Eflornithine (DFMO) for patients with high-risk neuroblastoma who have completed multiagent, multimodality therapy

Oncologic Drugs Advisory Committee (ODAC) Meeting

FDA Introductory Comments
October 4, 2023

Diana Bradford, MD
Cross Disciplinary Team Leader
Division of Oncology 2
Office of Oncologic Diseases

APPLICANT'S PROPOSED INDICATION

To reduce the risk of relapse in pediatric patients with high-risk neuroblastoma who have completed multiagent, multimodality therapy

Proposed dosage: DFMO oral tablets taken twice daily for two years

- One tablet = 192 mg eflornithine free base = 250 mg eflornithine HCl monohydrate salt
- BSA-based dosing:

Body Surface Area (m^2)	Recommended Dosage
>1.5	768 mg (Four tablets) orally twice a day
0.75 to 1.5	576 mg (Three tablets) orally twice a day
0.5 to < 0.75	384 mg (Two tablets) orally twice a day
0.25 to < 0.5	192 mg (One tablet) orally twice a day

Basis for the Application

Externally Controlled Trial	
Investigational Arm, DFMO	**External Control Arm, no DFMO**
Study 3(b): Single-arm trial of DFMO for patients with high-risk neuroblastoma (HRNB) after up-front therapy including immunotherapy Primary endpoint: event free survival (**EFS) at 2 years** compared to ANBL0032 historical control rate (70%)	Study ANBL0032: Randomized, open-label trial of cis-RA vs. cis-RA + immunotherapy (dinutuximab + GM-CSF + IL-2) for patients with newly diagnosed HRNB Patients in immunotherapy arm form **external control (EC) arm** in NDA

Study Design to Establish Effectiveness: Single Externally Controlled Trial

"In an **externally controlled trial**, outcomes in participants receiving the test treatment according to a protocol are compared to outcomes in a group of people external to the trial who had not received the same treatment."[1]

"The treatment and control arm populations **should be as similar as possible**"[1]

"Tests of statistical significance carried out in such studies are less reliable than in randomized trials."[2]

[1]FDA Draft Guidance: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products, 2023.
[2]ICH Harmonized Guideline: Choice of Control Group and Related Issues in Clinical Trials E10. 2000.

Time-to-event endpoints should be evaluated in randomized studies

- Externally controlled trials (ECTs) 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)

Outline

- Background: Neuroblastoma and DFMO
- Study 3(b) and ANBL0032
- Regulatory framework for approval and use of external controls
- Discussion topic and voting question for ODAC

Neuroblastoma

- **Rare pediatric disease**
  - 700-800 patients/year in U.S.[1]
  - 8-10% of childhood cancers, 15% of childhood cancer deaths [2]
  - Median age 17 months at diagnosis[3]

- **Malignant solid tumor of neural crest cells**
  - 50% “high risk” based on age, stage, *MYCN* status, histology[4]

[1] ASCO 2023; [2] Park, 2010; [3]NCI PDQ Neuroblastoma; [4] Monclair, 2009

High Risk Neuroblastoma: Up-Front Therapy

Induction
Chemotherapy
Surgical resection
Consolidation
Autologous stem cell transplant (ASCT)
Radiation
Immunotherapy
13-cis-retinoic acid (isotretinoin/cis-RA)
Anti-GD2 antibody (e.g., dinutuximab)

- **Goal of Up-Front therapy:**
  No evidence of disease/no active disease
- **SOC after up-front therapy:**
  Observation & routine imaging
- **Risk of relapse:**
  ~50% of patients are refractory to treatment or experience relapse
- **Prognosis poor at relapse:**
  5-year OS <10%[1]

[1]Moreno, 2020

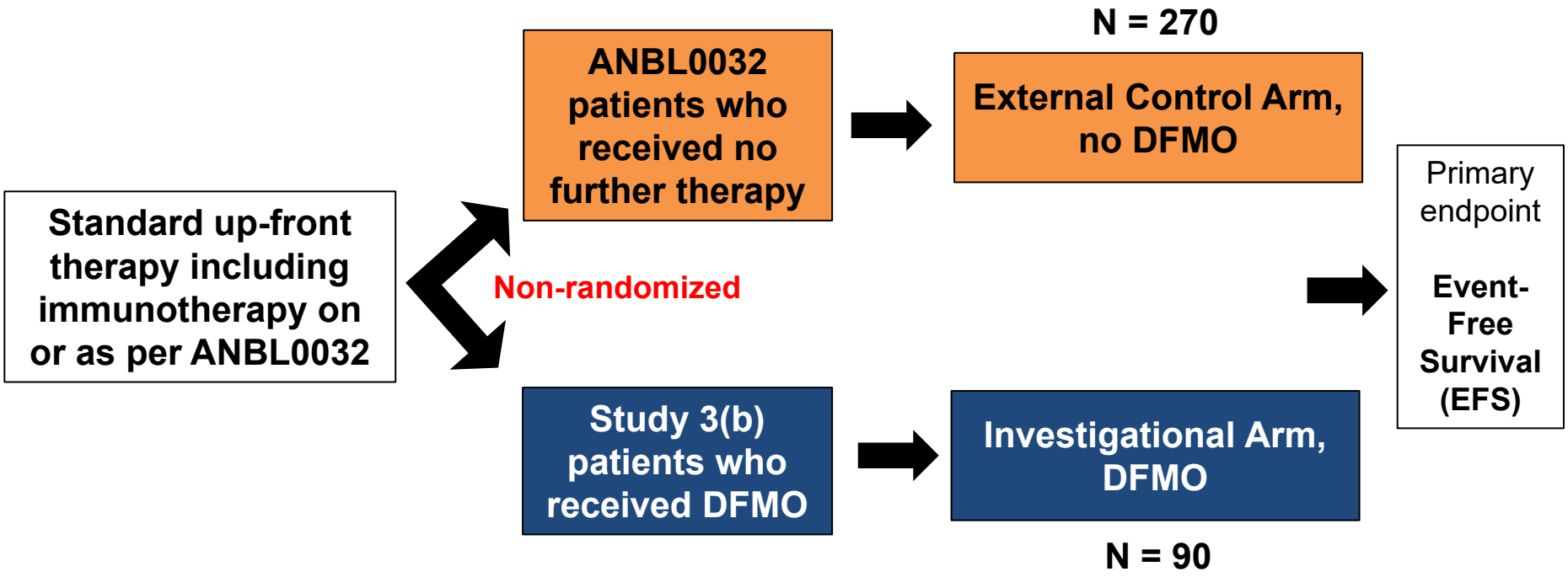
DFMO

- Oral ornithine decarboxylase (ODC) inhibitor
  - Rate-limiting enzyme in polyamine biosynthesis
  - *ODC* gene upstream of *MYCN*
- Cytostatic mechanism of action

Regulatory History

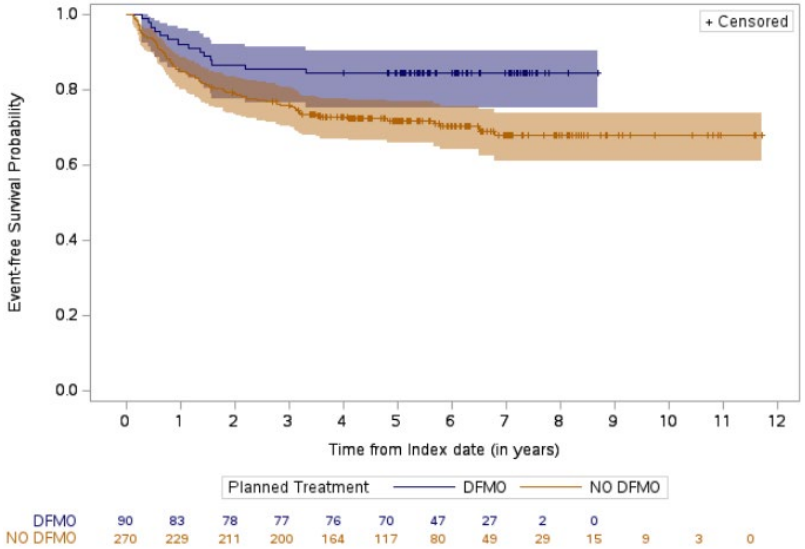
Date	Event
6/1/2012	**Study 3b** initiated (investigator sponsor)
11/18/2015	End of Phase 2 meeting (investigator sponsor) discussing preliminary results of Study 3b. FDA stated that a **randomized, controlled trial would be required** to assess the effect of DFMO in this setting.
12/19/2018	Preliminary Breakthrough Therapy Designation (BTD) discussion of EFS results from Study 3b vs. historical control rate from Children's Oncology Group (COG) Study ANBL0032; **FDA recommended sponsor provide patient-level data from ANBL0032**
4/3/2020	BTD granted based on **propensity score matched external control data from ANBL0032**
10/25/2021	Type B pre-NDA meeting; **FDA stated proposed comparison to ANBL0032 appeared acceptable but determination of substantial evidence of effectiveness would be based on overall assessment of results**
11/21/2022	505(b)(2) NDA Submission

ECT: Single-Arm Study 3(b) vs. Clinical Trial Data from ANBL0032



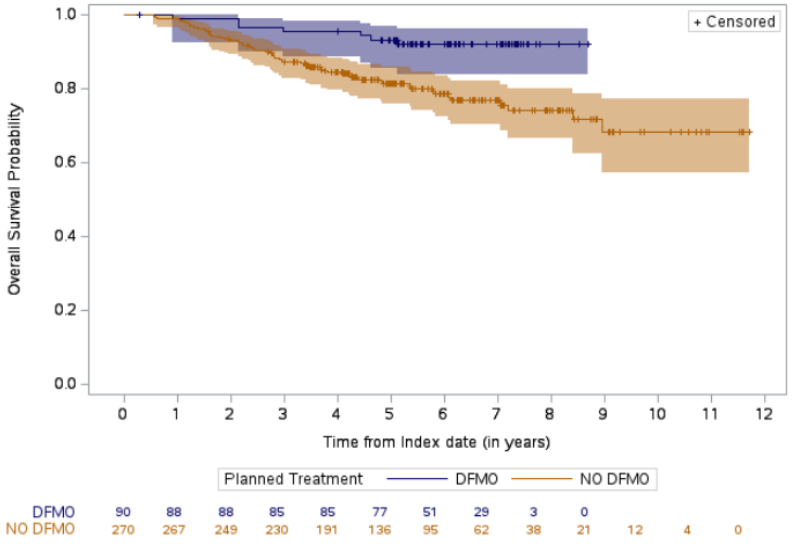
Applicant's Proposed Primary Analysis

Event-free Survival



EFS Hazard Ratio: 0.48 (0.27, 0.85)

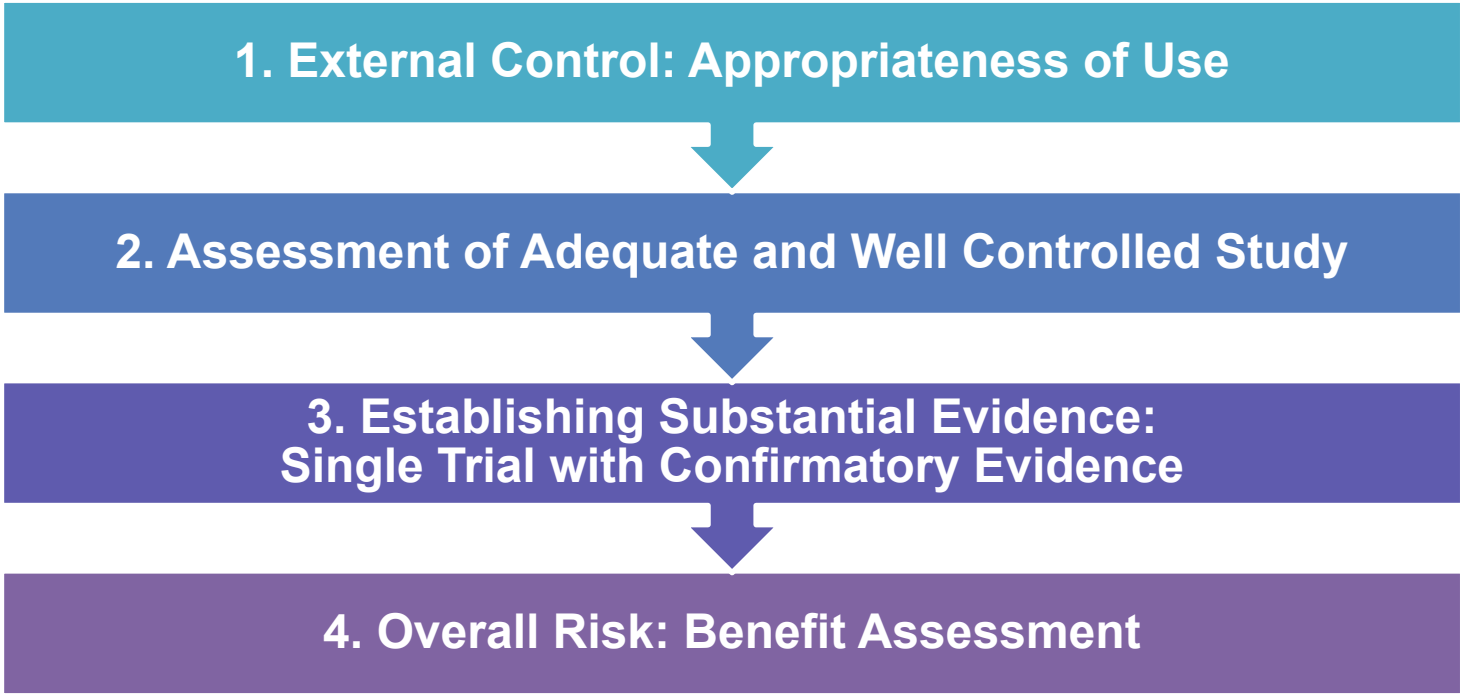
Overall Survival

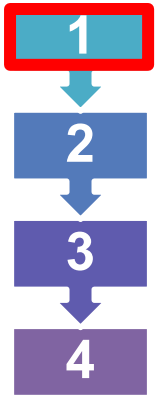


OS Hazard Ratio: 0.32 (0.15, 0.70)

FDA performed multiple sensitivity analyses to address potential sources of bias and characterize the treatment effect estimate

FDA Approach



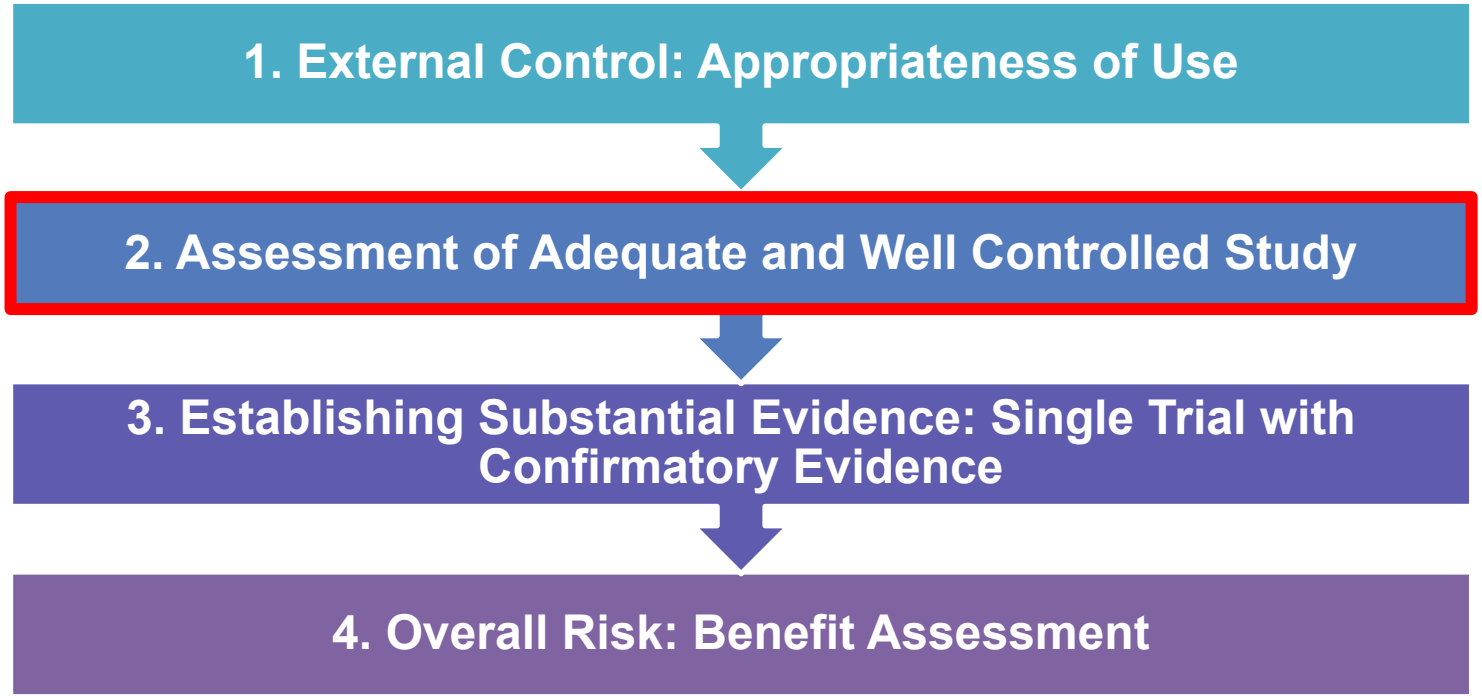


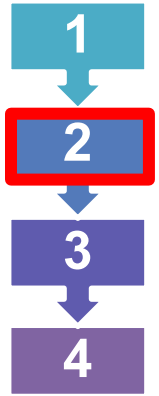
"Strong support for effectiveness can emerge from ECTs," especially when:

- Well-defined natural history
- External control population is very similar to treatment group
- Concomitant treatments that affect the primary endpoint are not substantially different
- Estimated treatment effect is large

FDA guidance for industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products,* (2019)

FDA Approach





Evidence of Effectiveness for Approval

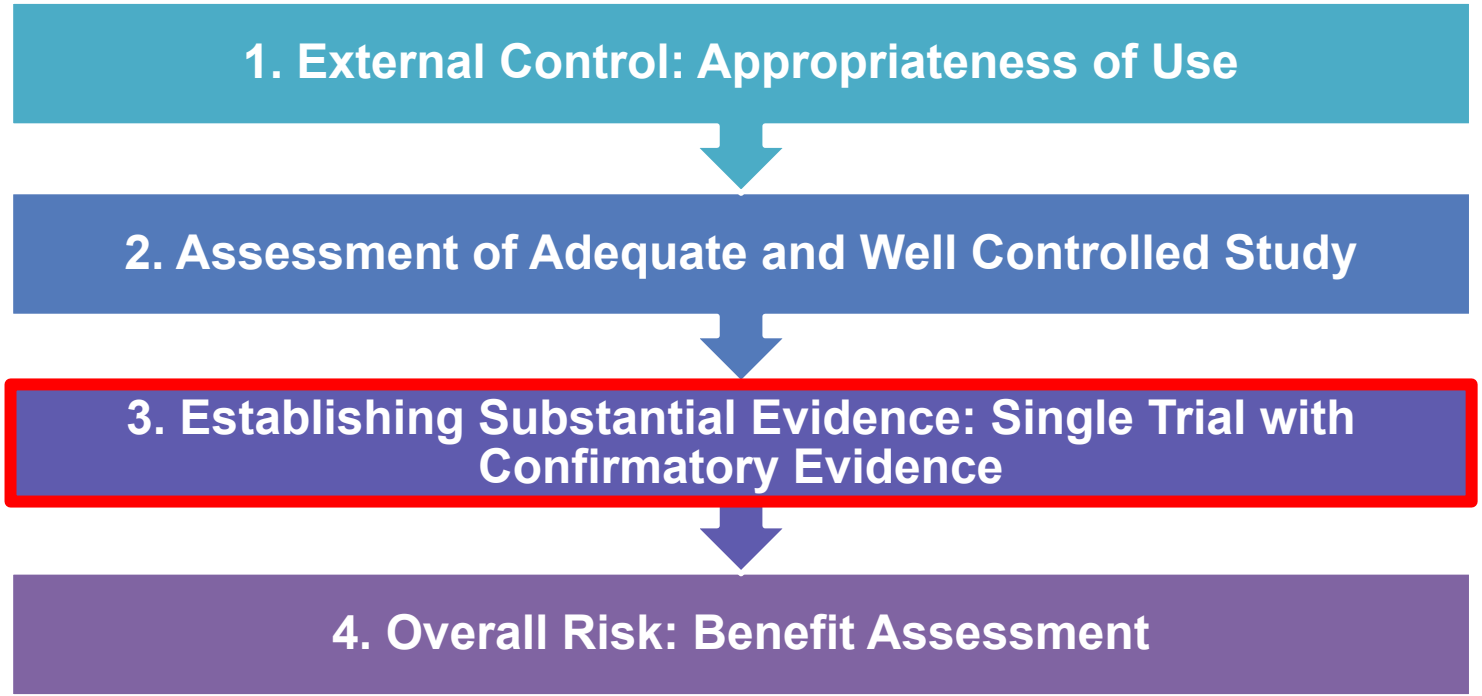
21 CFR 314.126 A drug or biologic must demonstrate substantial evidence of effectiveness through **adequate and well controlled studies**

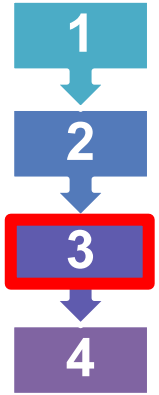
Features of adequate and well controlled studies:

- Clear statement of objectives and methods of analysis
- Design permits a **valid comparison with a control**
- Adequate measures to minimize bias in subject assignment to treatment group
- **Adequate measures to minimize bias** on the part of subjects, observers, and analysts of the data
- Well-defined and **reliable methods to assess response**
- **Adequate analysis** of the results of the study to assess the effect of the drug

- Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products *Guidance for Industry,* 2019;
- 21 CFR 314.126

FDA Approach





Evidence of Effectiveness for Approval

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

Acceptability depends on:

- Persuasiveness of single adequate and well-controlled trial
- Robustness of confirmatory evidence
- Seriousness of disease and unmet medical need
- Ethics and practicability of conducting additional trials

- Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products *Guidance for Industry,* 2019

Potential Confirmatory Evidence

- Existing AWC investigation demonstrating effectiveness of drug in a closely related indication
- Data providing strong mechanistic support (e.g., PD marker, animal model, etc.)
- Data from a relevant animal model
- Additional data from natural history source
- Scientific knowledge of effectiveness of other drugs in the same pharmacological class
- Real world data/ evidence source
- Data from expanded access use

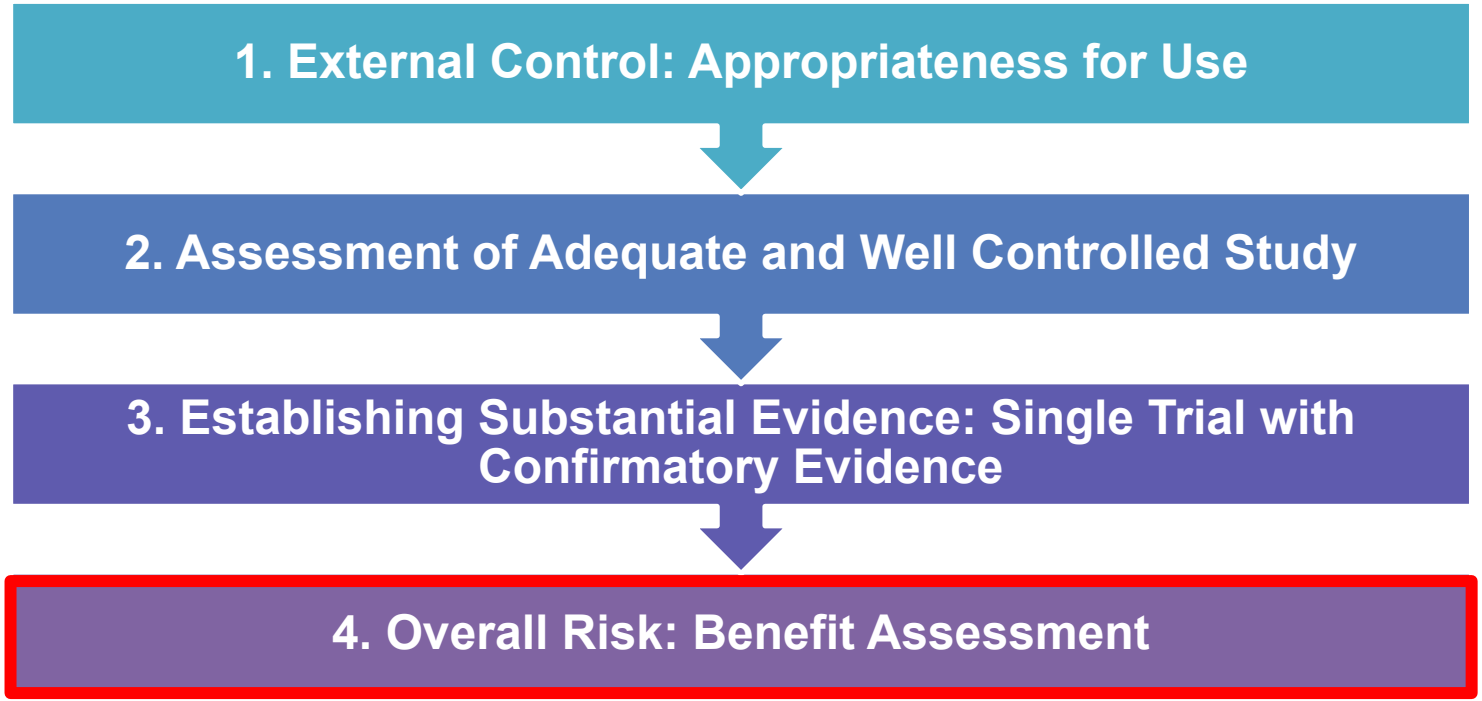
Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence, *Draft Guidance for Industry,* September 2023

Potential Confirmatory Evidence Considered by FDA

- Nonclinical data
  - Applicant-submitted data
  - Independent literature search
- Preliminary clinical data
  - NMTRC002 – DFMO + oral etoposide in R/R HRNB
  - Study 3(b) Stratum 2 – DFMO in R/R NB with no active disease
  - Expanded access experience

HRNB = High-Risk Neuroblastoma; R/R = Relapsed/Refractory

FDA Approach



Discussion Topics

1. Discuss the strengths and limitations of the externally controlled trial results to support the use of DFMO in pediatric patients with high-risk neuroblastoma.

2. Discuss the strengths and limitations of the additional nonclinical and clinical data to support the use of DFMO in pediatric patients with high-risk neuroblastoma.

Voting Question

Has the Applicant provided sufficient evidence to conclude that DFMO improves event-free survival in patients with high-risk neuroblastoma?

Eflornithine (DFMO) for patients with high-risk neuroblastoma who have completed multiagent, multimodality therapy

FDA Presentation
Oncologic Drugs Advisory Committee (ODAC) Meeting
October 4, 2023

Elizabeth Duke, MD
Clinical Reviewer,
Division of Oncology 2,
Office of Oncologic Diseases

Arup Sinha, PhD
Statistics Reviewer,
Division of Biometrics V,
Office of Biostatistics

Emily Wearne, PhD
Nonclinical Reviewer,
Division of Hematology Oncology Toxicology

FDA Review Team

Richard Pazdur, Director, Oncology Center of Excellence (OCE)	Shenghui Tang, Director, Department of Biometrics V (DBV)
Paul Kluetz, Deputy Director, OCE	Pallavi Mishra-Kalyani, Deputy Director, DBV
Martha Donoghue, Associate Director for Pediatric Oncology and Rare Cancers, OCE	Arup Sinha, Statistics Reviewer, DBV
Harpreet Singh, Director, Division of Oncology 2 (DO2)	John Leighton, Director, Division of Hematology Oncology Toxicology (DHOT)
Nicole Drezner, Deputy Director, DO2	Claudia Miller, Nonclinical Team Leader, DHOT
Diana Bradford, Cross Disciplinary Team Leader, DO2	Emily Wearne, Nonclinical Reviewer, DHOT
Elizabeth Duke, Clinical Reviewer, DO2	Hong Zhao, Clinical Pharmacology Team Leader, DO2
Donna Rivera, Associate Director for Pharmacoepidemiology, OCE	Hairat Sabit, Clinical Pharmacology Reviewer, DO2
Catherine Lerro, Epidemiology Reviewer, OCE	Ashley Lane, Regulatory Project Manager, DO2

Applicant's Proposed Indication

To reduce the risk of relapse in pediatric patients with high-risk neuroblastoma who have completed multiagent, multimodality therapy.

Proposed Dosage: DFMO oral tablets taken twice daily for two years

- One tablet = 192 mg eflornithine free base = 250 mg eflornithine HCl salt
- BSA-based dosing:

Body Surface Area (m^2)	Recommended Dosage
>1.5	768 mg (Four tablets) orally twice a day
0.75 to 1.5	576 mg (Three tablets) orally twice a day
0.5 to < 0.75	384 mg (Two tablets) orally twice a day
0.25 to < 0.5	192 mg (One tablet) orally twice a day

Outline

- Study 3(b) and Use of External Control

- Efficacy Considerations
  - **Comparability**: Externally controlled trial populations
  - **Results**: Magnitude of effect and potential sources of bias
  - **Additional Data**: Nonclinical and Clinical

- Safety Considerations

High-Risk Neuroblastoma (HRNB)

- **Rare pediatric solid tumor**
  - 700-800 patients/year in U.S.[1]
  - 8% of childhood cancers, 15% of childhood cancer deaths[2]
  - Median age at diagnosis: 17 months[3]
  - 50% "high risk" based on age, stage, *MYCN* status, histology[4]

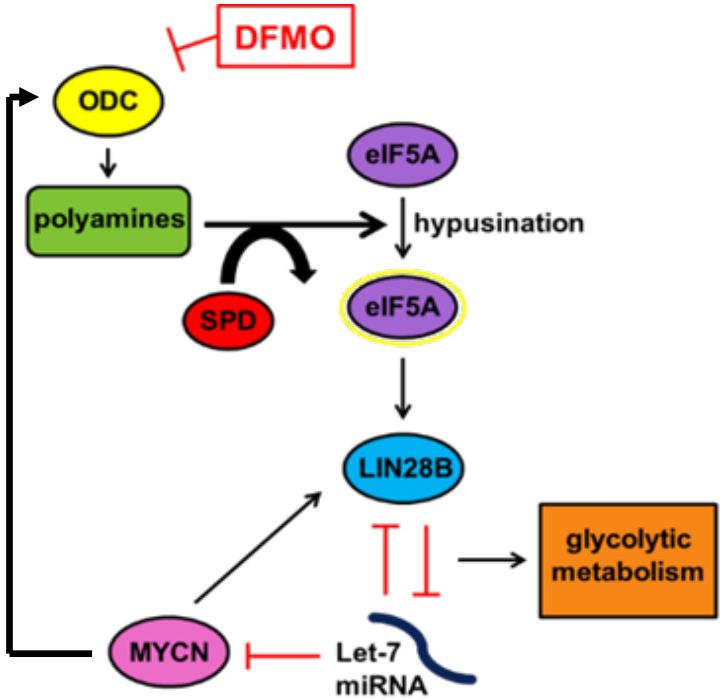
- **Risk of relapse after up-front therapy with poor prognosis at relapse**
  - ~50% are refractory to treatment or experience relapse
  - 5-year OS <10% after relapse[5]

Standard of Care Up-Front Therapy for HRNB
Induction
Chemotherapy
Surgical resection
Consolidation
Autologous stem cell transplant (ASCT)
Radiation
Immunotherapy
13-cis-retinoic acid (isotretinoin/cis-RA)
Anti-GD2 antibody (e.g., dinutuximab)

[1]ASCO 2023; [2]Park, 2010; [3]NCI PDQ Neuroblastoma; [4]Monclair, 2009; [5]Moreno, 2020

DFMO: Cytostatic Mechanism of Action

- **Oral ornithine decarboxylase (ODC) inhibitor**
  - Rate-limiting enzyme in polyamine biosynthesis
  - Inhibition of ODC restores the balance of LIN28/Let-7 metabolic pathway
  - *ODC* gene upstream of *MYCN*
- **Cytostatic MOA** = suppresses tumor-initiating cells, thereby preventing or delaying tumor formation



Adapted/modified from figure in 1) NDA 215500, Summary of Clinical Pharmacology, page 62; and 2) Lozier et al. Oncotarget. 2014; 6(1):196-206.

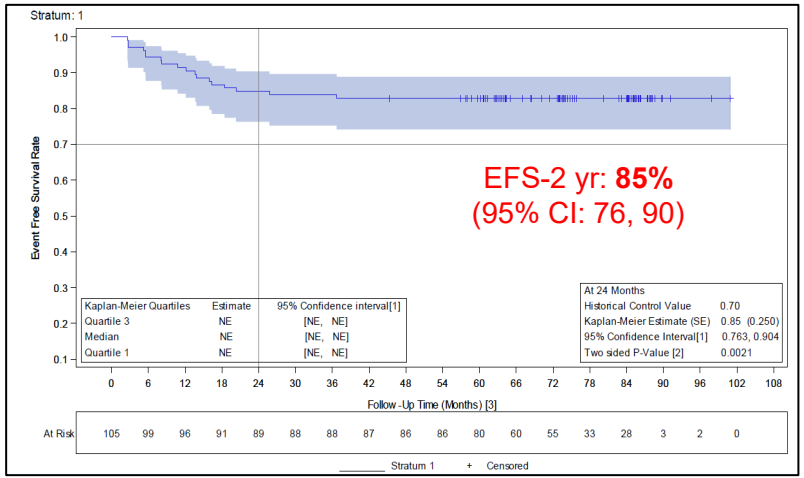
Primary Evidence of Efficacy

	Externally Controlled Trial	
	Investigational Arm, DFMO	**External Control Arm, no DFMO**
Original clinical trial contributing patients	**Study 3(b)**	**ANBL0032**
Study design	Single-arm trial of DFMO in HRNB after up-front therapy including immunotherapy	Randomized trial of standard up-front therapy +/- immunotherapy in newly diagnosed HRNB
Patients enrolled	105	1440
Primary endpoint	2-year EFS	EFS
Enrollment period	2012 - 2016	2001 - 2015

HRNB = high-risk neuroblastoma; EFS = event-free survival

Data Informing Development of Externally Controlled Trial (ECT)

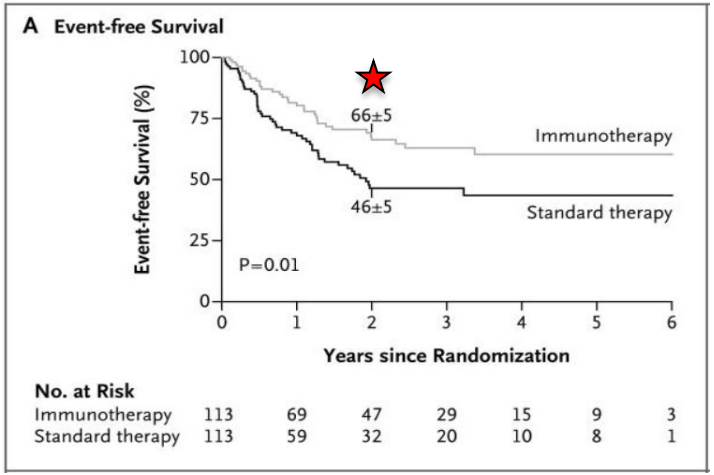
Investigational Arm



Applicant's Summary of Clinical Efficacy, page 39

Study 3(b): patients form investigational arm in this application

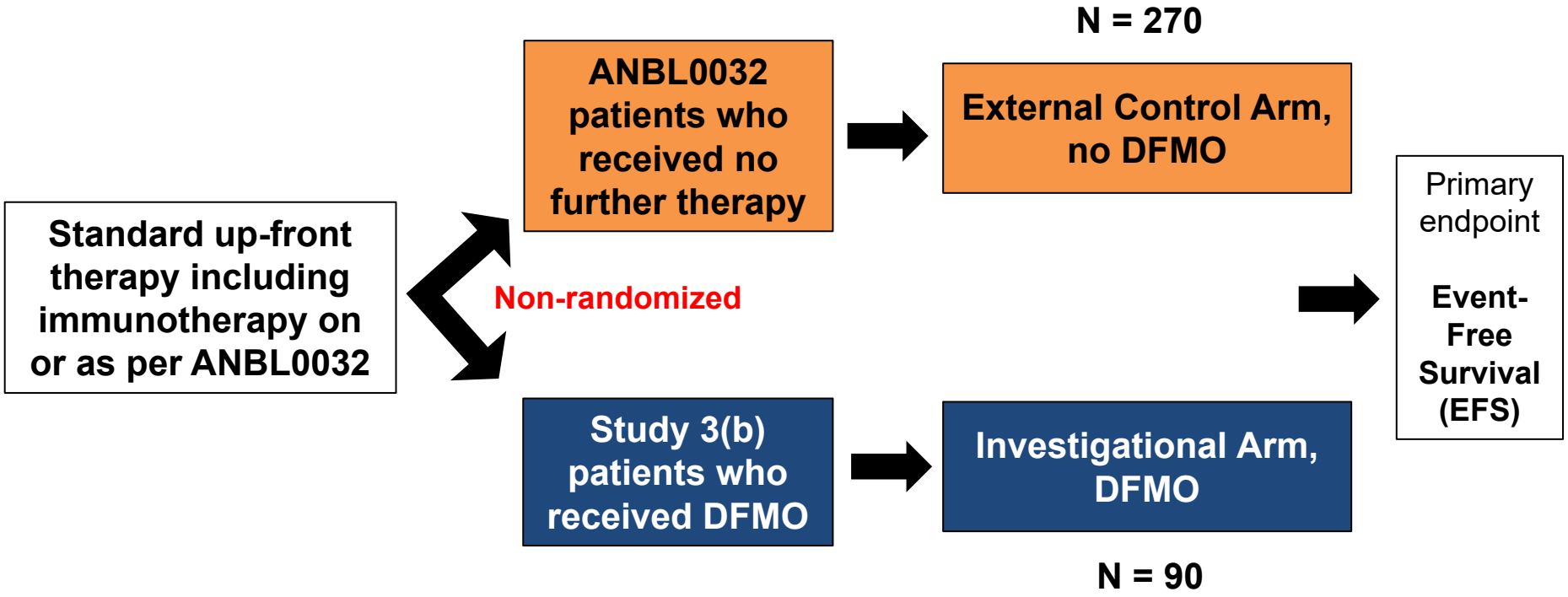
External Control Arm



Yu et al, *NEJM,* 2010

ANBL0032: patients in immunotherapy arm form external control arm in this application

ECT: Single-Arm Study 3(b) vs. Clinical Trial Data from ANBL0032



Time-to-event endpoints should be evaluated in randomized studies

- Externally controlled trials (ECTs) 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)

Appropriateness of Proposed ECT

STRENGTHS:

- Natural history established by prior clinical trials
- EC data source is clinical trial data, verified by FDA inspections
- Both arms treated on same up-front trial, no subsequent anti-cancer therapy
- Comparable definitions and ascertainment of endpoints

LIMITATIONS:

- Study 3(b) and ANBL0032 results known prior to ECT design
- Differing enrollment time periods
- Uncertainty in treatment effect estimate due to ECT design
- Retrospective analyses may not include all covariates which could be potential confounders (e.g., bias)

Outline

- Study 3(b) and Use of External Control

- Efficacy Considerations
  - **Comparability**: Externally controlled trial populations
  - **Results**: Magnitude of effect and potential sources of bias
  - **Additional Data**: Nonclinical and Clinical

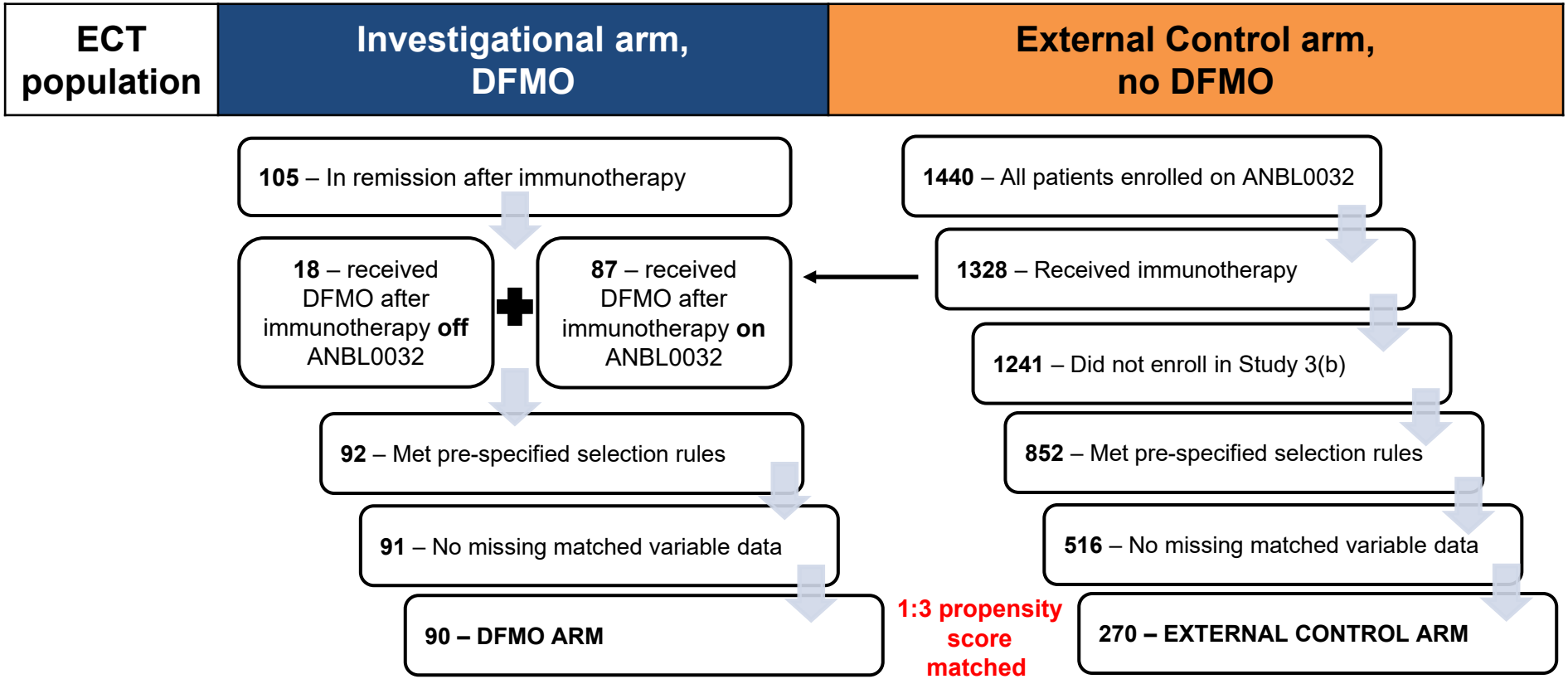
- Safety Considerations

Similarities Between Investigational & External Control Arms

Eligibility	• 0 - 21 years of age • Histologic verification of HRNB • At least PR prior to transplant • In remission at end of immunotherapy • > 30 days and < 120 days from up-front therapy • Lansky score ≥ 60%, adequate organ function
Tumor Assessments	• Baseline: MRI or CT scan; MIBG and/or FDG-PET, bone marrow aspiration + biopsy • Required*: 3, 6, 9, 12, 18, 24 months after end of immunotherapy (then per institutional standard)
Endpoints	• Primary: EFS** • Secondary: OS

*Imaging required; bone marrow biopsy and aspirate performed if treating physician concerned for progression
**Per each study protocol, endpoints were EFS at 2 years for Study 3(b) and EFS for ANBL0032
EFS = event-free survival; HRNB = high-risk neuroblastoma; MIBG = metaiodobenzylguanidine; OS = overall survival

Matched Population Selection

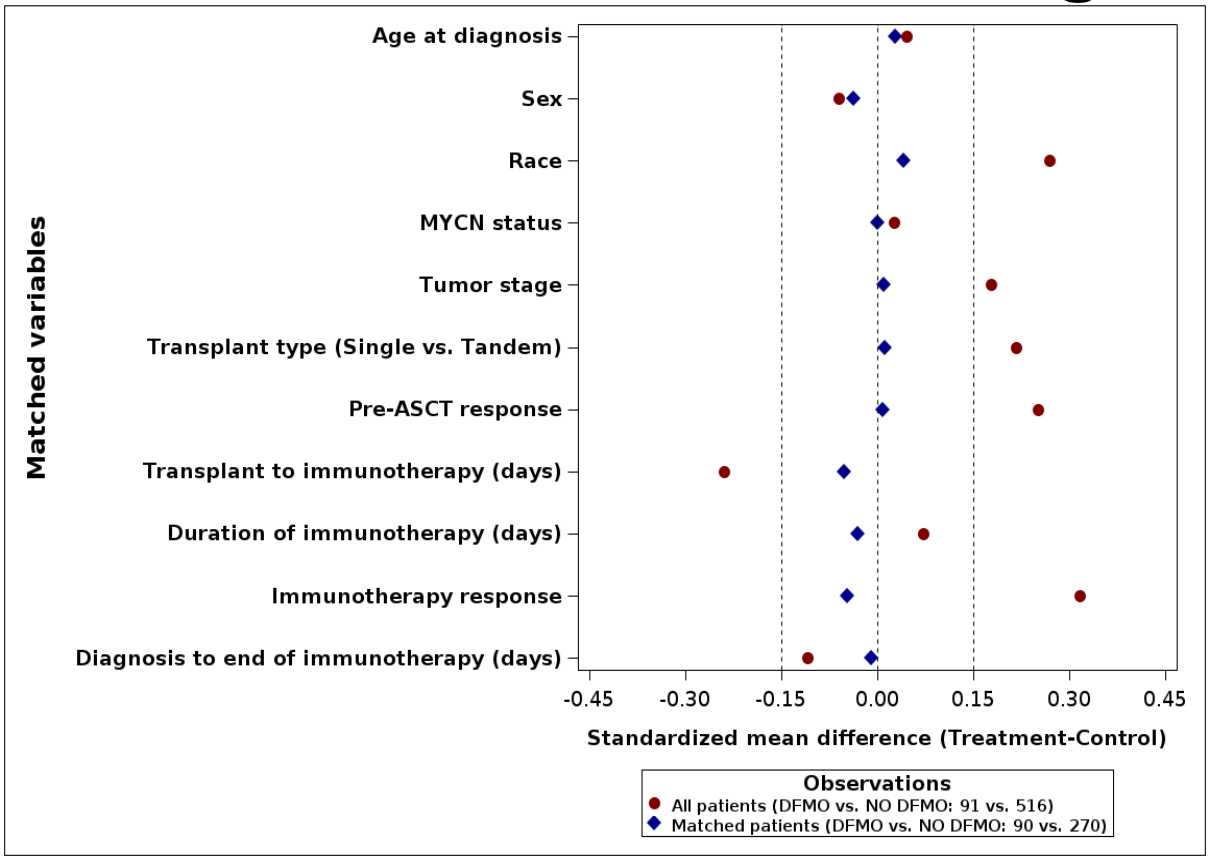


11 Matched Clinical Characteristics

		DFMO (N=90)	External Control (N=270)
Age at diagnosis (years), median (range)		2.9 (0.1 – 15.8)	3.1 (0.2 – 20.1)
Sex, %	Male	60	58
	Female	40	42
***MYCN* status (exact match)**, %	Amplified	44	44
	Not amplified	56	56
Stage at diagnosis, %	4	87	86
	Other (1, 2, 3, 4S)	13	14
End of immunotherapy overall response, %	CR	86	87
	VGPR or PR	14	13
Duration of immunotherapy in days, median (range)		185 (108, 328)	185 (34, 259)

Other matched characteristics: race, pre-transplant response, single vs. tandem transplant, days from transplant to start of immunotherapy, days from diagnosis to end of immunotherapy

Comparison of Matched Characteristics Before and After Matching



Non-Matched Clinical Characteristics

		DFMO (N=90), %	External Control (N=270), %
Geographic site of enrollment on ANBL0032[a]	US	99	86
	Outside US[b]	1	14
Cycles of immunotherapy	< 6 cycles	3	< 1
	6 cycles	97	99
Histology	Favorable	7	5
	Unfavorable	83	85
	Missing	10	10
Tumor Cytogenetics	Chromosomal aberration (1p, 11q, 17q)	29	-
	ALK mutation	3	-
	Missing	68	100
Primary Tumor Location[c]	Adrenal	56	28
	Non-adrenal	43	28
	Missing	4	51

[a] All Study 3(b) sites were in the United States (US); [b] Canada, Australia, or New Zealand;
[c] Patients may have multiple primary tumor locations

Non-Matched Clinical Characteristics

Dates of End of Immunotherapy	06/03/2005 – 01/28/2016	External Control (N = 270)
	03/22/2012 – 01/25/2016	DFMO (N = 90)

Patient Demographics:

- Ethnicity
- Social determinants of health (e.g., socioeconomic status)

Treatment-Related Characteristics:

- Days from diagnosis to transplant
- Surgery during induction
- Radiation during consolidation
- Transplant regimen
- End of immunotherapy bone marrow response
- Performance status at end of immunotherapy
- End of immunotherapy date

Comparability of ECT Populations

STRENGTHS:

- Similar eligibility and tumor assessment criteria per protocol
- Patients matched on 11 relevant clinical characteristics
- No additional treatment after up-front therapy
- Comparable index dates (end of immunotherapy)
- Study 3(b) sites were also ANBL0032 sites

LIMITATIONS:

- Unknown factors in decision to enroll vs. not enroll on Study 3(b)
- Unmeasured variables may result in confounding
- Non-contemporaneous index dates
- Imaging protocol-specified for 2 years post-immunotherapy & limited after 5 years
- Patients treated on ANBL0032 outside U.S. (14% of matched control arm)

Comparability of ECT Populations

STRENGTHS:

- Similar eligibility and tumor assessment criteria per protocol
- Patients matched on 11 relevant clinical characteristics
- No additional treatment after up-front therapy
- Comparable index dates (end of immunotherapy)
- Study 3(b) sites were also ANBL0032 sites

LIMITATIONS:

- Unknown factors in decision to enroll vs. not enroll on Study 3(b)
- Unmeasured variables may result in confounding
- Non-contemporaneous index dates
- Imaging protocol-specified for 2 years post-immunotherapy & limited after 5 years
- Patients treated on ANBL0032 outside U.S. (14% of matched control arm)

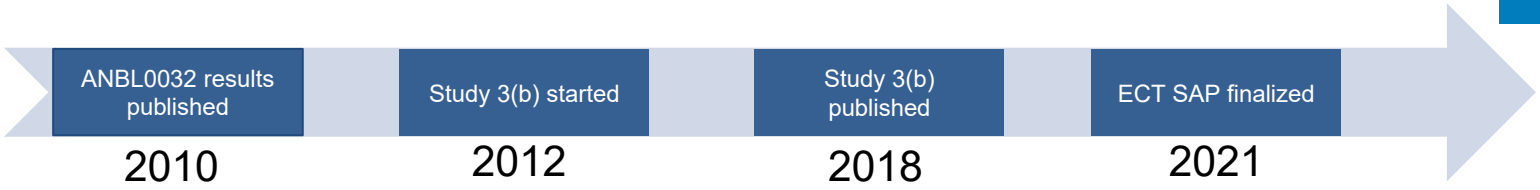
Outline

- Study 3(b) and Use of External Control

- Efficacy Considerations
  - **Comparability**: Externally controlled trial populations
  - **Results**: Magnitude of effect and potential sources of bias
  - **Additional Data**: Nonclinical and Clinical

- Safety Considerations

Development of ECT Statistical Analysis Plan



- During the IND stage, ANBL0032 data was considered likely to be an appropriate EC data source and initial assessment indicated reasonable comparability to support the development of a statistical analysis plan
- Some results of ANBL0032 and Study 3(b) were known at this time; however, FDA was blinded to patient-level data when making recommendations regarding analysis plan
- Applicant proposed a primary analysis using propensity score matched populations to estimate the effect of DFMO
- FDA agreed this was a reasonable approach, but that **several additional sensitivity and supportive analyses would be required**

Characterizing Treatment Effect of DFMO Based on ECT

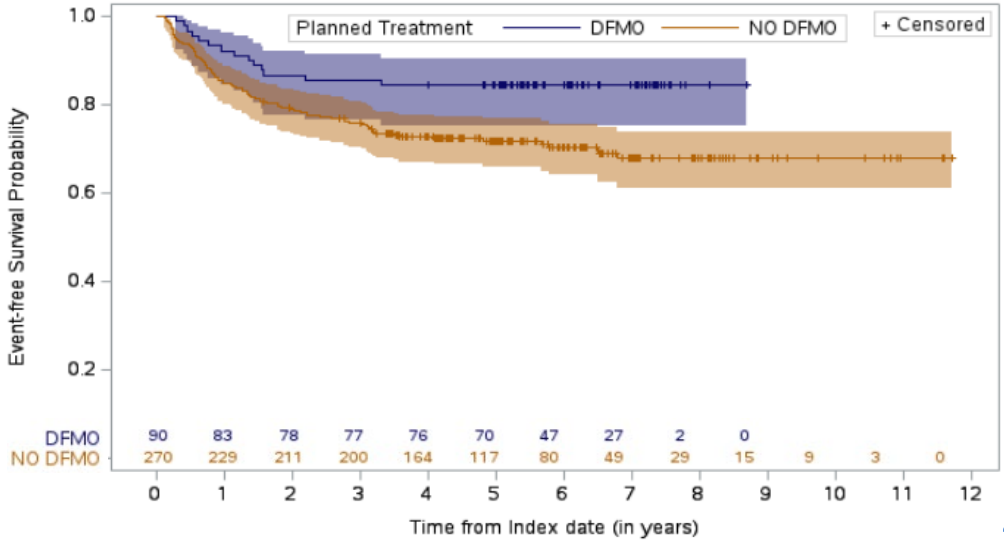
- Noting the limitations of the comparative populations, FDA conducted groups of sensitivity analyses (SA) to characterize treatment effect with a focus on 3 potential threats to study validity:
  - **SA Group 1: Study design and data limitations**
  - **SA Group 2: Unmeasured confounding**
  - **SA Group 3: Statistical analysis methods**

SA Group 1: Assessing Study Design and Data Limitations

LIMITATIONS:

- Non-contemporaneous index dates
- Imaging pre-specified for 2 years post-immunotherapy & limited after 5 years
- Patients treated on ANBL0032 outside U.S. (14% of matched control arm)

Results of Applicant's Primary Analysis			
Description	n	EFS HR	OS HR
Applicant's Proposed Primary Analysis	360	**0.48** (0.27, 0.85)	**0.32** (0.15, 0.70)



SA Group 1: Assessing Study Design and Data Limitations

LIMITATIONS:

Non-contemporaneous index dates

Results of FDA Sensitivity Analyses			
Description	n	EFS HR	OS HR
Applicant's Proposed Primary Analysis	360	**0.48** (0.27, 0.85)	**0.32** (0.15, 0.70)
Use EC patients with index dates in same period as DFMO arm	359	**0.63** (0.36, 1.11)	**0.45** (0.21, 0.98)
Exclude controls with early events (those in immortal time period)	360	**0.54** (0.31, 0.96)	**0.43** (0.19, 0.96)

SA Group 1: Assessing Study Design and Data Limitations

LIMITATIONS:

Imaging pre-specified for 2 years post-immunotherapy & limited after 5 years

Results of FDA Sensitivity Analyses			
Description	n	EFS HR	OS HR
Applicant's Proposed Primary Analysis	360	**0.48** (0.27, 0.85)	**0.32** (0.15, 0.70)
Use EC patients with index dates in same period as DFMO arm	359	**0.63** (0.36, 1.11)	**0.45** (0.21, 0.98)
Exclude controls with early events (those in immortal time period)	360	**0.54** (0.31, 0.96)	**0.43** (0.19, 0.96)
Limit analysis to first 5 years of follow-up	360	**0.51** (0.29, 0.91)	**0.34** (0.14, 0.79)
Use BICR assessment of EFS (only for DFMO arm)	352	**0.49** (0.27, 0.89)	**0.30** (0.13, 0.71)

SA Group 1: Assessing Study Design and Data Limitations

LIMITATIONS:

Results of FDA Sensitivity Analyses			
Description	n	EFS HR	OS HR
Applicant's Proposed Primary Analysis	360	**0.48** (0.27, 0.85)	**0.32** (0.15, 0.70)
Use EC patients with index dates in same period as DFMO arm	359	**0.63** (0.36, 1.11)	**0.45** (0.21, 0.98)
Exclude controls with early events (those in immortal time period)	360	**0.54** (0.31, 0.96)	**0.43** (0.19, 0.96)
Limit analysis to first 5 years of follow-up	360	**0.51** (0.29, 0.91)	**0.34** (0.14, 0.79)
Use BICR assessment of EFS (only for DFMO arm)	352	**0.49** (0.27, 0.89)	**0.30** (0.13, 0.71)
Restrict to U.S. patients only	352	**0.43** (0.23, 0.79)	**0.29** (0.11, 0.72)

Patients treated on ANBL0032 outside U.S. (14% of matched control arm)

SA Group 1: Assessing Study Design and Data Limitations

LIMITATIONS:

- Non-contemporaneous index dates
- Imaging pre-specified for 2 years post-immunotherapy & limited after 5 years
- Patients treated on ANBL0032 outside U.S. (14% of matched control arm)

As a conservative approach, FDA adjusted for multiple limitations in the study design and data concurrently

Results of FDA Sensitivity Analyses			
Description	n	EFS HR	OS HR
Applicant's Proposed Primary Analysis	360	**0.48** (0.27, 0.85)	**0.32** (0.15, 0.70)
FDA Conservative Approach to Sensitivity Analysis (with additive exclusions/adjustments)[1,2]	152	**0.59** (0.28, 1.27)	**0.16** (0.05, 0.57)

[1]US patients only, Contemporary population per index date, uses equivocal events per BICR for patients with events per INV, excludes all patients with treatment-timing/index date related discrepancies, excludes control EFS events prior to 75 days (75% of time between index and DFMO administration for calculation of immortal time bias); [2]1:1 matching due to reduced sample size

SA Group 2: Considering Impact of Unmeasured Confounding

LIMITATIONS:

Unknown factors in decision to enroll vs. not enroll on Study 3(b)

Unmeasured variables may result in confounding

- In non-randomized comparisons, there are concerns of bias due to confounding by both measured and unmeasured variables
- FDA sensitivity analyses explored how different the results might be if potential confounding variables were measured

SA Group 2: Considering Impact of Unmeasured Confounding

- FDA's analysis estimates a treatment effect that adjusts for potential unmeasured confounders[1] using the following steps:
  1. Use literature to identify association of confounder with outcome and expected prevalence
  2. Assume prevalence from same literature source in DFMO arm and 2x prevalence in control
  3. Estimate the new hazard ratio accounting for confounder

Potential Unmeasured Confounder		Supporting Literature	Association with Outcome	Prevalence in DFMO arm	Prevalence in Control Arm	Adjusted DFMO HR (95% CI)
Applicant's Proposed Primary Analysis of EFS						**0.48** (0.27, 0.85)
Social Determinants of Health	Household poverty	Bona (2021)	EFS HR = 1.9	35%	70%	**0.59** (0.53, 0.67)

[1] Lin, DY, Psaty, BM, & Kronmal, RA (1998). Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics*, 948-963.

SA Group 2: Considering Impact of Unmeasured Confounding

Potential Unmeasured Confounder		Supporting Literature	Association with Outcome	Prevalence in DFMO arm	Prevalence in Control Arm	Adjusted DFMO HR (95% CI)
Applicant's Proposed Primary Analysis of EFS						**0.48** (0.27, 0.85)
Social Determinants of Health	Household poverty	Bona (2021)	EFS HR = 1.9	35%	70%	**0.59** (0.53, 0.67)
	Neighborhood & household poverty	Bona (2021)	EFS HR = 2.2	14%	42%*	**0.62** (0.54, 0.71)
Primary Tumor Location	Adrenal vs. Non-adrenal	Kieuhoa (2014)	EFS HR = 1.1	47%	94%	**0.50** (0.48, 0.52)
	Non-thoracic vs. Thoracic	Kieuhoa (2014)	EFS HR = 1.3	85%	100%**	**0.50** (0.49, 0.50)
Applicant's Proposed Primary Analysis of OS						**0.32** (0.15, 0.70)
Cytogenetics	Chromosome 1p deletion	Bown (1999)	OS HR = 1.9	47%	94%	**0.42** (0.33, 0.48)
	Chromosome 17q gain	Bown (1999)	OS HR = 3.4	54%	100%**	**0.47** (0.39, 0.52)

*Triple prevalence considered due to low expected prevalence; **If double prevalence exceeds 100%, the prevalence is capped to 100%

SA Group 3: Alternative Statistical Approaches

- For the primary analysis, the Applicant proposed **propensity-score matching** to achieve 2 balanced arms
- To evaluate whether the results are robust to the chosen primary method, FDA considered several alternative statistical approaches
- One approach was propensity-score based weighting
  - The matching process may exclude some patients from the final analysis population for comparison
  - Weighting allows the analysis to utilize all patient information

SA Group 3: Alternative Statistical Approaches

	Primary: Propensity Score Matching[1]	Alternative: Propensity Score Weighting (ATT)[2]	Alternative: Propensity Score Weighting (ATE)[3]
EFS Hazard Ratio (95% CI)	**0.48** (0.27, 0.85)	**0.50** (0.26, 0.96)	**0.39** (0.30, 0.52)
OS Hazard Ratio (95% CI)	**0.32** (0.15, 0.70)	**0.38** (0.16, 0.92)	**0.34** (0.24, 0.49)

[1] N=360 (90 in DFMO arm, 270 in No DFMO arm); [2]N=180.5 (90 in DFMO arm, and 90.5 in no DFMO arm); [3]N= 1179.9 (595.4 in DFMO arm, and 584.5 in no DFMO arm)

Additionally, consistent results were achieved when SA Group 1 analyses were repeated using a propensity score weighting approach

ECT: Summary of Efficacy

- FDA has not previously relied upon a single ECT as the primary source of evidence in oncology
- However, this ECT has specific strengths due to provenance of the external control data
- While the sensitivity analyses results suggest the observed treatment effect in this ECT is unlikely to be fully attributable to potential sources of bias, there is uncertainty in exact magnitude of effect

Outline

- Study 3(b) and Use of External Control

- Efficacy Considerations
  - **Comparability**: Externally controlled trial populations
  - **Results**: Magnitude of effect and potential sources of bias
  - **Additional Data**: Nonclinical and Clinical

- Safety Considerations

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.

Food and Drug Administration Modernization Act (FDAMA) of 1997; Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, *Guidance for Industry,* 2019

Confirmatory Evidence: Nonclinical

- Under certain circumstances, strong **mechanistic evidence** of the drug's treatment effect in a particular disease may be appropriate to use as confirmatory evidence
  - Generally obtained from clinical testing using a relevant and well-understood pharmacodynamic endpoint
  - Can be obtained from relevant in vitro testing

- Evidence from a **relevant animal model**
  - Depends on similarity of pathophysiology and manifestations of disease in animal model and humans
  - Only models that have proved to be translational are likely to be considered as confirmatory evidence

Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence, *Draft Guidance for Industry,* 2023

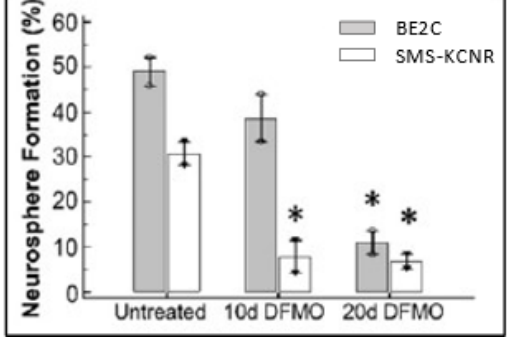
Additional Nonclinical Data: In Vitro

- Applicant's data consistent with published literature → CYTOSTATIC MOA

  - **In Vitro NB cell lines**
    - Inhibited polyamine synthesis
    - Induced G1 cell cycle arrest
    - ↓ MYCN, ↓ LIN28B; ↑ Let-7
    - Induced in vitro senescence & suppressed neurosphere formation in *MYCN*-amplified **and** *MYCN* non-amplified NB cells

MYCN amplified neuroblastoma cell lines

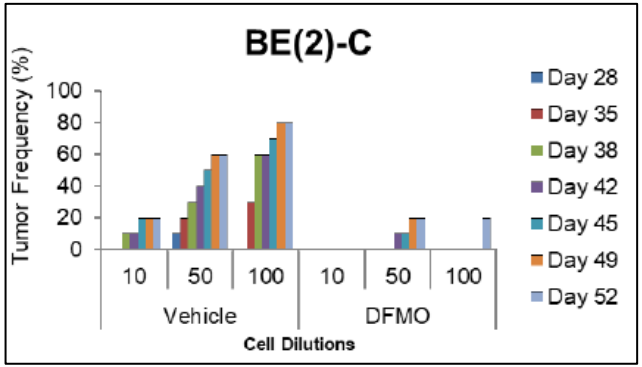
	Vehicle	10d DFMO	20d DFMO
BE(2)-C	49.0%	38.5%	10.9%
SMS-KCNR	30.7%	7.8%	6.8%

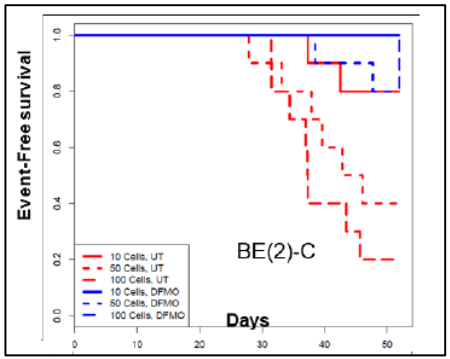


Source: NDA 215500, Applicant Information Amendment, submitted 1/30/2023; page 31

Additional Nonclinical Data: In Vivo

- **ELDA Tumor Prevention Mouse Model**
  - Injected mice with limiting dilutions of *MYCN*-amplified NB cells
  - 2% DFMO beginning on day of injection prevented/delayed tumor formation, improved EFS
  - DFMO ↓ LIN28B & MYCN in tumors (on-target)





ELDA = Extreme Limiting Dilution Analysis; Source: NDA 215500, Applicant Information Amendment, submitted 1/30/2023; page 32

Additional Nonclinical Data: In Vivo

***TH-MYCN* Transgenic Mice**

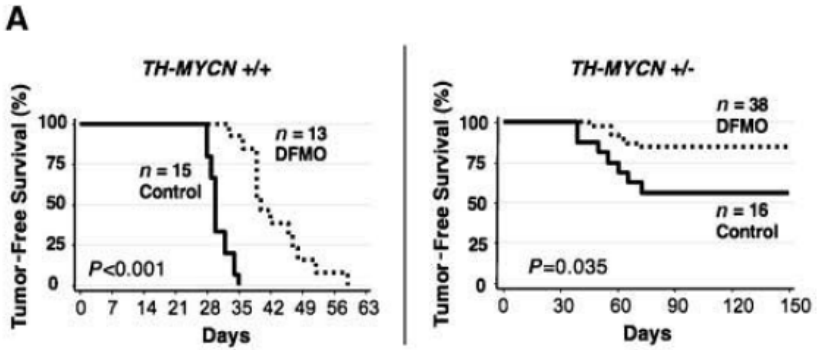
- Overexpress human *MYCN* in neural crest cells; recapitulates human NB

Methods/Results:

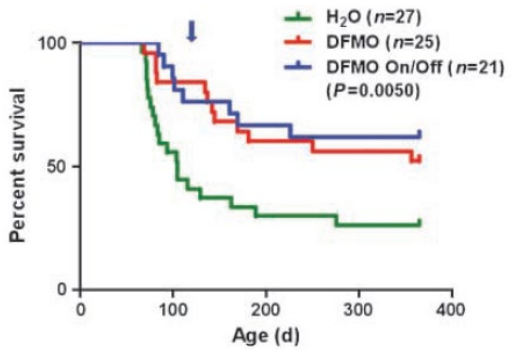
- 1% DFMO in drinking water from birth onward ↑ tumor-free survival in *TH-MYCN* +/+ mice and prevented tumor formation in ~84% of treated *TH-MYCN* +/- mice
- DFMO-treated tumors harvested from *TH-MYCN* +/+ mice exhibited ↓ polyamine levels

Conclusion:

➢ DFMO prevents/delays tumor formation, ↑ survival in transgenic NB mouse model



Hogarty et al., Cancer Res. 2008; 68(23): 9735-45



Rounbehler et al., Cancer Res. 2009; Jan 15; 69(2): 547-53

Nonclinical Data Summary

- In vitro mechanistic data (targets driver of NB pathophysiology)
  - Inhibits ODC; ↓ polyamines, LIN28B, MYCN; induces senescence

- Evidence from 2 established, relevant animal models of NB (ELDA; *TH-MYCN* transgenic mice) showing that DFMO prevents/delays tumor formation in mice with no evidence of disease; relevant endpoints
  - Provide PD evidence of on-target activity
  - Limitation: Doses ~2-9x-fold higher than recommended human dose

➢ DFMO is ***CYTOSTATIC*** and targets tumor-initiating cells

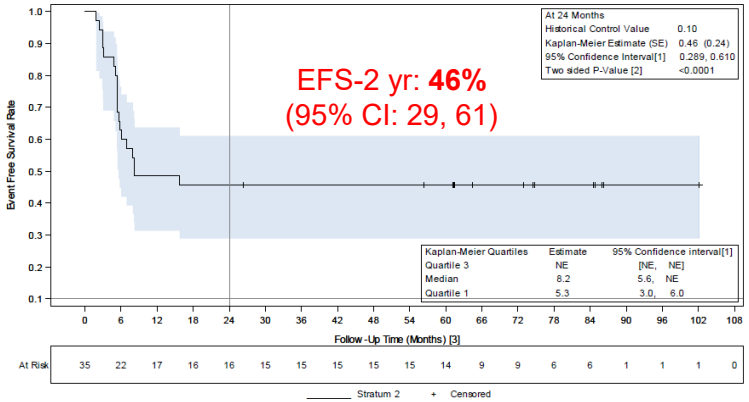
Additional Clinical Data

	Design	Results
Study NMTRC002	Multi-center, single-arm, dose-escalation study of DFMO monotherapy (one cycle) followed by DFMO + oral etoposide in R/R HRNB	• 21 enrolled, 18 evaluable • 3 patients with active disease resolved after 1 cycle of DFMO alone, later progressed
Expanded Access Program	Ongoing intermediate access protocol for DFMO for pediatric patients with MYC, ODC or LIN28/Let7-driven tumors	• 27 patients with HRNB in remission as of Jan 2023 • **Up-front therapy alone** (N=13): 8 in remission at 2 years • **Any prior R/R therapy** (N=14): 5 in remission at 2 years

HRNB = high-risk neuroblastoma; R/R = relapsed/refractory

Additional Clinical Data

	Design	Results
Study 3(b) Stratum 2	Multi-center, single-arm study of DFMO monotherapy in patients with HRNB in remission after any previous R/R therapy	• 35 patients treated from 2012-2016 • Variable type & timing of prior therapies • EFS at 2 years **46%** (95% CI: 29, 61) for DFMO vs. pre-specified historical control rate of **10%** based on publication of HRNB studies enrolling from 1991-2002



HRNB = high-risk neuroblastoma; R/R = relapsed/refractory; EFS = event-free survival; Source: Study 3(b), Clinical Study Report

Additional Clinical Data

	Strengths	Limitations
Study NMTRC002	• Early clinical data suggest potential activity of DFMO in patients with HRNB	• Findings exploratory • Variable prior therapies • Combination therapy after 1st cycle
Expanded Access Program		• Findings exploratory • Variable disease characteristics • Response criteria not pre-specified
Study 3(b) Stratum 2	• Independent cohort • Suggests EFS improvement for patients with R/R HRNB in remission who received DFMO	• Small population • Variable prior therapies • Historical rate based on single institution data from 1991-2002, likely underestimates current rate given improved SOC

DFMO in Other Populations

- Few supportive clinical trials despite numerous studies in multiple tumor types, including non-melanoma skin cancer, familial adenomatous polyposis, colorectal cancer, and bladder cancer
    - One prior NDA submission for oral eflornithine + sulindac in adult patients with familial adenomatous polyposis (FAP)[1]
    - One Breakthrough Therapy Designation granted for the treatment of patients with anaplastic glioma[2]
- To date, there are no approved oncology indications for eflornithine/DFMO

NDA = New Drug Application;

[1] https://www.sec.gov/Archives/edgar/data/1029125/000143774923001188/pbla20230113_s1a.htm;
[2] https://www.orbustherapeutics.com/eflornithine

Ongoing Trials with DFMO in HRNB

	Trial Design / Population	Endpoints	Status per clinicaltrials.gov	
			Study Start Date	Estimated Study Completion Date
NMTRC014 (supports safety in this NDA)	**Single-arm trial / HRNB in remission after up-front therapy** Same design as Study 3(b)	Primary: **EFS** vs. historical control at 4 years Secondary: OS	2016	2029
NMTRC012	**Randomized trial / Newly diagnosed HRNB** Randomization to immunotherapy alone vs. immunotherapy + DFMO; all patients then receive DFMO for 2 years	Primary: **EFS** Secondary: OS	2015	2032
COG ANBL1821	**Randomized trial / Relapsed or Refractory HRNB** Randomization to dinutuximab + irinotecan + temozolomide with or without DFMO	Primary: **ORR** Secondary: PFS, OS	2019	2024

COG = Children's Oncology Group; EFS = event-free survival; PFS = progression-free survival; ORR = overall response rate; OS = overall survival

Outline

- Study 3(b) and Use of External Control

- Efficacy Considerations
  - **Comparability**: Externally controlled trial populations
  - **Results**: Magnitude of effect and potential sources of bias
  - **Additional Data**: Nonclinical and Clinical

- **Safety Considerations**

Summary of Safety

- Proposed Warnings: myelosuppression, hepatotoxicity, hearing loss
- Most common adverse reactions (incidence ≥ 5%): hearing loss, otitis media, pyrexia, pneumonia, and diarrhea
- Grade 3 or 4 AEs in 42%; Discontinuations in 7%
- No deaths due to AEs
- Limited data collected
  - Study 3(b) (N=101): collected **Grade 2** or higher AE; no lab data
  - Study 14 (N=259): collected **Grade 3** or higher AEs

Summary of Safety

- **Myelosuppression**
  - 1 AE of bone marrow failure
  - Dose modifications in 1.7%
  - Discontinuations in 1%
- **Hepatotoxicity**
  - No liver failure
  - Dose modifications in 2.5%
  - Discontinuations in 0.6%

	Grade 3 or 4 AEs in Study 3b + Study 14, (N=360)
Myelosuppression	
Decreased neutrophils	4.2%
Decreased hemoglobin	3.3%
Decreased platelets	1.4%
Hepatotoxicity	
Increased ALT	7%
Increased AST	6%
Increased alkaline phosphatase	2.4%

Safety: Hearing Loss

- Identified risk in non-oncology populations and chemoprevention trials
- 81% with abnormal audiogram at baseline (related to 1L therapy)
- Audiogram data: new or worsening hearing loss in **13%**
  - 12% worsened from baseline to Grade 3 or 4 (e.g., hearing aids indicated)
  - 7% dose interruptions or reductions
  - 1.4% required discontinuation
  - 9% resolved

Application Strengths and Limitations

STRENGTHS:	LIMITATIONS:
High quality external control data	Lack of randomized design to interpret effect on time-to-event endpoint
Consistency of EFS and OS results in multiple sensitivity analyses	Uncertainty in magnitude of effect remains inherent to design

Application Strengths and Limitations

STRENGTHS:	LIMITATIONS:
High quality external control data	Lack of randomized design to interpret effect on time-to-event endpoint
Consistency of EFS and OS results in multiple sensitivity analyses	Uncertainty in magnitude of effect remains inherent to design
Nonclinical data supports delay in tumor formation in 2 animal models with on-target pharmacodynamic activity	Nonclinical data rarely used as primary source of confirmatory evidence
Nonclinical data supports cytostatic mechanism of action (rationale for lack of clinical ORR)	Lack of response data to confirm activity (e.g., ORR); other supportive clinical data has limitations to interpretability

Discussion Topics

1. Discuss the strengths and limitations of the externally controlled trial results to support the use of DFMO in pediatric patients with high-risk neuroblastoma.

2. Discuss the strengths and limitations of the additional nonclinical and clinical data to support the use of DFMO in pediatric patients with high-risk neuroblastoma.

Voting Question

Has the Applicant provided sufficient evidence to conclude that DFMO improves event-free survival in patients with high-risk neuroblastoma?

Acknowledgements

FDA recognizes the time and effort necessary to conduct cancer clinical trials. We would like to particularly thank the children and their families as well as the investigators and research staff who participated in the research studies discussed today.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Eflornithine (DFMO) for the maintenance treatment of pediatric patients with high-risk neuroblastoma

FDA Summary
Oncologic Drugs Advisory Committee (ODAC) Meeting
October 4, 2023

Nicole Drezner, MD
Deputy Division Director
Division of Oncology 2, Office of Oncologic Diseases

Substantial evidence of effectiveness

FD&C Act section 505(d) (21 U.S.C. § 355(d))

A drug's effectiveness must be established by substantial evidence

> *"...evidence consisting of **adequate and well-controlled investigations**...by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could **fairly and responsibly be concluded by such experts** that the drug will have the effect it purports or is represented to have."*

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

FDA Guidance for Industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products,* (2019)

Application Strengths and Limitations

STRENGTHS:	LIMITATIONS:
High quality external control data	Lack of randomized design to interpret effect on time-to-event endpoint
Consistency of EFS and OS results in multiple sensitivity analyses	Uncertainty in magnitude of effect remains inherent to design
Nonclinical data supports delay in tumor formation in 2 animal models with on-target pharmacodynamic activity	Nonclinical data rarely used as primary source of confirmatory evidence
Nonclinical data supports cytostatic mechanism of action (rationale for lack of clinical ORR)	Lack of response data to confirm activity (e.g., ORR); other supportive clinical data has limitations to interpretability

Substantial evidence of effectiveness: When additional flexibility may be warranted

"FDA may rely on less certain study designs when a better design is not feasible"

- Major feasibility challenges for an RCT of DFMO due to…
  - Small patient population
  - Length of time required (approx. 8 years for ANBL0032)
  - Likelihood for asymmetric dropout and/or difficulty accruing

FDA **must** reach the conclusion that there is SEE to approve a drug

FDA Guidance for Industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products,* (2019)

FDA Summary

- Single ECT with EFS results in DFMO arm robust to sensitivity analyses but with residual uncertainty in magnitude
- Confirmatory evidence is predominately non-clinical with limited additional supportive clinical data
- Acceptable safety profile in the context of the disease
- RCT of DFMO in the proposed indication is likely infeasible
- Serious and life-threatening disease with high unmet need

Discussion Topics

1. Discuss the strengths and limitations of the externally controlled trial results to support the use of DFMO in pediatric patients with high-risk neuroblastoma.

2. Discuss the strengths and limitations of the additional nonclinical and clinical data to support the use of DFMO in pediatric patients with high-risk neuroblastoma.

Voting Question

Has the Applicant provided sufficient evidence to conclude that DFMO improves event-free survival in patients with high-risk neuroblastoma?


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Back-up Slides Shown

Efficacy Results
Applicant Proposed Primary Analysis

	DFMO (N=90)[1]	NO DFMO (N=270)[2]
Event-free Survival (EFS)[3,4]		
EFS events, n (%)[5]	14 (16)	79 (29)
Censored, n (%)	76 (84)	191 (71)
Hazard Ratio (95% CI)	0.48 (0.27, 0.85)	
Overall Survival (OS)[6]		
Deaths, n (%)	7 (8)	57 (21)
Censored, n (%)	83 (92)	213 (79)
Hazard Ratio (95% CI)	0.32 (0.15, 0.70)	

[1]Derived from 91 patients with no missing data out of 92 total eligible patients; [2]Derived from 516 patients with no missing data out of 852 total eligible patients; [3]Final analysis; DCO: Study NMRTC003b, June 2021; Study ANBL0032, June 2019 [4]Descriptive p-value from unstratified log-rank test = 0.0096; [5]2 events were deaths (both in the NO DFMO arm); [6]Descriptive p-value from unstratified log-rank test = 0.0027

Source: FDA analysis using Applicant submitted datasets in NDA

Analysis of EFS and OS using patients in both arms who received immunotherapy at common sites

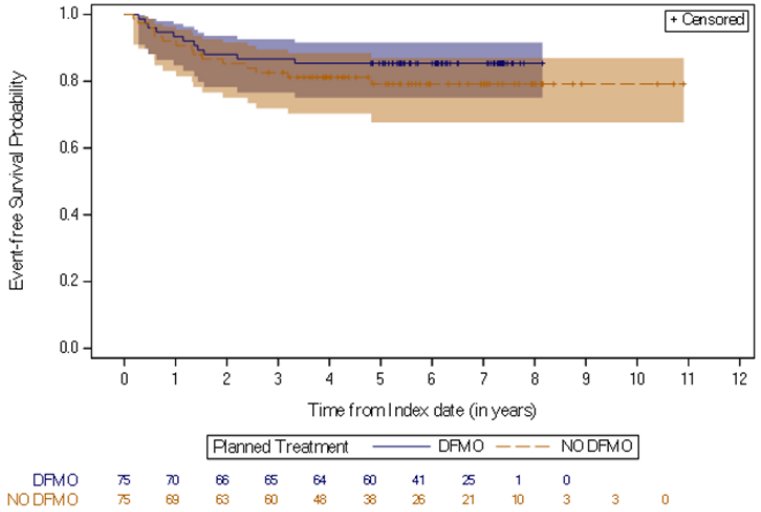
	Primary: Propensity Score Matching[1,2]	Alternative: Propensity Score Weighting (ATT)[3]	Alternative: Propensity Score Weighting (ATE)[4]
EFS Hazard Ratio (95% CI)	0.60 (0.23, 1.54)	0.57 (0.27, 1.19)	0.51 (0.33, 0.80)
OS Hazard Ratio (95% CI)	0.15 (0.02, 1.28)	0.35 (0.11, 1.10)	0.42 (0.22, 0.77)

[1] N=150 (75 in DFMO arm, 75 in No DFMO arm), [2] Stratified analysis stratified by site of enrollment; [3]N=152.1 (75 in DFMO arm, and 77.1 in no DFMO arm); [4]N= 426.7 (215.6 in DFMO arm, and 211.1 in no DFMO arm)

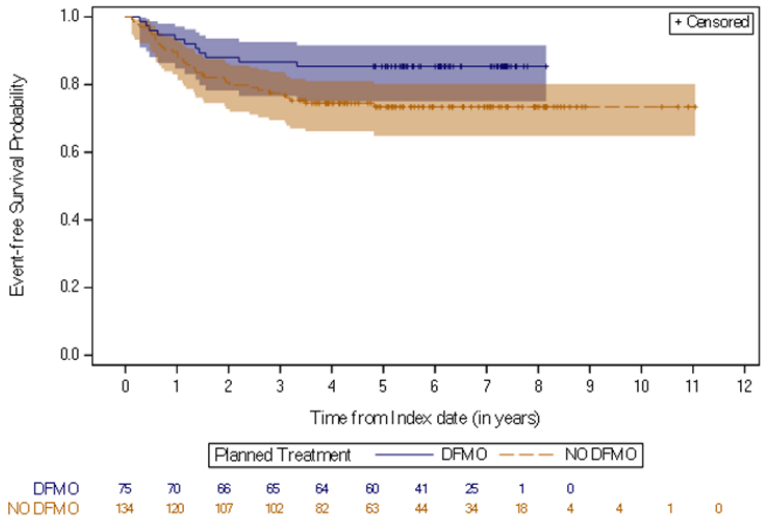
Source: FDA analysis using Applicant submitted datasets in NDA

Kaplan-Meier plots of EFS using patients in both arms who received immunotherapy at common sites

a. Event-free Survival: Matched (1:1) Analysis



b. Event-free Survival: Weighted (ATT) Analysis



Source: FDA analysis using Applicant submitted datasets in NDA

Impact of Potential Unmeasured Confounders

Table 20: Adjusted Event-free Survival hazard ratios comparing DFMO vs. NO DFMO adjusting for an unmeasured binary confounder having a hazard ratio of 2.0 and the observed hazard ratio in the current trial of 0.48

	P_1					
P_0	0.0	0.1	0.2	0.3	0.4	0.5
0.0	**0.48**	0.44	0.40	0.37	0.34	0.32
0.1	0.53	**0.48**	0.44	0.41	0.38	0.35
0.2	0.58	0.52	**0.48**	0.44	0.41	0.38
0.3	0.62	0.57	0.52	**0.48**	0.45	0.42
0.4	0.67	0.61	0.56	0.52	**0.48**	0.45
0.5	0.72	0.65	0.60	0.55	0.51	**0.48**
0.6	0.77	0.70	0.64	0.59	0.55	0.51
0.7	0.82	0.74	0.68	0.63	0.58	0.54
0.8	0.86	0.79	0.72	0.66	0.62	0.58
0.9	0.91	0.83	0.76	0.70	0.65	0.61
1.0	0.96	0.87	0.80	0.74	0.69	0.64

Note. P_1 and P_0 are the prevalence of the unmeasured confounder in the DFMO arm and in the control arm, respectively.

FDA ODAC Briefing Document, page 63

Non-Matched Clinical Characteristics (2)

Treatment Characteristics			DFMO (N=90) %	External Control (N=270) %
Pre-Immunotherapy	Surgery during induction[a]	Yes	93	71
		Missing	2	29
	Radiation during consolidation[b]	Yes	83	90
		Missing	17	10
	Transplant regimen	Bu/Mel	36	11
		CEM	53	22
		TC and CEM	7	3
		Other/Missing	4	64
Post-Immunotherapy	Lansky performance status at end of immunotherapy	100	59	-
		80-90	18	-
		Missing	23	100
	End of immunotherapy bone marrow response	No evidence of disease	100	74
		Missing	0	1% no change; <1% improved; 25% missing[c]

[a] extent of surgery not specified; [b] information regarding dose and type of radiation limited; [c] All patients with missing BM response had an overall response documented of CR or VGPR;
Bu/Mel = busulfan and melphalan; CEM = carboplatin/etoposide/melphalan; TC = cyclophosphamide-thiotepa

Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence: Evidence from a Relevant Animal Model

Whether data from an established animal model of disease would be suitable as confirmatory evidence depends on several factors, including similarity of pathophysiology and manifestations of the disease in the animal model and in humans, elucidation of the drug's mechanism of action with evidence of similar pharmacology and pharmacodynamics in the animal model and humans with disease, and evidence that the results of efficacy studies conducted in the animal model reasonably support clinical benefits and outcomes in humans with disease (e.g., if the disease in humans leads to renal failure and the drug is intended to preserve renal function, showing that the animal model of disease also is characterized by renal failure and the drug reduces progression of renal failure when tested in the animal model). Although animal models are useful in the preclinical stages of drug development, only a few such models may accurately predict human responses quantitatively or even qualitatively. Only models that have proved to be translational (i.e., prior drugs with the same intended clinical effect have been shown to have this effect observed in the animal model, with similar exposure-response) are likely to be considered as confirmatory evidence.

FDA Guidance for Industry, September 2023

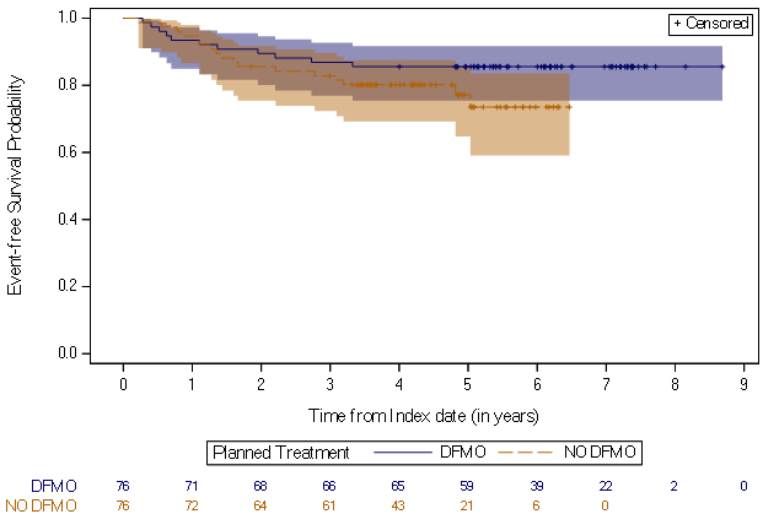
Post-Relapse Therapies

	DFMO (N=90)	External Control (N=270)
EFS events, N (%)	**14 (16)**	**79 (29)**
Relapse	14	76
Death	0	2
Secondary malignancy	0	1
Known Relapse Count, N		
Single	9	44
Multiple	5	22
Missing	-	13
Number of post-relapse therapies, median (range)	3 (1, 5)	Unknown
Chemotherapy	13	-
Antibody therapy	8	-
Radiation	7	-
Other (e.g., vaccine trial)	7	-
Number of patients alive at DCO*, N (%)	6 (43)	22 (28)

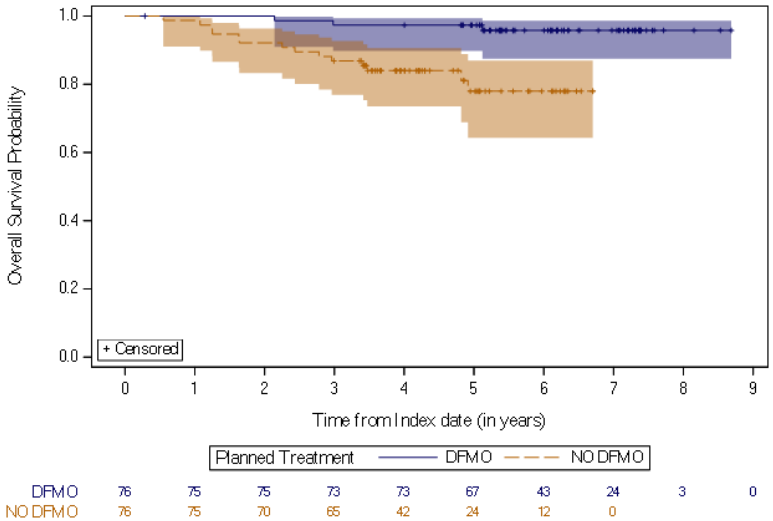
*DFMO DCO: 6/30/2021; Control DCO: 6/30/2019

Kaplan-Meier Plots:
FDA Conservative (Additive) Sensitivity Analysis[1]

Event-free Survival



Overall Survival



[1]Contemporary population per index date, uses equivocal events per BICR for patients with later unequivocal events, excludes all patients with treatment administration or index date related discrepancies, excludes control observed EFS dates prior to 75 days, US sites only; 1:1 matching ratio