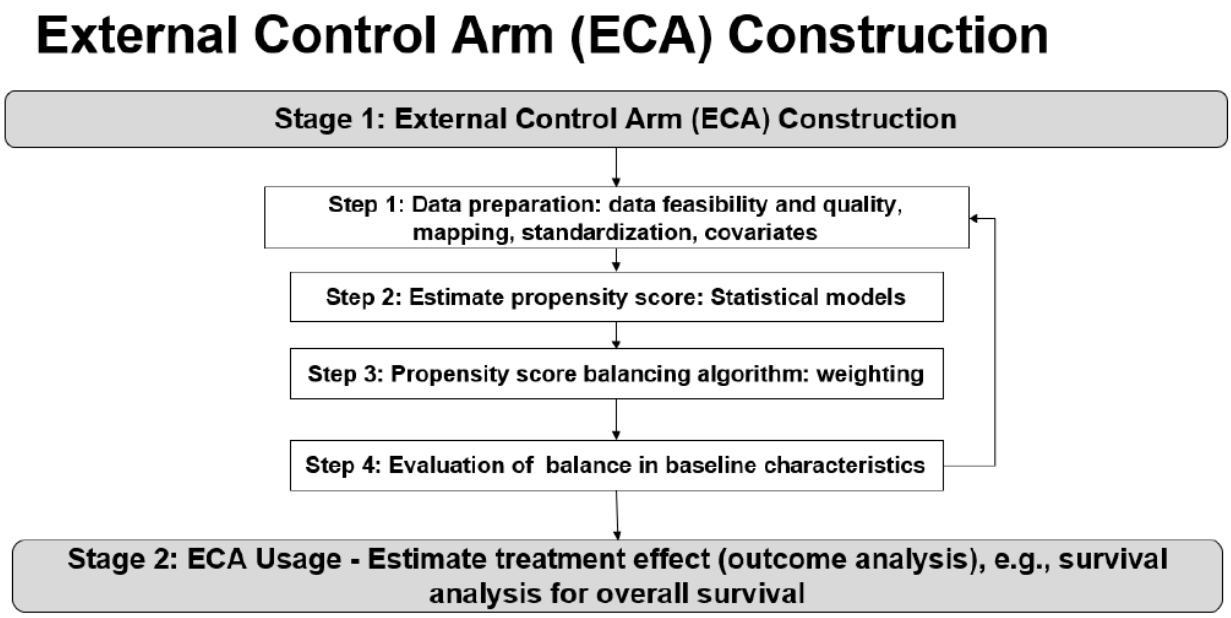
1.2 Overview of External Control Arm Construction

Propensity score (PS) methods are commonly used to analyze observational data to reduce bias due to confounding variables that are unbalanced between groups of interest (e.g., subjects that received the treatment of interest and those that did not). Since the treatments were not randomly assigned between the external control patients and investigational subjects from the target Trial 03-133, the propensity score method was applied to balance the baseline characteristics of the external control patients with that of the omburtamab-treated subjects from Trial 03-133. This balancing is in addition to the alignment of the Trial 03-133 and ECA groups and creation of modality group 2 described in the previous section.

The propensity score of a subject is the probability of treatment assignment conditional on the observed pretreatment characteristics of the subject. Balancing algorithms such as matching or weighting subjects by propensity score or functions of propensity score can create controls in which treatment assignment is independent of observed baseline covariates and allows analysis to obtain unbiased estimates of treatment effects[1-3]. Case studies have indicated that external controls created in this way can mimic randomized controls[4].

Figure 2 flowchart illustrates the two-stage process including ECA construction (Stage 1) and subsequent ECA usage as a comparator in outcome analysis (Stage 2).

Figure 2: Two-stage process for ECA construction and usage



1.3 Estimate Propensity Scores

The propensity score in this analysis is defined as the probability of a subject belonging to the Trial 03-133 trial and receiving the investigational therapy ^{131}I-omburtamab, conditional on the baseline characteristics (i.e., potential confounders) using logistic regression

$$p(x) = P\ (T = 1 \mid X = x)$$

where T = 1 if a subject belongs to Trial 03-133 trial and received omburtamab or 0 otherwise; and X is a vector representing the covariates to be included in the PS model. The covariates included in the propensity score model included demographic variables (e.g., age at neuroblastoma diagnosis) and baseline disease characteristics which are common to both target trial and external controls, and considered as potential confounders (e.g., MYCN status, time from neuroblastoma diagnosis to CNS relapse). These baseline covariates were utilized without further variable selection to obtain optimal balance between the Trial 03-133 subjects and external controls[5]. The statistical methods were prespecified in the ECA statistical analysis plan.

1.4 Create ECAs Using Propensity Score Method

A weighting scheme called average treatment effect on the treated (ATT) weighting (i.e., ATT weighting, also called weighting by odds) was used[6]. It is a variation of the inverse probability of treatment weighting (IPTW) and can be used to estimate the average treatment effect in the subjects treated, similar in definition to the treatment effect estimated in a randomized clinical trial. The weights for subjects j in the investigational therapy group Trial 03-133 and ECA were calculated as:

$$W_j = \begin{cases} 1, & \textit{for patients in Trial 03-133} \\ \dfrac{p_j}{1-p_j} \times 0.3333, & \textit{for patients in external control group} \end{cases} \qquad (1)$$

Trial 03-133 subjects received a weight of one and thus were being used as the reference population to which the ECA subjects were being standardized. Using ATT weights generally created a sample population with approximately a 1:1 ratio between the weighted controls and target trial group. In this analysis, the target trial 03-133 has a larger number of subjects than the external controls, therefore, to avoid overuse of external controls, the ATT weight of ECA patients were reduced to 1/3 such that the weighted sample size from the ECA group was approximately one third of the total number of subjects from the target group.

To mitigate the influence of large weights on the analysis results, that is, the estimation of treatment effects and variances, extreme weights were trimmed to stabilize the weights. No weight trimming was necessary for Trial 03-133 subjects since all Trial 03-133 subjects were assigned a weight of one in the ATT weighting approach. For the patients in the external control group, their weights were calculated from the propensity scores and can be extremely large when the propensity scores get close to 1. No common recommendation on the weight trimming level has been provided in literature. For all the analyses defined in the ECA SAP, if the weight from an ECA subject was greater than 5, the weight was trimmed (i.e., reassigned) to 5.

The selected subjects from the external control group and their corresponding weights were the components of ECA.

1.5 After-weighting Evaluation of Covariate Balance

The propensity score was being used as a balancing score. It was examined whether the distribution of measured baseline covariates was similar between the Trial 03-133 omburtamab-treated subjects and corresponding ECAs. Absolute standardized difference in covariate means was computed and compared. Assessment of propensity score balancing was carried out without any knowledge of patient level outcomes. For a continuous covariate, the standardized difference was calculated using the following formula:

$$d = \frac{\underline{x}_t - \underline{x}_c}{\sqrt{(s_t^2 + s_c^2)/2}} \qquad (2)$$

where x_t and x_c denote the sample mean of the covariate for Trial 03-133 omburtamab-treated

subjects and ECA subjects, respectively; S_t^2 and S_c^2 denote the sample variance of the covariate for Trial 03-133 omburtamab-treated subjects and ECA subjects, respectively.

The sample means and sample variances in formula (2) are unweighted estimates. However, weighted absolute standardized differences were calculated to evaluate the balance between target trial 03-133 subjects and ECA. Each sample estimate was replaced by its weighted equivalent. The weighted mean is defined as:

$$\underline{x}_{WT} = \frac{\Sigma w_i x_i}{\Sigma w_i}$$

and weighted sample variance is defined as:

$$s_{WT}^2 = \frac{\Sigma w_i}{(\Sigma w_i)^2 - \Sigma w_i^2} \Sigma w_i (x_i - \underline{x}_{WT})^2$$

where w_i is the weight assigned to the i^{th} subject[3]. The standardized difference was developed for comparing continuous variables; however, it can justifiably be used for comparing dichotomous variables[7]. For categorical covariates with more than 2 levels of categories, the standardized differences for all pairwise levels of the categorical variable were calculated.

The absolute standardized differences should generally be less than 0.25[8]. An absolute standardized difference of less than 0.10 has been taken to indicate a negligible difference in the mean or prevalence of a covariate between treatment groups[9].

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