^{131}I-Omburtamab for neuroblastoma with central nervous system or leptomeningeal metastases

Oncologic Drugs Advisory Committee (ODAC) Meeting

FDA Introductory Comments
October 28, 2022

Amy Barone, MD
Cross Disciplinary Team Leader
Division of Oncology 2
Office of Oncologic Diseases

APPLICANT'S PROPOSED INDICATION

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

Proposed dosage: Two doses (25 to 50 millicuries based on age) given 4 weeks apart as intracerebroventricular infusions

Proposed pathway: Traditional approval

Basis for the Application

- Study 03-133
  - Single-arm study conducted by Memorial Sloan Kettering Cancer Center (MSKCC),
  - Applicant obtained the rights to commercial development (2015)
  - Overall survival (OS) endpoint compared to an external control (EC)
- Study 101 (supportive)
  - Multicenter, single-arm study
  - Response data systematically collected

Outline

- Neuroblastoma background
- Regulatory framework for approval and use of external controls
- Study 03-133 and External Control
- Key efficacy issues
- Discussion topic and voting question for ODAC

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Neuroblastoma with CNS/LM Metastases

- Disease background
  - Childhood cancer of neural crest origin (e.g., adrenal gland)[1]
  - 650 cases diagnosed per year in the US[2]
  - 6% of patients with high-risk NBL who experience metastatic relapse include metastases to the CNS parenchyma or LM[3]

- No approved or curative therapies
  - Surgery
  - Radiation therapy (e.g., craniospinal irradiation) has been suggested to provide benefit in single-arm studies
  - Off-label systemic chemotherapy (e.g., temozolomide and irinotecan)

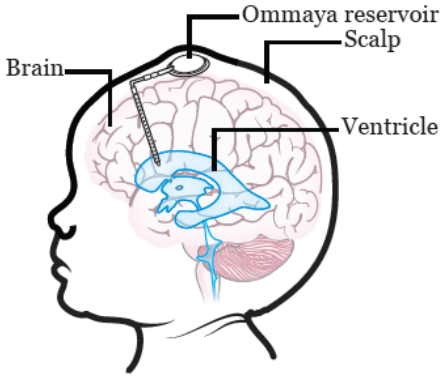
[1]PDQ® PDQ Neuroblastoma
[2]SEER Cancer Statistics Review
[3]Berlanga 2021

^{131}I-omburtamab

- Radiolabeled monoclonal antibody
  - Binds to B7-H3 expressed on neuroblastoma cells
  - Beta-emission from iodine-131 causes cell death

- "When administered directly into the intraventricular space…^{131}I-omburtamab will reach and target B7-H3 expressing tumor cells in the entire CSF compartment, including micro-metastatic CNS disease" (Applicant Briefing Document)

- Mechanistic plausibility: Lack of robust clinical or preclinical data to support parenchymal tumor uptake via CSF delivery



Source: Applicant Briefing Document, ref Memorial Sloan Kettering Cancer Center Frequently Asked Questions About Ommaya Reservoirs and Ommaya Taps for Pediatric Patients

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Evidence of Effectiveness for Approval

21 CFR 314.126 A drug or biologic must demonstrate substantial evidence of effectiveness through **adequate and well controlled studies**

Under certain circumstances…FDA can conclude that one adequate and well-controlled clinical investigation plus confirmatory evidence is sufficient to establish effectiveness.

- Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products *Guidance for Industry*

Relevant Endpoints in Oncology Trials

- Overall survival (OS)
  - "Gold standard"
  - Direct measure of clinical benefit and easy to measure
  - Randomized controlled trial

- Objective response rate (ORR)
  - Direct measure of intervention
  - Can be assessed in a single-arm study

FDA Guidance, Clinical study Endpoints for the Approval of Cancer Drugs and Biologics (December 2018)

OS should be evaluated in randomized studies

- ECs can have reliability and interpretability challenges
- Apparent differences in outcome may arise from factors other than the investigational drug
- Randomized studies minimize the effect of known and unknown differences between populations

FDA Guidance, Clinical study Endpoints for the Approval of Cancer Drugs and Biologics (December 2018)

Characteristics strengthening level of support for effectiveness by an EC

- High unmet medical need with a well-defined natural history
- The EC population is very similar to treatment group
- Concomitant treatments that affect the primary endpoint are not substantially different
- Evidence of change in the established progression of disease (e.g., tumor shrinkage)

FDA guidance for industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products,* (2019) and *Rare Diseases: Common Issues in Drug Development* (2019)

Key Regulatory History

- Applicant considered a randomized controlled trial (RCT) infeasible and proposed an EC

- Consistent FDA advice:
  - Cautioned re: complexity of EC-controlled trials
  - Ability to interpret an EC-based OS comparison would largely depend on the comparability of the populations
  - Isolation of the treatment effect of ^{131}I-omburtamab from other CNS-direct therapies important
  - **Response rate data needed to establish effectiveness**

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Study 03-133 Pre-Omburtamab Treatment

Time	Recommended Treatment for CNS Relapse
Week -12	**Resection** when possible
Week -11	**Irinotecan**
Week -10	**Craniospinal irradiation**
Week -5	**Irinotecan and Temozolomide**
	Carboplatin if systemic disease present
	Stem cell rescue if necessary
Study start	**^{131}I-omburtamab** administration

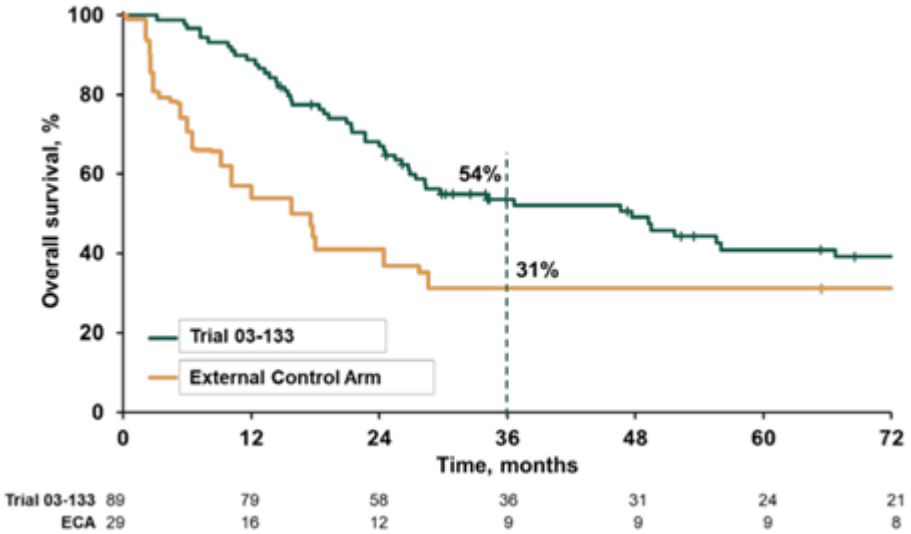
Proposed External Control

- Central German Childhood Cancer Registry (CGCCR)
  - Patients diagnosed between 1990 and 2015
  - 99% of children diagnosed with cancer in Germany enrolled in registry
  - Patients followed until 18 years old
- 85 patients identified who received at least one treatment for CNS relapse
  - Missing data regarding frequency and type of treatments

	Study 03-133	External Control
Number of Treatments	Surgery, radiation, chemo (recommended)	At least 2 (including radiation)
Enrollment	2004-2019	1990-2015

Applicant's Primary OS Analysis (Study 03-133)

(source: Applicant Briefing document)



ECA=external control arm

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

CI=confidence intervals

Key Issue: Clinically important differences between the study and control populations are likely to bias results in favor of the study arm

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Major Efficacy Review Issues

1. The External Control is not a relevant comparator due to clinically important differences between the populations

2. Comparisons of survival not reliable

3. Lack of supportive response rate data

1. The EC is not a relevant comparator due to clinically important differences in the populations

	Study 03-133	External Control
Concomitant therapy (e.g., radiation)	95% patients received CSI	No patient received CSI
Baseline Clinical Status	Well enough to travel and recover from intensive treatment	Unknown
Treatment era	2005-2018	1991-2020
Unknown	Example: Differences in clinical care between the United States and Germany.	

CSI= craniospinal irradiation

2. Comparisons of survival not reliable

- No statistical method can overcome uncertainty created with an EC that is not fit-for-purpose

- Multiple sensitivity analyses conducted:
  - OS differences between populations attenuated when adjusting for some sources of bias

➡ Apparent differences in survival cannot be attributed to ^{131}I-omburtamab

3. Lack of supportive response rate data

- Response data collected in Study 101

- Issues
  - Lack of confirmation of response
  - Baseline assessment of disease
  - Concerns for measurement error
  - Timing of response in relation to other CNS-directed therapy

Cannot conclude that ^{131}I-omburtamab contributed to any apparent difference in survival

- If the German registry data are not an appropriate comparator, the externally controlled trial cannot be adequate and well-controlled
- Variable results of statistical analyses highlight uncertainties regarding causal effect of ^{131}I-omburtamab
- Insufficient data to support mechanistic plausibility and objective response in CNS/LM disease

Outline

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Discussion Topic

Discuss whether data provided by the Applicant isolates the treatment effect of ^{131}I-omburtamab from the effects of multimodality therapy for CNS/LM relapse, or if additional data are needed.

Voting Question

The Applicant has provided a comparison of ^{131}I-omburtamab following multimodality treatment in single-arm Study 03-133 to an external control derived from a German registry.

Has the Applicant provided sufficient evidence to conclude that ^{131}I-omburtamab improves overall survival?


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ADMINISTRATION

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OMBLASTYS™ (^{131}I-Omburtamab) for neuroblastoma with central nervous system or leptomeningeal metastases

FDA Presentation
Oncologic Drugs Advisory Committee (ODAC) Meeting
October 28, 2022

Gautam U. Mehta, MD
Clinical Reviewer, Nervous System, Pediatrics and Rare Cancers
Division of Oncology 2, Office of Oncologic Diseases

FDA Review Team

Richard Pazdur, Director, Oncology Center of Excellence (OCE)	Donna Rivera, Associate Director of Pharmacoepidemiology, OCE
Paul Kluetz, Supervisory Deputy Director (Acting), Office of Oncologic Diseases	Catherine Lerro, Epidemiology Reviewer, OCE
Harpreet Singh, Director, Division of Oncology 2 (DO2)	Anthony Fotenos, Team Leader, Division of Imaging and Radiation Medicine
Martha Donoghue, Deputy Director, DO2	Donika Plyku, Reviewer, Division of Imaging and Radiation
Amy Barone, Cross Disciplinary Team Leader, DO2	Yuan-Li Shen, Deputy Division Director, Division of Biometrics V (DBV)
Gautam Mehta, Clinical Reviewer, DO2	Pallavi Mishra-Kalyani, Supervisory Mathematical Statistician, DBV
Marjilla Seddiq, Clinical Reviewer, DO2	Joyce Cheng, Statistics Team Leader, DBV
Jeanne Fourie Zirkelbach, Team Leader, Clinical Pharmacology	Somak Chatterjee, Statistics Reviewer, DBV
Catherine Bulik, Reviewer, Clinical Pharmacology	Yen-Chih Lin, Reviewer, Center for Devices and Radiologic Health
Christy John, Reviewer, Clinical Pharmacology	Dhanalakshmi Kasi, Reviewer, Chemistry Manufacturing and Controls

Applicant's Proposed Indication

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

Proposed dose: Two doses of 50 millicurie (mCi) administered 4 weeks apart as intracerebroventricular infusions

Proposed pathway: Traditional approval

Outline

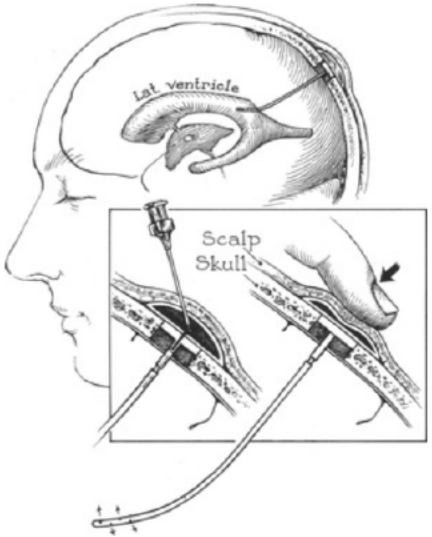
- Study 03-133 design and use of external control

- Major efficacy issues
  1. Differences in the trial and external control populations
  2. Reliability of comparisons of survival
  3. Lack of supportive response rate data

- Safety considerations

Limited Mechanistic Plausibility of Intraventricular Therapy for CNS Metastases

- "^{131}I-omburtamab will reach and target B7-H3-expressing tumor cells in the entire CSF compartment" (*Applicant's Briefing Document*)
- 70+% in each trial had CNS parenchymal metastases
  - Not in the "CSF compartment"
- CSF administration of drugs results in limited brain penetration*
- Lack of robust nonclinical or PET evidence to support mechanism of targeted parenchymal tumor uptake



Ratcheson RA, *et al.*, NEJM, 1968

CSF = cerebrospinal fluid
PET = positron emission tomography

*Blasberg RG, *et al.*, J Pharm Exp, 1975
Yan Q, *et al.*, Exp Neurol, 1994

Evidence of Effectiveness for Traditional Approval

Under certain circumstances…FDA can conclude that one adequate and well-controlled clinical investigation plus confirmatory evidence is sufficient to establish effectiveness.

- Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products *Guidance for Industry*

Primary Evidence of Efficacy: Study 03-133

Study	Study 03-133
Status	Completed (2004-2019)
Design	Single-center, single-arm trial
Primary Efficacy Endpoint	3-year Overall Survival (OS) rate
Tumor Responses	Not routinely assessed
Sample Size	94

Use of an External Control in the Current Application

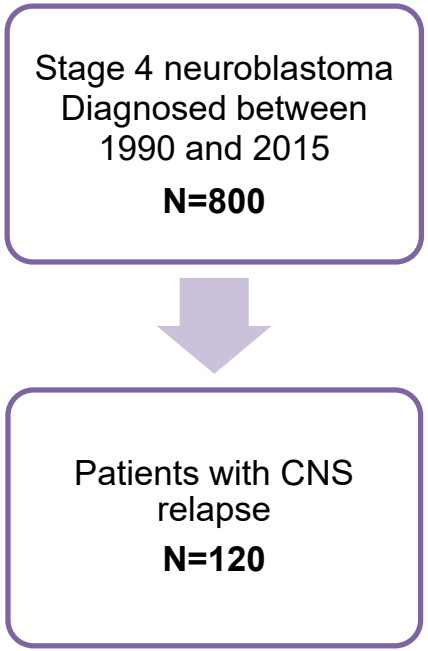
- Breakthrough therapy designation granted in May 2017 based on a comparison to literature

- External Control *could* provide context for single-arm trial with time-to-event primary endpoint
  - Lack of available therapy as control
  - High unmet need

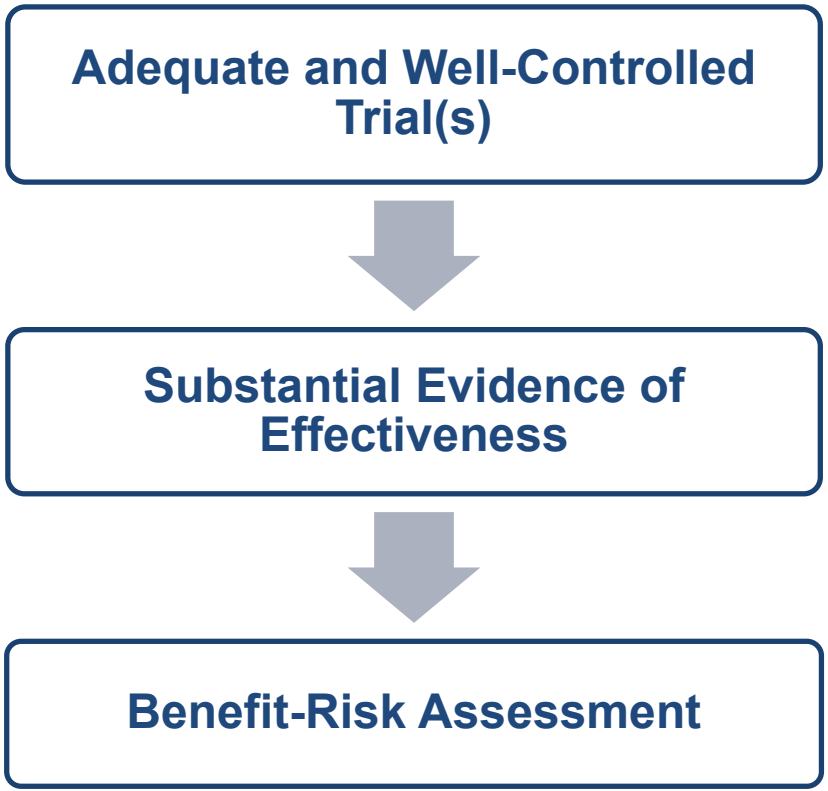
Central German Childhood Cancer Registry (CGCCR)

- Largest data source identified by Applicant documenting outcomes of children with neuroblastoma and CNS relapse

- ≥95% of children diagnosed with cancer in Germany enrolled in registry
  - Patients diagnosed between 1990 and 2015
  - Patients followed until 18 years old



Regulatory Framework for Approval



Major Efficacy Review Issues

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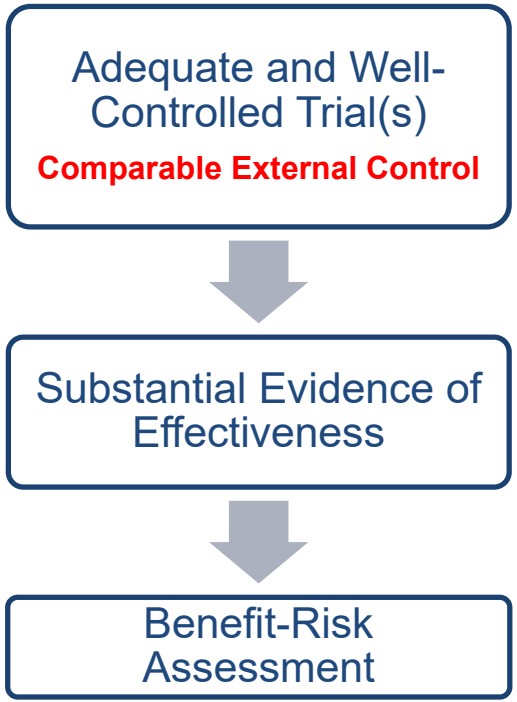
External Control Population Must Be Comparable



For Adequate and Well-Controlled Trials "the following types of control are recognized:

- *(v) Historical control.* The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, **in comparable patients or populations."**

– 21 CFR 314.126

FDA Efficacy Analyses

- FDA's analysis population includes patients treated at the proposed recommended dose and with no missing data (complete cases only)

- FDA consistently advised Applicant that multiple sensitivity analyses would be conducted during the review given uncertainties introduced by comparison to External Control

External Control Limited to Patients Receiving Post-CNS Relapse Therapy to Improve Comparability

Baseline Covariate	Study 03-133 (n=94*)	CGCCR (n=120)
Age at neuroblastoma diagnosis, mean ± SD (years)	3.0 ± 2.2	3.0 ± 2.6
MYCN Amplified	51 (54%)	52 (43%)
Time from neuroblastoma diagnosis to CNS relapse, mean (months)	19.8 ± 13.0	19.4 ± 18.2
Any post-CNS relapse chemotherapy, radiation therapy, or surgery	94 (100%)	79 (66%)
Primary analysis population: Patients who received post-CNS relapse radiation therapy and at least one other modality of treatment and complete case data	**77 (82%)**	**34 (28%)**

*Includes only patients who received the proposed recommended dose

Pre-^{131}I-Omburtamab Treatment for CNS Relapse

Time	Suggested Pre-treatment for Study 03-133
Week -12	**Resection** when possible
Week -11	**Irinotecan**
Week -10	**Craniospinal irradiation**
Week -5	**Irinotecan and Temozolomide**
	Carboplatin if systemic disease present
	Stem cell rescue if necessary
Study start	**^{131}I-omburtamab** administration

Imbalance in Timing and Type of Post-Relapse Radiation Therapy (RT)

Study 03-133 (n=77)	External Control (n=34)
Median time from relapse to first RT was 21 days (3, 266)	Median time from relapse to first RT was 69 days (3, 414)
95% of patients received craniospinal irradiation 18 or 21 Gray +/- boost	No patient received craniospinal irradiation No further details on type/dose of RT available

Imbalance in Frequency and Type of Post-Relapse Chemotherapy

Study 03-133 (n=77)	External Control (n=34)
99% received chemotherapy post-relapse, prior to omburtamab	88% received chemotherapy post-relapse
Most patients received temozolomide/irinotecan	Most patients received topotecan/etoposide No patients reported to have received temozolomide or irinotecan

Extent of Treatment Intensity Unknown in Study 03-133

- Post-^{131}I-omburtamab therapies not systematically recorded

- Likely a **large unmeasured imbalance** in overall treatment intensity received by Trial and External Control patients

Major Issue: External Control Not Fit for Purpose of Comparison

- Fundamental known differences:
  - No patient in external control received craniospinal irradiation
  - Differences in types of chemotherapy received

- Potential for additional unknown differences:
  - Trial patients likely to be healthier than intended use population
  - Additional treatment following ^{131}I-omburtamab not captured
  - Differences in clinical care in U.S. and Germany
  - Dose/type of CNS radiation not captured for external control

Major Efficacy Review Issues

1. The External Control is not a relevant comparator due to clinically important differences between the populations

2. Comparisons of survival not reliable due to bias and sample size

3. Lack of response data to verify anti-tumor activity

Statistical Approach to Survival Analyses

- Major sources of bias
  - Population selection
  - Differences in study time periods
  - Index date selection

- Approaches to mitigate affect of bias in analysis

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External Control Subgroups Receiving More Modalities of Post-CNS Relapse Therapy were More Similar to Trial

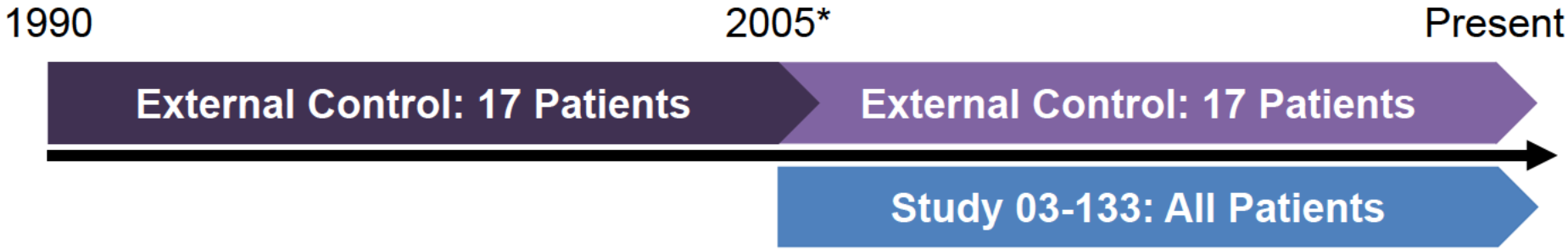
Group	Treatment Modalities	Study 03-133 (n=94)	External Control (n=120)
Group 1	Received at least one post-relapse therapy	84 (89%)	74 (62%)
Group 2	Received post-relapse radiation therapy and at least one other therapy (surgery or chemo)	77 (82%)	34 (28%)
Group 3	Received post-relapse radiation therapy, surgery, and chemotherapy	63 (67%)	21 (18%)

Greater Survival with More Modalities of Post-CNS Relapse Therapy

Group	Treatment Modalities	External Control N	External Control Median OS* (months)
Group 1	Received at least one post-relapse therapy	74	10.0 (95% CI: 6.9, 15.2)
Group 2	**Received post-relapse radiation therapy and at least one other therapy (surgery or chemo)**	**34**	**16.6 (95% CI: 9.8, 31.3)**
Group 3	Received post-relapse radiation therapy, surgery, and chemotherapy	21	29.8 (95% CI: 11.7, NE)

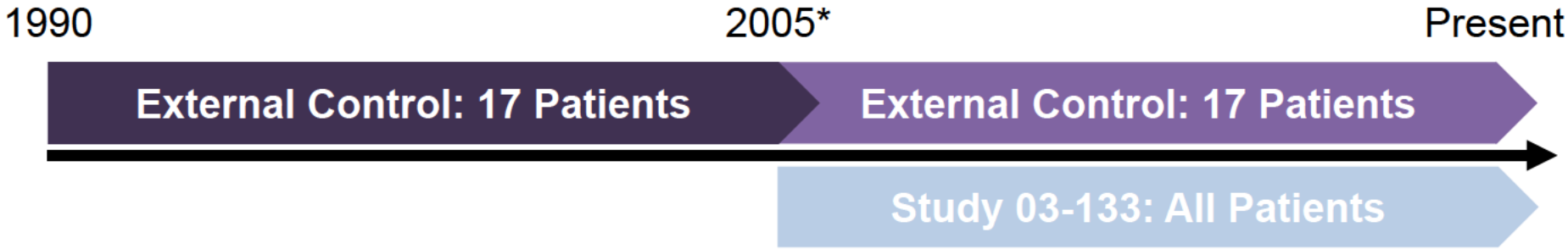
*Overall Survival (OS) defined as time from CNS relapse to death
CI = confidence interval, NE = not evaluable

Trial and External Control Populations Were Not Contemporaneous



*Based on first date of CNS relapse in Study 03-133 analysis population: September 21, 2005

External Control Patients in Contemporaneous Era May Be Better Matched to Study 03-133



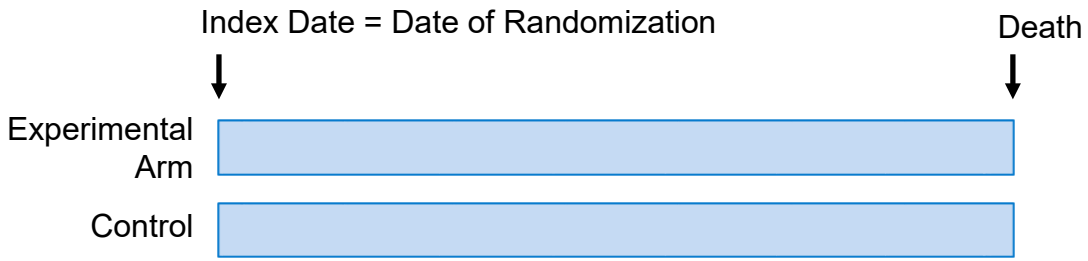
External Control Before Study 03-133
Median OS: 11.4 months
(95% CI: 6.8, 17.9)

External Control Contemporaneous Subgroup
Median OS: 31.3 months
(95% CI: 10.0, NE)

*Based on first date of CNS relapse in Study 03-133 analysis population: September 21, 2005

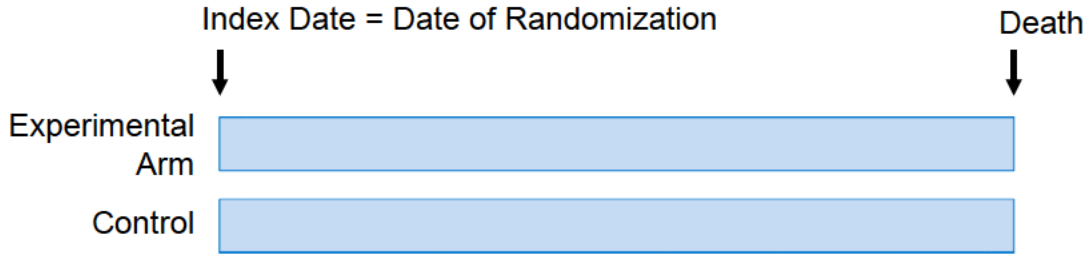
Choice of Index Date in a Randomized Trial

Randomized Trial:
measures survival from the date of randomization

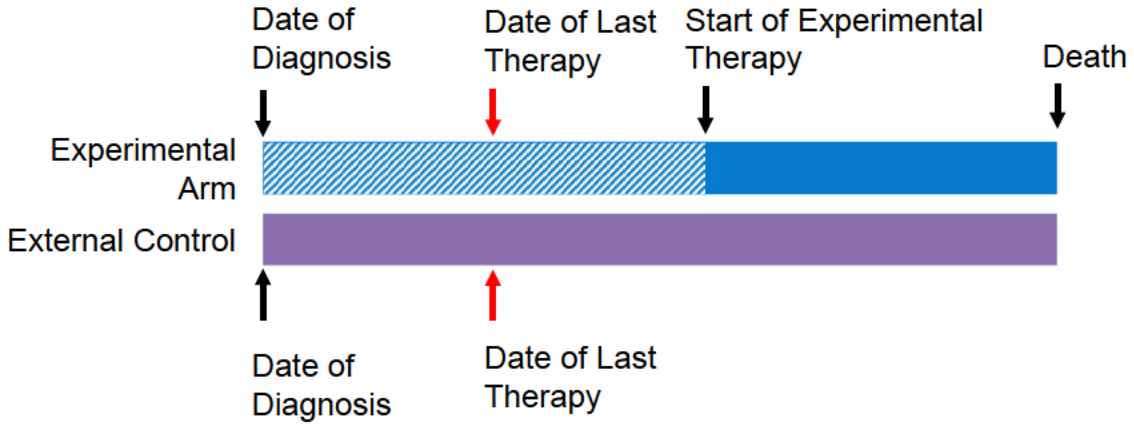


Choice of Index Date in an Externally-Controlled Trial

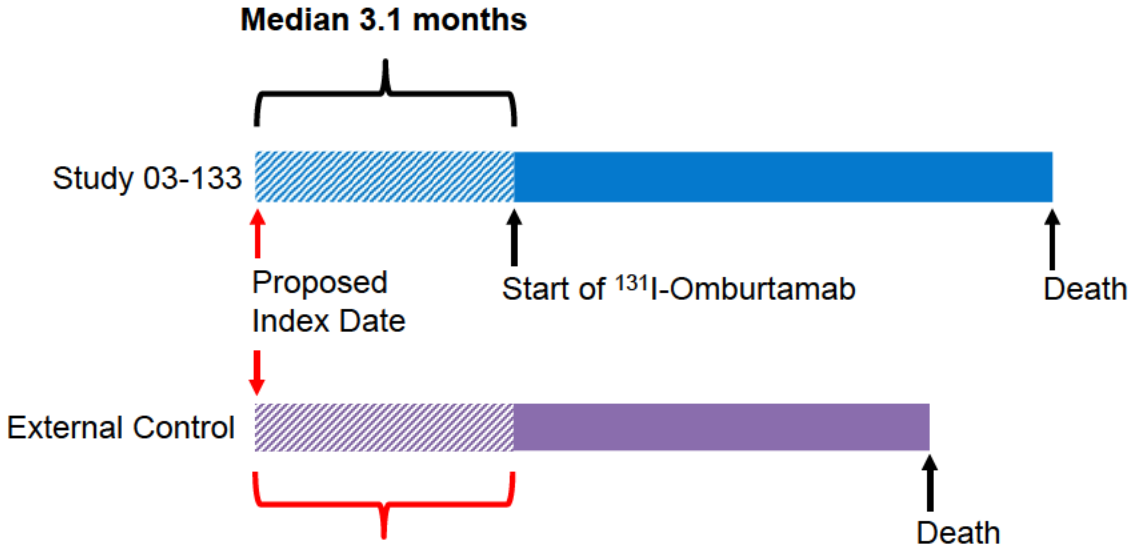
Randomized Trial:



Externally-Controlled Trial:
No optimal index date



Applicant's Proposed Index Date (A) Favors Longer Survival Time in Study 03-133



Concern: Unfair comparison results in bias in favor of ^{131}I-Omburtamab treatment group

Effects of Major Sources of Bias

- Population selection and confounding
  - External control patients with more treatments were more similar to Study 03-133 and survived longer
- Differences in study time periods
  - External control patients diagnosed in the era contemporaneous with Study 03-133 lived longer than patients diagnosed before Study 03-133 began
- Index date selection
  - Use of the Applicant's proposed index dates for survival analyses favors survival in Study 03-133

Statistical Approach to Survival Analyses

- Major sources of bias
  - Population selection
  - Differences in study time periods
  - Choice of index date

- Approaches to mitigate affect of bias in analysis

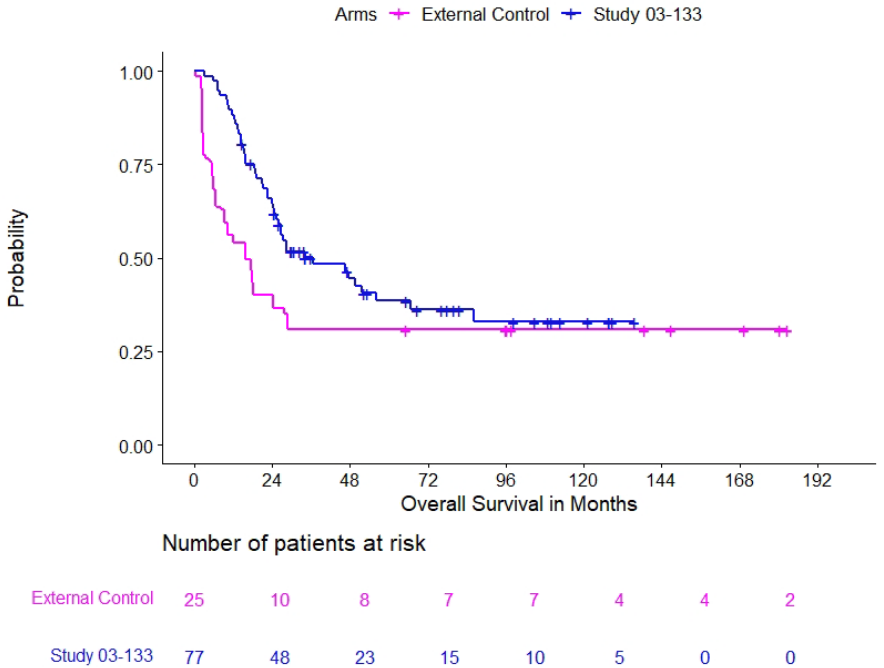
Approach to Control for Major Bias

- Population selection and confounding
  - Limit comparison to Modality Group 2: patients who received radiation therapy and at least one other therapy
  - Propensity score-based weighting
- Differences in study time periods
  - Limit comparison to contemporaneous patients
- Index date selection
  - Use start of ^{131}I-omburtamab treatment for index date in Study 03-133

Primary Analysis Adjusts for Only Some Aspects of Selection Bias

	Study 03-133 (N=77)	External Control (N=34)
Weighted sample size, N	77	24.8
Hazard ratio (95% CI)	**0.62 (0.32, 1.20)**	

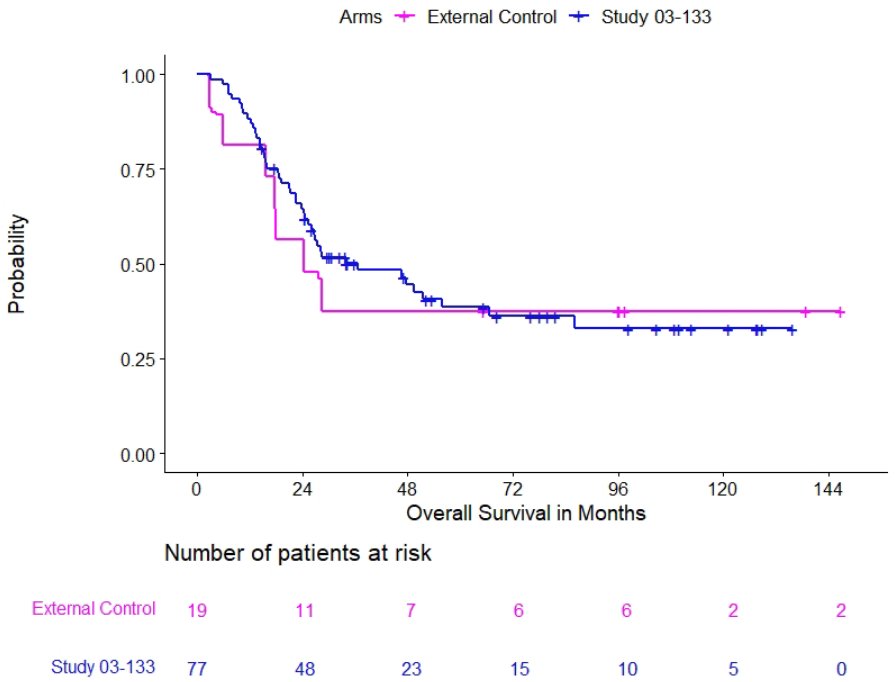
- **Limiting to patients with radiation therapy plus at least 1 other therapy helps make the populations more comparable**
- **However, we know there are other major prognostic differences across populations, including treatment era**



Restricting Analysis to Contemporaneous Subgroup Reduces Observed Differences in Survival

	Study 03-133 (N=77)	External Control (N=17)
Weighted sample size, N	77	19.3
Hazard ratio (95% CI)	**0.91 (0.41, 2.02)**	

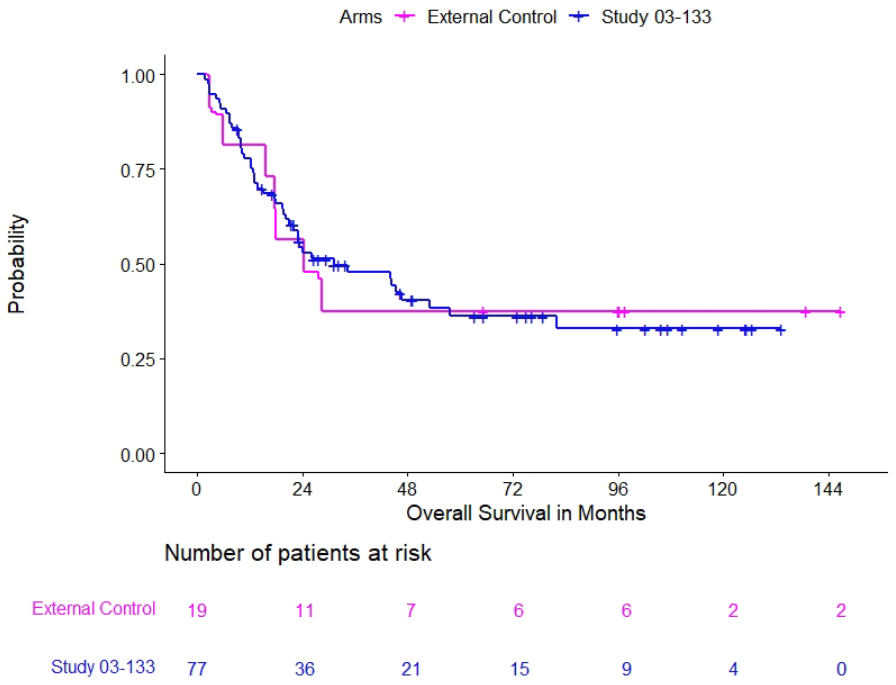
- When comparing patients with CNS relapse in the same era as those in Trial 03-133 (2005-present) the Kaplan-Meier curves of OS come closer together
- Sample size is now extremely small



Calculating OS Time from Start of ^{131}I-Omburtamab Demonstrates Impact of Index Date Selection*

	Study 03-133 (N=77)	External Control (N=17)
Weighted sample size, N	77	19.3
Hazard ratio (95% CI)	**1.02 (0.48, 2.16)**	

- **Sample size remains very small**
- **Trial patients are still more heavily treated than External Control patients**



*Calculation of OS for Study 03-133 from the start of ^{131}I-Omburtamab treatment, index date for control is unchanged

Major Issue: Survival Analyses Unable to Establish a Treatment Effect

- Survival analyses limited by several known sources of biases
- Adjusting analyses to create more similar populations results in small sample sizes and greater uncertainty, but diminishing differences in survival
- Cannot control for important unmeasured baseline prognostic factors (e.g., type of RT) and receipt of post-^{131}I-omburtamab treatment
- Variable results of statistical analyses highlight uncertainties regarding causal effect of ^{131}I-omburtamab

Major Efficacy Review Issues

1. The External Control is not a relevant comparator due to clinically important differences between the populations

2. Comparisons of survival not reliable due to bias and sample size

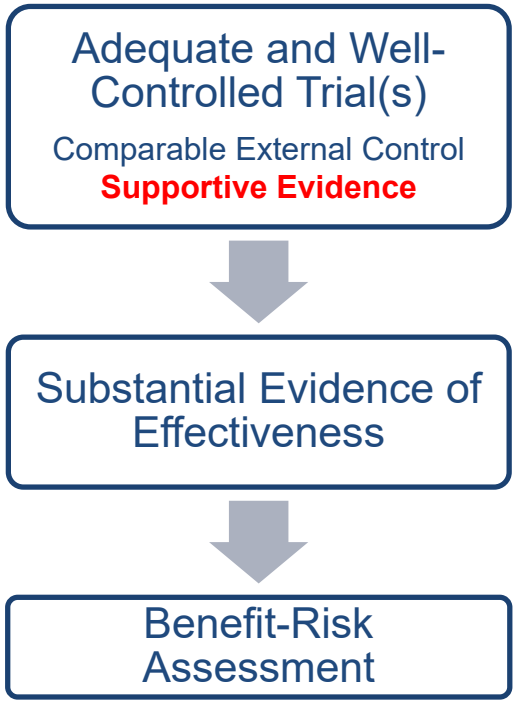
3. Lack of response data to verify anti-tumor activity

Tumor Response Data in Study 101 were Unable to Verify Anti-Tumor Activity

- Baseline Assessment
  1. Diagnosis of leptomeningeal disease
  2. Contribution of effect of ^{131}I-omburtamab

- Response Assessment
  1. Lack of confirmed responses
  2. Concerns for measurement error

Supportive Evidence Required for Traditional Approval



"Under certain circumstances…FDA can conclude that **one adequate and well-controlled clinical investigation <u>plus confirmatory evidence</u>** is sufficient to establish effectiveness."

- Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products *Guidance for Industry*

Study 101: Supportive Trial

Study	101
Status	Ongoing (2017-present)
Design	Multi-center, single-arm trial
Primary Efficacy Endpoint	3-year OS rate
Tumor Responses	5-, 10-, 26-week imaging Blinded independent central review RANO-BM and EANO-ESMO (LM) for response assessment
Sample Size	50

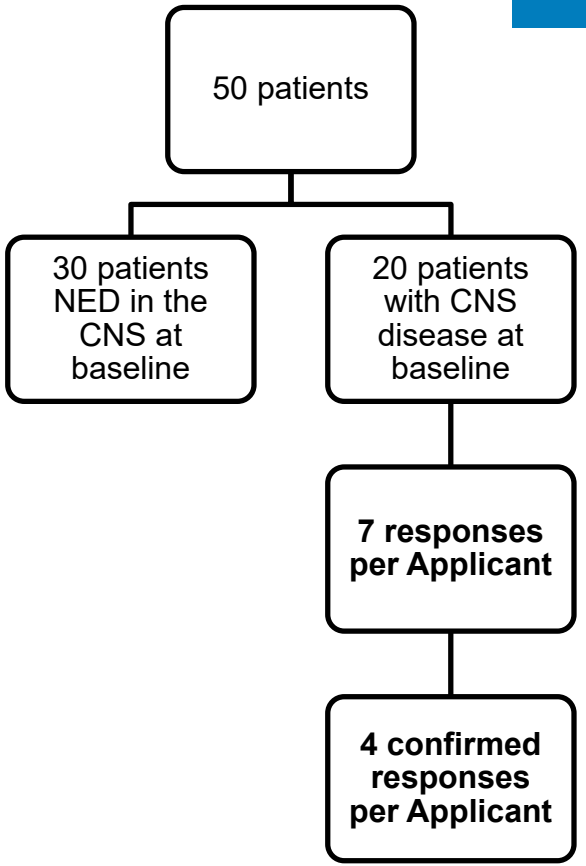
RANO-BM = Response Assessment in Neuro-Oncology Brain Metastases
EANO-ESMO = European Association of Neuro-Oncology-European Society for Medical Oncology

Protocol-Specified Pre-^{131}I-Omburtamab Treatment for CNS Relapse

Time	Protocol-Specified Pre-treatment for Trial 101
Week -12	**Resection** when possible
Week -11	**Irinotecan**
Week -10	**Craniospinal irradiation**
Week -5	**Irinotecan and Temozolomide**
	Carboplatin if systemic disease present
	Stem cell rescue if necessary
Study start	**^{131}I-omburtamab** administration

Study 101 Responses

- Patients were heavily pre-treated and <u>had minimal CNS disease at baseline</u>
  - 47 of 48 (98%) CSF cytology negative at baseline
  - 30 of 50 (60%) with no evidence of disease (NED) in CNS per blinded independent central review



Inadequate Diagnosis of Leptomeningeal Metastasis (LM)

- All patients with LM were CSF cytology negative at baseline
- Clinical sequelae not incorporated into assessment

- EANO-ESMO diagnostic criteria*
  - Positive cytology required for “confirmed” LM diagnosis
  - Clinical signs required for “probable” LM diagnosis
  - **Patients met criteria for “possible” LM diagnosis at baseline**

*Le Rhun E, *et al*., Ann Oncol, 2017

Uncertainty with Contribution of Effect

- Inadequate time from radiation therapy or chemotherapy to baseline scan in half of confirmed responders

Limited washout of prior therapies creates uncertainty regarding the contribution of effect of ^{131}I-omburtamab

Lack of Confirmation of Response

- Only 4 patients with reported **confirmed** responses
  - RANO-BM*: “For non-randomised trials in which CNS response is the primary endpoint, **confirmation of partial response or complete response at least 4 weeks later is necessary**”
  - Most received chemotherapy between initial response and confirmation

Lack of confirmation of response raises concerns for measurement error and lack of durability with treatment

*Lin NU, *et al*., Lancet Oncol, 2015

Concern for Measurement Error

- Disagreement between primary reviewers in all cases
  - All required adjudication
  - Second reviewer recorded no evidence of disease at baseline for most reported responders

Lack of agreement between reviewers raises concerns for measurement error

Major Issue: No Reliable Evidence of Anti-Tumor Activity

- Baseline Assessment
  1. Diagnosis of leptomeningeal disease
  2. Contribution of effect of ^{131}I-omburtamab

- Response Assessment
  1. Lack of confirmed responses
  2. Concerns for measurement error

No unequivocal tumor response in Study 101

Major Issue: No Reliable Evidence of Anti-Tumor Activity

Applicant's Briefing Document: "^{131}I-omburtamab will reach and target B7-H3-expressing tumor cells in the entire CSF compartment, including micro-metastatic CNS disease."

- Limited biologic plausibility of intraventricular therapy for CNS **parenchymal metastases:**
  - These lesions are not in the CSF compartment
  - Present in most patients in both studies

- Limited evidence of micro-metastatic disease in these studies
  - Only one patient had positive CSF cytology at baseline (developed progressive disease)

Key Safety Concerns

1. Risks from off-target radiation exposure

2. Risks associated with placement and use of Ommaya reservoir or shunt

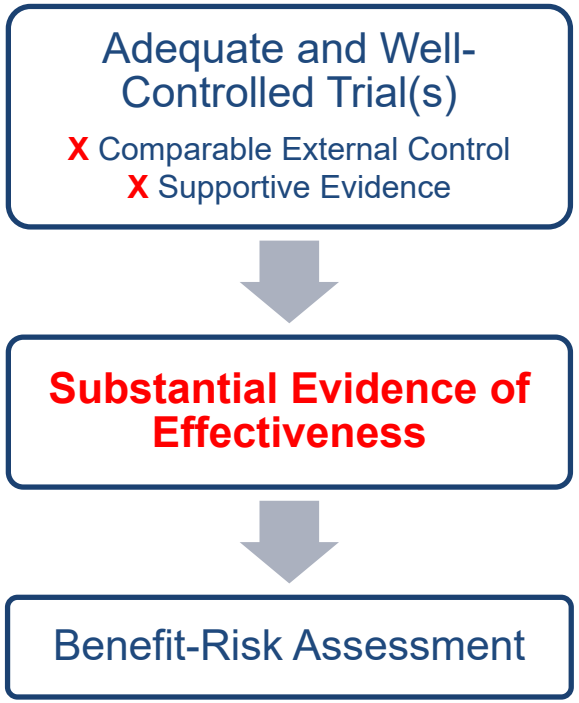
Key Safety Concerns

- Myelosuppression, chemical meningitis, infusion-related reactions, neurotoxicity, and late effects from radiation exposure

- 41-50% of patients experienced a serious adverse event
  - Myelosuppression
  - 1 fatal adverse reaction (intracranial hemorrhage)

- 19-28% did not receive second dose due to adverse reactions

FDA Concerns Regarding Evidence of Effectiveness



1. The External Control is not a relevant comparator due to clinically important differences between the populations

2. Comparisons of survival not reliable due to bias and sample size

3. Lack of response data to verify anti-tumor activity

Discussion Topic

Discuss whether data provided by the Applicant isolates the treatment effect of ^{131}I-omburtamab from the effects of multimodality therapy for CNS/LM relapse, or if additional data are needed.

Voting Question

The Applicant has provided a comparison of ^{131}I-omburtamab following multimodality treatment in single-arm Study 03-133 to an external control derived from a German registry.

Has the Applicant provided sufficient evidence to conclude that ^{131}I-omburtamab improves overall survival?

U.S. FOOD & DRUG ADMINISTRATION

BACKUP SLIDES SHOWN

Craniospinal Irradiation (CSI) for CNS Relapse

- Only retrospective analyses to date
- Suggests role for craniospinal irradiation in long-term survival
- Comparative analysis from MSKCC (Croog V.J. *et al.*):
  - "our findings suggest that targeting the entire neuraxis with CSI rather than delivering focal RT is an important component of management along with IO-RIT."
  - Outcomes by RT cohort:

Vital Status	CSI (n=16)	No CSI (n=13)
Alive, n (%)	13 (81%)	0
Alive, NED	10	0
Alive, non-CNS relapse	2	0
Alive, CNS relapse	1	0
Time CNS relapse to last contact/death (mos), median (range)	28.4 (1.5, 62.7)	8.8 (4.2, 23.9)

Croog, V. J., Kramer, K., *et al.* (2010). Whole neuraxis irradiation to address central nervous system relapse in high-risk neuroblastoma. *Int J of Rad Onc, Biol and Phys*, *78*(3), 849–854.

Reported Confirmed Responses

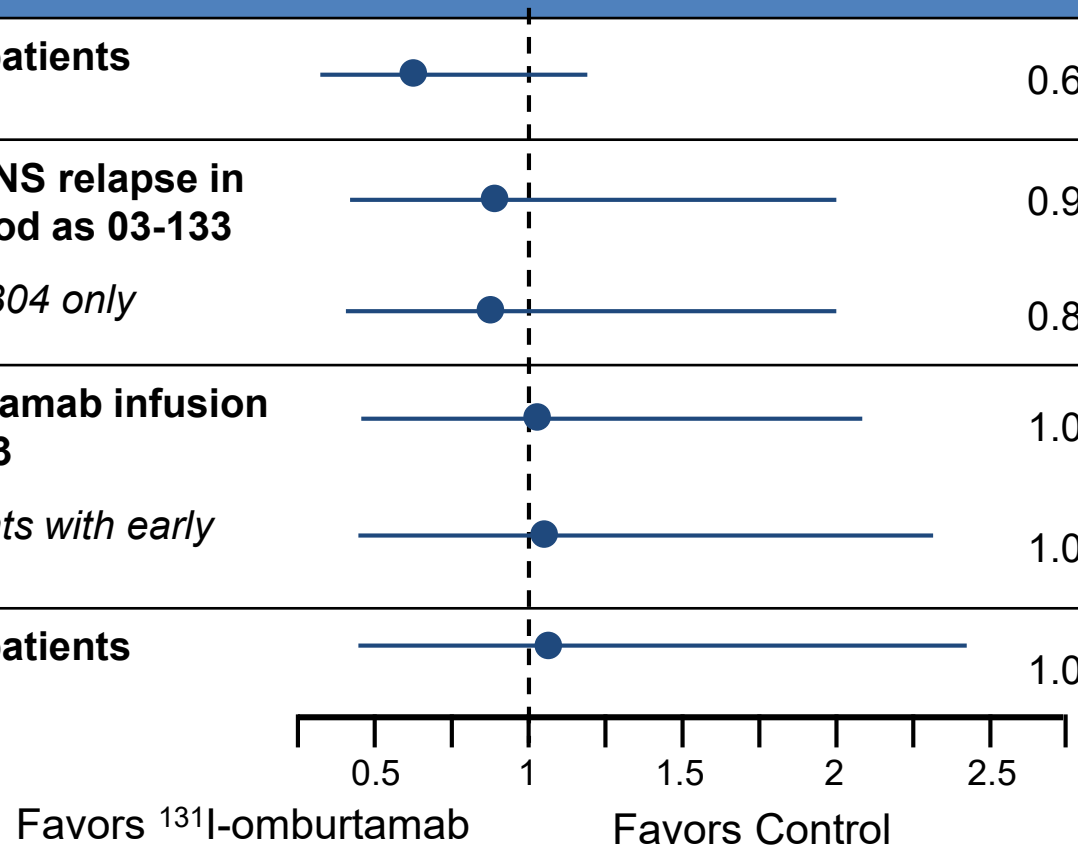
Reported Response	BIRC Reviewer	Scan				Factors Limiting Assessment
		Baseline	5 weeks	10 weeks	26 weeks	
1	1	LM	SD	SD	SD	• CSF cytology negative • Received TMZ between 10 and 26 week scans
	2*	LM	SD	CR	CR	
2	1	LM + parenchymal	PR	PR	PR	• CSF cytology negative • 30-day washout period from radiation therapy to baseline MRI
	2*	LM	CR	CR	CR	
3	1*	LM + parenchymal	SD	PR	CR	• 19-day washout period from chemotherapy and 29-day washout from radiation therapy to baseline MRI • ^{131}I-omburtamab given 60 days after baseline MRI^ • Received TMZ, IRN, and DTX between first response and “confirmation” scan
	2	NED	NED	PD	PD	
4	1*	Parenchymal	SD	CR	CR	• No target lesions at baseline • Received naxitamab + GM-CSF between first response and “confirmation” scan
	2	NED	NED	NED	NED	

*denotes adjudicated response selected by reviewer 3

DTX= dinutuximab, IRN=irinotecan, LM=leptomeningeal, NED=no evidence of disease, CR=complete response, PR=partial response, SD=stable disease, PD= progressive disease, BICR=blinded independent central review, TMZ=temozolomide

Analyses Adjusting for Multiple Sources of Bias Concurrently Improves Ability to Evaluate the Causal Effect of ^{131}I-Omburtamab

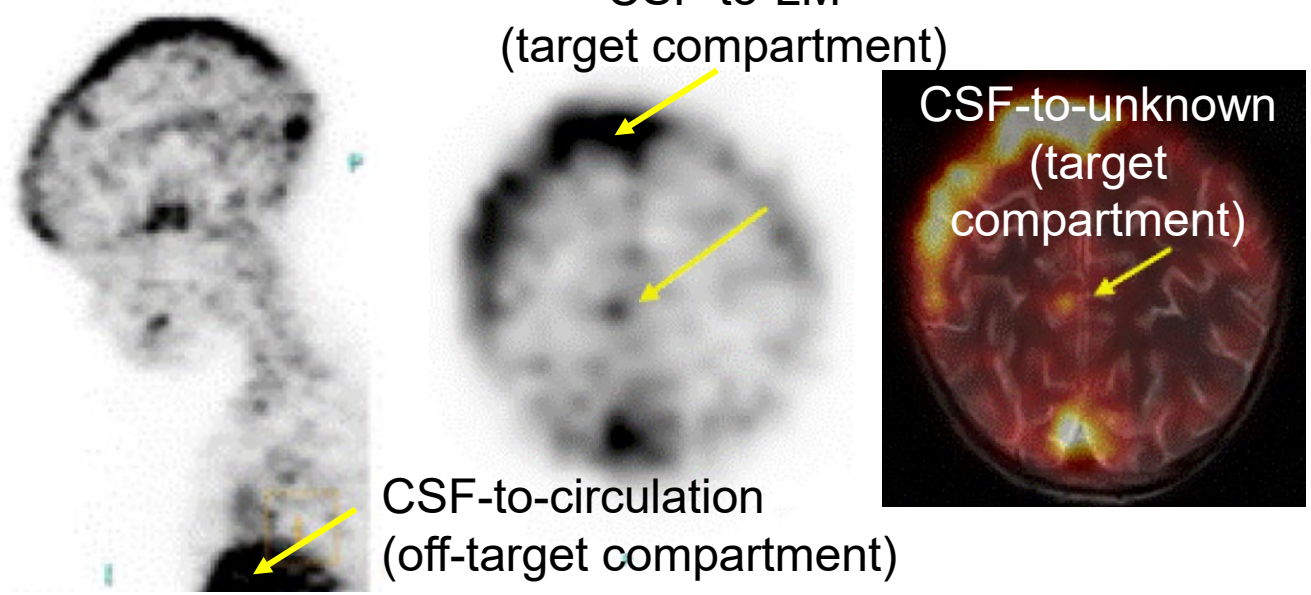
	Description	OS Hazard Ratio (95% CI)	N 03-133/ECA
Applicant's proposed Primary analysis	**Modality Group 2 patients**	0.62 (0.32, 1.20)	77/34
Removing Differences in Treatment Era	**EC patients with CNS relapse in the same time period as 03-133**	0.91 (0.41, 2.02)	77/17
	EC patients from NB04 only	0.89 (0.39, 2.02)	77/19
Sensitivity Analyses for Immortal Time Bias	**Start of ^{131}I-omburtamab infusion (index D) for 03-133**	1.02 (0.48, 2.16)	77/17
	*Excluding EC patients with early deaths**	1.03 (0.45, 2.35)	77/15
Improving Similarity by Prior Treatment	**Modality Group 3 patients**	1.05 (0.45, 2.45)	63/12



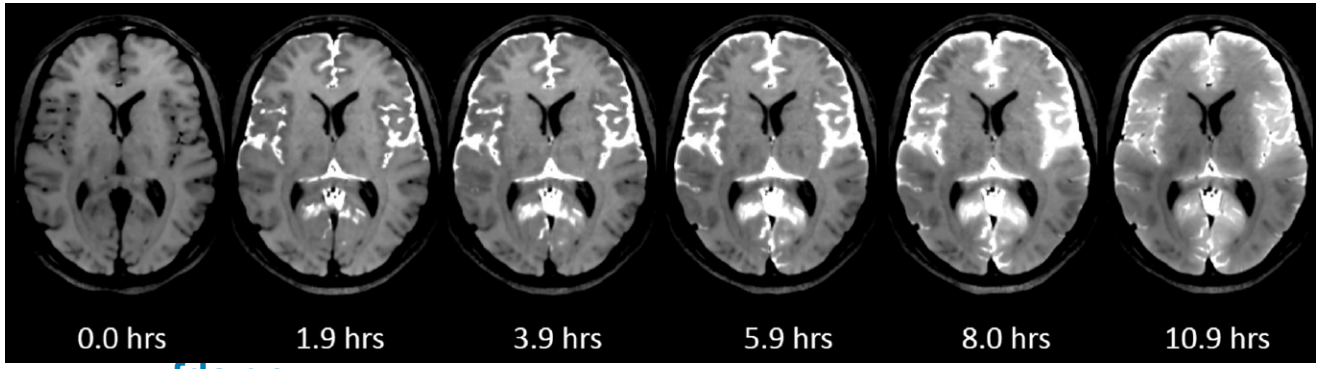
*Deaths in the median time period between Index A and start of Start of ^{131}I-omburtamab therapy in Study 03-133 (3.1 months)

Delivery to LM vs CNS target compartments

Study 03-133: ^{124}I-omburtamab PET



Small molecule contrast on MRI after intrathecal admin



- No therapeutic radioactive drug or biologic has been approved for ventricular administration
- Except for single unknown lesion example, no imaging or radiation dosimetry data from LM and CNS compartments has been submitted for review
- Among CNS lesions from 42 patients with ^{124}I-omburtamab PET co-investigation under Study 03-133, the number with visible uptake remains unknown
- Internal radiation delivery to the LM compartment is likely higher and more consistent than radiation delivery to the CNS compartment
- Additional investigation of ^{124}I-omburtamab for selection of CNS patients may be needed to determine whether patients with no CNS uptake benefit

Source: sponsor submission 10/21/2022 (top); Dyke JP *et al.* Clinical Imaging 68 (2020) 1–6 (bottom)