

### EFLORNITHINE (DFMO) TABLETS TO REDUCE THE RISK OF RELAPSE IN PEDIATRIC PATIENTS WITH HIGH-RISK NEUROBLASTOMA WHO HAVE COMPLETED MULTIAGENT, MULTIMODALITY THERAPY

### SPONSOR BRIEFING DOCUMENT

### **ONCOLOGIC DRUGS ADVISORY COMMITTEE**

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#### List of Abbreviations

| Abbreviation | Definition  |
|--------------|---|
| AE           | adverse event   |
| ALT          | alanine aminotransferase                              |
| anti-GD2     | anti-ganglioside 2                                    |
| ASCT         | autologous stem cell transplantation                  |
| AST          | aspartate aminotransferase                            |
| BCC          | Beat Childhood Cancer                                 |
| BICR         | blinded independent central review                    |
| BID          | twice daily   |
| BSA          | body surface area                                     |
| BUN          | Blood urea nitrogen                                   |
| C&T          | cyclophosphamide and thiotepa                         |
| CEM          | carboplatin, etoposide and melphalan                  |
| ch14.18      | with chimeric anti-GD2 antibody                       |
| cis-RA       | 13-cisretinoic acid                                   |
| CMC          | chemistry, manufacturing, and controls                |
| COG          | Children's Oncology Group                             |
| CPH          | Cox proportional hazards                              |
| CR           | complete response                                     |
| CSC          | cancer stem cell                                      |
| СТ           | computed tomography                                   |
| CTCAE        | Common Terminology Criteria for Adverse Events        |
| CV           | coefficient of variation                              |
| CYP          | cytochrome P450                                       |
| DDI          | drug-drug interactions                                |
| DFMO         | eflornithine hydrochloride                            |
| DLT          | dose-limiting toxicities                              |
| ECG          | electrocardiogram                                     |
| EFS          | event free survival                                   |
| ELDA         | extreme limiting dilutions analysis                   |
| FDA          | US Food and Drug Administration                       |
| FDG          | fluorodeoxyglucose                                    |
| GD2          | ganglioside 2   |
| GFR          | glomerular filtration rate                            |
| GM-SCF       | granulocyte-macrophage colony-stimulating factor      |
| HCI          | hydrochloric acid                                     |
| HRNB         | high-risk neuroblastoma                               |
| IND          | investigational new drug application                  |
| INRC         | International Neuroblastoma Response Criteria         |
| INRG         | International Neuroblastoma Risk Group                |
| INRGSS       | International Neuroblastoma Risk Group Staging System |
| INSS         | International Neuroblastoma Staging System            |
| IR           | immediate release                                     |
| ITT          | intent-to-treat                                       |
| KM           | Kaplan-Meier  |
| LDH          | lactate dehydrogenase                                 |
| LE           | local evaluator                                       |
| MIBG         | meta-iodobenzylguanidine                              |
| MICE         | Multiple-imputation-by-chained-equations              |
| MR           | mixed response  |
| MRI          | magnetic resonance imaging                            |

| Abbreviation | Definition   |
|--------------|--|
| NAD          | no active disease                                  |
| NANT         | New Approaches to Neuroblastoma Therapy            |
| NB           | neuroblastoma                                      |
| NDA          | new drug application                               |
| NECT         | nifurtimox-effornithine combination therapy        |
| NED          | no evidence of disease                             |
| NK           | natural killer                                     |
| NR           | no response  |
| ODC          | ornithine decarboxylase                            |
| OR           | objective response                                 |
| OS           | overall survival                                   |
| PD           | progressive disease                                |
| PDUFA        | Prescription Drug User Fee Act                     |
| PET          | positron emission tomography                       |
| PFS          | progression free survival                          |
| PK           | pharmacokinetics                                   |
| PR           | partial response                                   |
| PSM          | propensity score matching                          |
| RCT          | randomized controlled trial                        |
| R/R          | relapsed or refractors                             |
| RTOR         | Real Time Oncology Review                          |
| SAE          | serious adverse event                              |
| SAP          | statistical analysis plan                          |
| SD           | stable disease                                     |
| SIOPEN       | Society of Pediatric Oncology Europe Neuroblastoma |
| SoC          | standard of care                                   |
| SUV          | Standardized uptake value                          |
| TLG          | Total lesion glycolysis                            |
| TTP          | time to progression                                |
| TVD          | Topotecan, vincristine and doxorubicin             |
| US           | United States                                      |
| USWM         | US WorldMeds                                       |
| VGPR         | very good partial response                         |

#### 1 EXECUTIVE SUMMARY

#### 1.1 Introduction

US WorldMeds (USWM) is seeking approval of eflornithine hydrochloride (DFMO) to reduce the risk of relapse in pediatric patients with high-risk neuroblastoma (HRNB) who have completed multiagent, multimodality therapy. Children diagnosed with HRNB undergo an intense and toxic standard of care (SoC) regimen that still leaves them vulnerable to relapse and death — a risk that is particularly acute during the first 2 years (Basta 2016). Approximately 30% of patients who attain remission following upfront therapy will relapse, resulting in a dire prognosis and low likelihood for long-term survival (e.g., estimates as low as 15% of patients will live for 5 years after relapsing) (London 2017). Avoiding relapse is key to long-term survival, yet no approved therapies exist to sustain remission following SoC treatment. The data presented in this briefing document demonstrate that using DFMO as maintenance therapy extends remission and reduces risk of relapse in patients with HRNB.

The efficacy of DFMO maintenance in HRNB is primarily supported by results from Study 3b, a single-arm study of DFMO maintenance treatment following the immunotherapy phase of Children's Oncology Group (COG) SoC. Study 3b, led by Dr. Giselle Sholler and the Beat Childhood Cancer (BCC) research consortium, was originally intended as a Phase 2 study to evaluate DFMO efficacy and safety using the dosing established by a Phase 1 dose-finding study. Importantly, the observed results were significantly better than published remission rates for this rare disease. As such, BCC sought guidance from the US Food and Drug Administration (FDA) regarding a pathway to pursue US registration at this point rather than completing a Phase 3 randomized controlled trial (RCT) that was estimated to take 10 or more years to enroll, significantly delaying access to a therapy with the potential to keep more patients with this rare disease alive.

Although FDA recommended an RCT as the preferred path to registration, the use of an external control was identified as a viable alternative. BCC initiated efforts to identify two sources of external control data, the first of which was BCC001, a retrospective chart review of patients with HRNB treated across BCC institutions. As the pivotal comparison, BCC also initiated a data transfer request and partnered with USWM to design, through collaborative discussions with FDA, a rigorous propensity score matched analysis using the landmark registration-quality study, ANBL0032, as an external control.

This external control approach allowed comparative analyses of similar patients completing the same upfront treatment and then either treated with DFMO maintenance in Study 3b or not in order to demonstrate efficacy. In study ANBL0032, patients were treated with HRNB SoC upfront treatment matching the pre-DFMO treatment in Study 3b, with systematic long-term follow-up monitoring and data collection closely aligned with that during and after Study 3b. This highly similar dataset allowed propensity score matching based on 11 important HRNB covariates to lessen bias by identifying control patients who would be expected to have a similar disease prognosis. Efficacy was further supported by confirmatory data from both nonclinical and clinical evaluations. The use of ANBL0032 as an external control is consistent with initiatives that support increased regulatory flexibility in the development of therapeutics for rare diseases. This program highlights the ability to comply with strict regulatory framework requirements while addressing unique challenges inherent in developing new therapies for rare disease populations, thereby accelerating the availability of innovative therapeutics, and bringing hope to those affected by

devastating, deadly conditions. The DFMO development program was conducted in accordance with extensive FDA guidance available under the product's Orphan Drug Designation, Breakthrough Therapy Designation, Real Time Oncology Review Program, and Project Orbis initiatives, which were all designed to accelerate the availability of promising new therapeutics for orphan diseases or specifically for cancers with high unmet needs.

In Study 3b, DFMO maintenance improved event free survival (EFS) and overall survival (OS) well beyond what is expected based on published historical rates or propensity matched populations, with few events occurring after patients completed 2 years of DFMO therapy. This benefit was attained in patients in remission following upfront treatment as well as relapse/refractory patients who regain remission after second-line therapy.

Safety data from Study 3b and ongoing open-label safety study, Study 14, established that DFMO was generally well tolerated. Adverse events (AEs), including events related to liver function changes, myelosuppression, and hearing loss, can be monitored with routine follow-up, and can be managed or mitigated through dose modifications or discontinuation.

The relapse risk reduction and long-term survival benefits from DFMO maintenance therapy in patients with HRNB who achieve remission greatly outweigh the risks. There is substantial evidence that DFMO extends remission, reduces the risk of relapse, and increases durable long-term survival beyond what is possible with upfront SoC alone — enabling more young patients with HRNB to survive into adulthood and live full lives.

#### 1.2 Background and Unmet Need

Neuroblastoma is a rare pediatric cancer affecting approximately 800 patients per year in North America. Although rare, neuroblastoma is the most common extracranial solid tumor in children, accounting for approximately 8% of all childhood cancers and 15% of childhood cancer mortality (Brodeur 2003; Johnson 2009; Maris 2010; Park, Eggert and Caron 2010). Neuroblastoma is a solid cancerous tumor that begins in the nerve cells outside the brain of infants and young children, most often initially forming in the adrenal glands, with 90% of diagnoses occurring by the age of 5 years.

Patients with neuroblastoma are stratified by several risk factors into low-, intermediate-, and highrisk groups in accordance with international guidelines developed by the International Neuroblastoma Risk Group (Irwin 2021; Cohn 2009). Children with low- or intermediate-risk neuroblastoma have 5-year OS probabilities > 90% with treatment generally comprising monitoring and limited therapy. However, half of children diagnosed with neuroblastoma are classified as having HRNB. These patients with HRNB have a much poorer prognosis, despite treatment with a far more aggressive and toxic series of therapies, than patients with low- or intermediate-risk neuroblastoma. Approximately half of children with HRNB will die within 5 years from the time of initial diagnosis (Bagatell 2023; Park 2013; Park, Eggert and Caron 2008; Yu 2010).

The current SoC for HRNB includes three main phases of treatment: induction, consolidation, and post-consolidation. Treatment includes chemotherapy and surgical resection (induction), high-dose chemotherapy with autologous stem cell transplantation (ASCT) and radiation (consolidation), followed by anti-ganglioside 2 (anti-GD2) immunotherapy and 13-cis-retinoic acid (also known as isotretinoin, cis-RA) (post-consolidation).

While these treatments aim to eradicate the cancer cells and improve survival rates, they come with significant toxicities, including acute safety risks with the potential for serious and even fatal complications, late effects that range from infertility and profound hearing loss to progressive organ damage, and exposure to interventions that put them at higher risk of a secondary malignancy. However, these risks are considered acceptable in the context of HRNB given that the addition of each of these aggressive treatments have incrementally improved long-term survival outcomes for patients over time.

The immunotherapy phase of the current SoC was introduced through the landmark COG trial, ANBL0032, which established efficacy of post-consolidation immunotherapy. ANBL0032 was a large Phase 3, randomized, open-label trial that investigated the anti-GD2 antibody ch14.18 (dinutuximab, Unituxin<sup>®</sup>) in patients with HRNB who had completed induction and consolidation. Results showed improved EFS when dinutuximab was added to post-consolidation cis-RA therapy (Yu 2010). The results of the study supported registration of the immunotherapy, dinutuximab, in the US in 2015. The interim results also supported continuation of ANBL0032 through a single-arm expansion that enabled adoption of the immunotherapy into the SoC across COG institutions several years before US regulatory approval (Yu 2010). Dinutuximab remains the recommended post-consolidation therapy for the standard COG HRNB upfront treatment paradigm today. Alternate upfront treatments paradigms have been developed by other groups, but importantly all incorporate post-consolidation anti-GD2 immunotherapy.

ANBL0032 is the largest prospective study of HRNB in the last two decades and is a recognized contemporary source of data on long-term outcomes for patients with HRNB who receive all current phases of upfront treatment. Between patients randomly and non-randomly assigned to treatment with dinutuximab, the study systematically monitored and evaluated outcomes for a total of 1328 patients receiving induction, consolidation, and immunotherapy, providing a large database from which current demography, disease attributes, and long-term outcomes for the HRNB population can be characterized.

ANBL0032 established a meaningful improvement in EFS rates with the addition of immunotherapy to the prior SoC. However, when adjusting the published data from ANBL0032 from the end of immunotherapy, long-term remission is only achieved in ~70% of patients 2 years from the end of immunotherapy (Desai 2022; Yu 2021). Given that no more than 30% of patients maintain durable remission following upfront first-line HRNB therapy, there remains a need for additional therapies that can further improve EFS and extend remission in this population, because avoiding relapse is key to survival.

Patients who experience relapse following upfront treatment are referred to second-line therapy to try to regain remission; however, the outlook for these patients is extremely poor. Based on a 2017 COG meta-analysis of neuroblastoma studies, 94% of relapsed high-risk neuroblastoma patients experience further disease progression, and 85% die within 4 years of relapsing (London 2017). These outcomes have remained largely unchanged from survival outcomes reported a decade earlier by Santana (2008). While the most recent advancements in relapse therapy have indicated the potential for incremental improvement in outcomes (Mody 2017; Mody 2020), relapse is still associated with high mortality.

There is a need to further improve long-term survival rates in HRNB by introducing therapies that can minimize the risk of relapse, which is associated with a high risk of death.

#### **1.3 Product Description**

DFMO is a specific, irreversible inhibitor of ornithine decarboxylase (ODC), an enzyme central to polyamine biosynthesis and neoplastic transformation, making ODC an attractive target for chemoprevention (Section 3.3 provides a detailed discussion of mechanism of action). Excessive polyamines drive oncogenesis through multiple processes including inducing oncogenic shifts in gene expression profiles, triggering multiple growth/proliferation signaling pathways, and driving a *MYCN*/Lin28/Let-7 signaling feedback loop. Direct inhibition of polyamine synthesis by DFMO suppresses tumor growth and formation with a multi-faceted approach, with the ability to affect multiple oncogenic mechanisms. This type of therapeutic approach is ideal for a highly heterogeneous disease like neuroblastoma.

#### 1.4 HRNB Development Program Overview

Following a Phase 1 dose ranging study in patients with active relapsed/refractory HRNB, Study 3b was specifically designed to investigate whether maintenance with single-agent DFMO for two years following the completion of immunotherapy could further improve EFS and OS beyond the rates reported from the landmark registration trial, ANBL0032, which introduced immunotherapy into the current upfront SoC treatment for HRNB (Section 6.3 provides additional details).

Following completion of Study 3b, Study 14 was initiated as a an open-label, single-arm study enrolling patients with HRNB in remission to expand the safety database and address specific safety requirements for registration. Study 14 enrollment remains ongoing; however, an interim data cut of safety data contributes to the pooled safety analysis population for characterizing DFMO exposures, AEs, laboratory abnormalities, and additional assessments.

#### 1.4.1 History Resulting in Registration Approach without Randomized Controlled Trial

Study 3b was a single-arm Phase 2 study, and the first study to evaluate potential benefits of DFMO maintenance therapy. At the time it was initiated, the goal was that positive hypothesis testing would then be used to inform the design of a Phase 3 study following the traditional development sequence. However, preliminary reporting of outcomes from Study 3b were considerably better than predicted, both in terms of exceeding the hypothesized EFS benefit and in terms of very high OS rates. These results prompted additional conversations between the Principal Investigator, Giselle Sholler MD, and FDA in 2015 and 2016. Although FDA recommended that a follow-on RCT be considered, the option of externally controlling Study 3b was discussed as a viable alternative. In parallel, efforts to plan an RCT that could introduce DFMO at an earlier point in upfront treatment, designed as NMTRC012 (NCT02559778), initiated in 2015, and the study remains ongoing today with regulatory read-out and reporting expected to occur in another 7 to 10 years. However, by 2018, the 2-year EFS data from Study 3b were available for reporting on all enrolled patients, demonstrating increasingly promising EFS results as well as encouraging OS rates in DFMO-treated patients compared to published rates for patients with HRNB. These outcomes and the availability of ANBL0032 as an optimal external control resulted in a decision to pursue registration with Study 3b, an approach guided by extensive FDA collaboration and executed through a BCC-USWM partnership (further details on the history of the registration approach are presented in Section 4.1.2).

#### 1.4.2 Program Designations and Sponsor Interactions

Under the program's Breakthrough Therapy Designation, frequent formal and informal meetings were held with FDA prior to submission of the NDA. A total of 5 Type B meetings were held

between 2020 and the NDA submission in late 2022, including two meetings dedicated to the methodology for the externally controlled comparison and a pre-NDA meeting where the results of the externally controlled analysis were discussed along with plans (and subsequent agreement) for the data package to support review of the NDA. FDA recommendations and guidance across these formal and additional informal interactions were closely followed.

#### 1.5 Dose Selection Background

Dose selection was informed by preclinical models establishing effective DFMO concentrations to inhibit neurosphere formation, adult studies establishing evidence of chemopreventative activity in other oncology indications, and preliminary signals of efficacy reported in the initial Phase 1 investigation of DFMO in HRNB. The initial investigation in patients with HRNB, NMTRC002 (Sholler 2015), was a typical dose escalation Phase 1 study in patients with active relapsed/refractory disease who were determined to have no further curative options available to them. The evaluated dose levels in NMTRC002 ranged from 500 mg/m<sup>2</sup> to 1500 mg/m<sup>2</sup> BID with urinary polyamine reduction and preliminary evidence of tumor stabilization and/or disease response (including 3 long-term survivors) observed across the dose range, supporting the selection of the target dose of 750 +/- 250 mg/m<sup>2</sup> BID for Study 3b, evaluating DFMO as a maintenance therapy for patients in remission. Pharmacokinetic evaluations in patients receiving the recommended dose confirm DFMO exposures above the threshold necessary for *in vitro* inhibition of ODC and concentrations achieving inhibition of neurosphere formation in preclinical models. Additional details of dose selection are provided in Section 3.5.

#### **1.6 Efficacy Findings**

#### 1.6.1 Study 3b

#### 1.6.1.1 <u>Study 3b Design</u>

NMTRC003/3b (referred to as Study 3b) is a prospectively designed, multicenter, open-label, single-agent study of DFMO in patients with HRNB in remission following completion of HRNB therapy.

Enrolled patients were to receive 27 consecutive cycles of oral DFMO at a (salt-based) dose of  $750 \pm 250 \text{ mg/m}^2 \text{ BID}$ , each cycle consisting of 28 days of treatment. Per protocol, patients were required to complete clinic visits for each 28-day cycle over the 2 years of DFMO treatment and were followed for EFS and OS until death or lost to follow-up for 5 years after DFMO treatment, totaling 7 years of study participation.

#### 1.6.1.2 Study Populations

Study 3b enrolled 140 patients into the intent-to-treat (ITT) population, which consisted of two cohorts with separate prespecified outcomes analyses due to recognized substantial differences in risk of disease relapse:

- 1) Stratum 1 (N=105) included patients who were in remission at the end of upfront first-line SoC therapy that included immunotherapy.
- 2) Stratum 2 (N=35) included patients who were in remission after therapy for a prior relapse or refractory disease.

#### 1.6.1.3 <u>Patients in Initial Remission After Upfront Treatment (Stratum 1)</u>

The Upfront Remission cohort (N=105) consisted of patients who achieved initial remission following standard upfront therapy of induction, consolidation, and anti-GD2 immunotherapy.

Study 3b Upfront Remission cohort results are presented first in terms of the prespecified endpoints comparing EFS and OS to the estimated point estimates from the historical EFS data published for ANBL0032 (Yu 2010), summarized in Section 1.6.1.4 and presented in detail in Section 6.2.2.3. These results led to the decision to continue the evaluation of Study 3b outcomes compared to patient-level data from ANBL0032 in order to rigorously compare outcomes with harmonization of the index date to the end of immunotherapy and propensity score matching to optimally balance prognostic factors between the groups being compared (summarized in Section 1.6.1.5 and presented in detail in Section 6.3).

#### 1.6.1.4 <u>Prespecified Study 3b Endpoints: Analyses of EFS and OS in Upfront Remission</u> <u>Patients (Stratum 1) vs Published Historical Rates</u>

Because of the inherent limitations of a single-arm study, the Sponsor and FDA agreed to utilize the COG Study ANBL0032 as an external reference population of patients who did not receive DFMO maintenance to compare against findings in Study 3b (detailed in Section 6.3.1).

The prespecified primary endpoint was a comparison of 2-year EFS between Upfront Remission patients (Stratum 1) from Study 3b and the ANBL0032 rate in patients with Upfront Remission following the end of immunotherapy that was estimated as 70%. The hypothesis was that DFMO maintenance could improve 2-year EFS by 10 percentage points over the historical rate. For the prespecified endpoint, EFS was measured from the first day of administration of DFMO until the first occurrence of relapse, progressive disease, secondary cancer, or death, or, if none of these events occurred, until the last contact with the patient. The median time from completion of immunotherapy to initiation of DFMO was 31 days.

The prespecified secondary endpoint was a comparison of OS against a 2-year historical rate from the ANBL0032 publication (Yu 2010), estimated at 85% from the end of immunotherapy. OS was measured from the first day of administration of DFMO until the first occurrence of relapse, progressive disease, secondary cancer, or death, or, if none of these events occurred, until the last contact with the patient.

All 105 Upfront Remission patients (Stratum 1) in Study 3b were included in the ITT population for the analysis. The Kaplan-Meier estimated EFS at 2 years was 0.85 (95% CI: 0.763, 0.904) in the DFMO group, with the lower bound of 76% higher than the prespecified historical control estimated rate of 70% (p=0.0021; Table 1). Results of the secondary endpoint of OS were also statistically significant in favor of the DFMO group (p=0.0030). Further, the 4-year EFS and OS demonstrated durable clinical benefit against the historical published rates beyond the DFMO two-year treatment period.

# Table 1:Kaplan-Meier Estimates of Event Free Survival (Primary) and OverallSurvival (Secondary) in Study 3b Upfront Remission Patients (Stratum 1) vsPrespecified Historical Control

|   | 2-Year Comparisons          |                            | 4-Year Comparisons          |                            |
|---|-----------------------------|----------------------------|-----------------------------|----------------------------|
| Parameter:                                      | Stratum 1<br>EFS<br>(N=105) | Stratum 1<br>OS<br>(N=105) | Stratum 1<br>EFS<br>(N=105) | Stratum 1<br>OS<br>(N=105) |
| Historical Control KM Estimate at 2-year/4-year | 0.7                         | 0.85                       | 0.6                         | 0.75                       |
| KM Estimate at 2-year/4-year                    | 0.85                        | 0.97                       | 0.83                        | 0.95                       |
| Standard Error                                  | 0.250                       | 0.577                      | 0.236                       | 0.447                      |
| p-value <sup>a</sup>                            | 0.0021                      | 0.0030                     | < 0.0001                    | < 0.0001                   |

EFS=event free survival; KM=Kaplan-Meier; OS=overall survival.

a. Two-sided p-value associated with z-score following a standard normal distribution derived using the Log-Log transformed observed and relevant historical KM Estimate as (observed value minus historical value)/standard error. The standard error is computed using the Log-Log transformation.

#### 1.6.1.5 Propensity Score Matched Analyses

The plan for the externally controlled comparison was developed in collaboration with FDA through a series of informal and formal meetings. Given the interpretation limitations of a single-arm study, patient-level data from ANBL0032 were identified as an appropriate external control to Study 3b, which was provided through a data transfer request from COG. The data transfer contained data from a total of 1328 patients receiving SoC that included immunotherapy. The majority of patients in the transfer were treated during the single-arm extension phase of ANBL0032 (see Section 6.3.2.1 for additional details).

The statistical analysis plan (SAP) incorporated FDA recommendations and was executed prior to the receipt of the final data transfer from COG, containing an additional 18 months of follow-up for outcome reporting in comparison to an earlier cut of data used for preliminary analyses.

#### 1.6.1.5.1 <u>Selection of External Control</u>

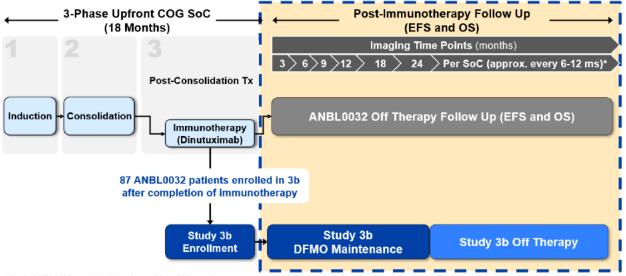
ANBL0032 was identified as an external control for Study 3b based on the following:

- Both studies enrolled mostly North American patients with HRNB with similar demographics and disease characteristics.
- Both studies had comprehensive data collection, including key covariates associated with outcome or heterogeneity.
- Study 3b enrolled patients treated with SoC HRNB therapy, predominately the current COG SoC for HRNB established by ANBL0032 (i.e., incorporating anti-GD2 immunotherapy following induction and consolidation).
- Study 3b was prospectively designed to include patients from ANBL0032, allowing comparison to EFS outcomes from the same study database, providing an opportunity to extend testing of the prospectively defined primary endpoint.
- The enrollment timelines for the two studies were partially overlapping, supporting upfront care practice similarity between treated and control patients (e.g., enrollment in ANBL0032 was the primary way to obtain dinutuximab in the enrollment timeline for Study 3b).

 EFS and OS outcomes for both studies were based on identical event criteria and were monitored with highly similar imaging modalities and frequency as well as comparable long-term follow-up practices.

Since the majority of Study 3b Upfront Remission patients (Stratum 1) directly participated in ANBL0032 prior to receiving DFMO, this provides a unique opportunity to compare groups of patients who received treatment in ANBL0032 that either did or did not receive subsequent DFMO maintenance, illustrated in Figure 1.

#### Figure 1: Schematic for ANBL0032 As External Control to Study 3b Supporting Comparisons of Patients with and without Post-Immunotherapy DFMO Maintenance



\* Study ANBL0032 mandated imaging at 30 and 36 months

COG=Children's Oncology Group; DFMO=eflornithine; EFS=event free survival; ms=months; OS=overall survival; SoC=standard of care; Tx=treatment

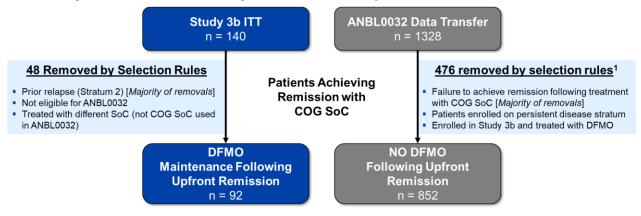
\* Study ANBL0032 mandated imaging at 30 and 36 months.

#### 1.6.1.5.2 Methods

In accordance with the FDA-negotiated SAP for the Propensity Score Match assessment, a series of selection rules were applied to the Study 3b ITT population to identify a group of patients who received upfront therapy on or consistent with ANBL0032 before achieving remission and being eligible to enroll on DFMO therapy (Figure 16). This primary treated group analysis population is the DFMO group (N=92). Within the DFMO group, 87 of 92 (94.6%) patients had participated directly in ANBL0032. The remaining 5 patients would have met eligibility criteria and received dinutuximab consistent with the study protocol.

Selection criteria were similarly applied to the ANBL0032 database of 1328 patients who were assigned (randomly or non-randomly) to dinutuximab therapy in order to identify a group of patients who could have been eligible to enroll on Study 3b, but did not receive DFMO. This primary control group analysis population is the NO DFMO group (N=852; Figure 2).

## Figure 2: Selection of Comparable Upfront Remission Patients for Study 3b and Study ANBL0032 Externally Controlled Comparison



<sup>1</sup>65% event rate observed in removed ANBL0032 population

COG=Children's Oncology Group; DFMO=eflornithine; ITT=intent-to-treat; SoC=standard of care

To optimize balance in important demographic and disease characteristics of the DFMO and NO DFMO populations to be compared, FDA advised the use of propensity score matching (PSM). Upon review of the literature and available data, 11 covariates were identified including factors that can influence prognosis or contribute to patient heterogeneity (Section 10.1.2).

The PSM model incorporated these 11 covariates in order to reduce the risk for bias. This includes a required exact matching on *MYCN* because of known important differences in tumor biology for patients with and without amplification of this oncogene. For PSM analyses, only patients with availability of data from all 11 covariates were eligible for the analysis, which restricted the treated group to N=91 and the control group to N=516, referred to as the DFMO-All Covariates and NO DFMO-All Covariates populations, respectively.

EFS and OS for both DFMO-All Covariates and NO DFMO-All Covariates were calculated to establish a common "Time Zero" defined as the time from end of immunotherapy to event or last contact in both populations. Using established PSM guidance, a propensity score was calculated for each patient in the All Covariates populations and patients within the overlapping range of scores for both groups were eligible for matching (resulting in removal of one DFMO patient with outlier score that could not be matched, for a total group of 90 to be matched).

The three NO DFMO-All Covariates group patients with closest propensity score were selected for comparison to each DFMO patient within the same *MYCN* category. In all cases, a target standardized difference of  $\pm$  0.1 was prespecified across all covariates and characteristics to strengthen the similarity of the populations (Section 6.3.2.3). For example, a *MYCN* amplified DFMO patient would be matched with 3 *MYCN* amplified NO DFMO patients with the closest propensity scores. The resulting 3:1 matched population (270 NO DFMO to 90 DFMO) was then compared for EFS (primary) and OS (secondary) outcomes.

#### 1.6.1.5.3 Externally Controlled Results

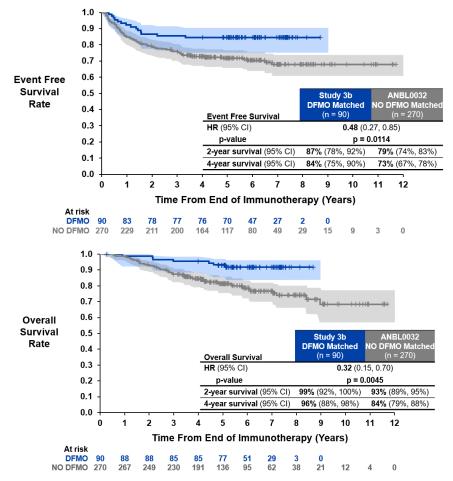
The resulting matched populations achieved excellent balance across key demographic and disease characteristics considered in the model, confirming that PSM was effective in identifying populations that were highly similar for comparison. Described below, the specified primary

endpoint and extensive sensitivity analyses of EFS and OS support consistent, statistically and clinically meaningful improvement in the DFMO group.

#### Primary and Secondary Endpoints

Figure 3 displays the Kaplan-Meier curves with 2-year and 4-year KM estimates along with the 95% confidence interval for EFS (top panel) as the primary endpoint and OS (bottom panel) as the secondary endpoint. The 4-year EFS rates were 84% and 73% for the DFMO and NO DFMO population, respectively (HR=0.48, 95% CI: 0.27, 0.85; p=0.0114). The OS comparison results in a hazard ratio of 0.32 (95% CI: 0.145, 0.702; p=0.0045). These results show the efficacy of DFMO in extending remission and support the conclusion that a lower rate of relapse predicts for a lower risk of death.

# Figure 3: Event Free Survival (top) and Overall Survival (bottom) Comparisons of Propensity Score-Matched Study 3b DFMO and ANBL0032 NO DFMO Populations



CI=confidence interval; COG=Children's Oncology Group; DFMO=eflornithine; EFS=event free survival; HR=hazard ratio; OS=overall survivalExternally Controlled Sensitivity Analyses

Extensive SAP-defined and post hoc sensitivity analyses were also conducted to assess the robustness of the primary PSM comparison results by testing for potential confounding or bias across covariates and patient characteristics. Extensive targeted sensitivity analyses were

conducted including suggestions or requests from the FDA. Sensitivity analyses included, but were not limited to, adjustments to:

- matching ratio,
- matching approach,
- changing patient selection criteria,
- changing timing variables,
- limiting the control population to only the overlapping era of enrollment to Study 3b,
- limiting the NO DFMO group to a more conservatively selected group of patients based on disease response and lead-in time,
- comparisons of overall populations without matching, and
- approaches to address missing data.

All sensitivity analyses consistently favored the DFMO group, with hazard ratios of approximately 0.4 to 0.6, similar to the primary result of approximately 0.5, and were statistically significant. A subset of the sensitivity analyses with the greatest potential clinical importance are shown in Figure 4 (full details are provided in Section 6.3.3.3.3).

## Figure 4: Selected PSM Sensitivity Analyses of Event Free Survival in Study 3b DFMO vs ANBL0032 NO DFMO-Matched Population

|  | # Events | / # Patients |                          |              |         |
|--|----------|--------------|--------------------------|--------------|---------|
|  | DFMO     | NO DFMO      | Favors treated with DFMO |              | p-value |
| Primary Analysis (DFMO vs NO DFMO 3:1)                               | 14 / 90  | 79 / 270     |                          |              | 0.0114  |
| Change PSM Model   |          |              |                          |              |         |
| Ratio 1:1  | 14 / 90  | 31 / 90      |                          |              | 0.0038  |
| Change Patient Selection   |          |              |                          |              |         |
| Remove NO DFMO patients with EFS ≤ 123 days                          | 14 / 90  | 72 / 270     | ⊢ <b>−</b> −−−−          |              | 0.0363  |
| Remove NO DFMO patients with a VGPR or PR at<br>end of Immunotherapy | 14 / 88  | 76 / 264     | <b>⊢</b> ●−−−−1          |              | 0.0164  |
| Landmark < 120 days with matched patients                            | 13 / 89  | 64 / 255     | <b>⊢</b>                 |              | 0.0440  |
| Remove 5 DFMO patients not treated on 0032                           | 13 / 84  | 74 / 252     | ⊢ <b>−</b> −−−−i         |              | 0.0125  |
| Keep only NO DFMO Contemporary patients (2:1)                        | 15 / 91  | 55 / 182     | ⊢ <b>●</b> −−−−1 ¦       |              | 0.0124  |
| MICE imputation of missing covariate data                            | 15 / 92  | 82 / 275     | ⊢ <b>●</b> −−−−1 ¦       |              | 0.0140  |
| Stratification of the propensity score                               | 15 / 91  | 150 / 516    |                          |              | 0.0125  |
| Inverse probability weighting  | 14 / 90  | 141 / 494    |                          |              | 0.0377  |
|  |          | 0            | .0 0.5 1.0               | 1.5          | 2.0     |
|  |          |              | Event Free Survival H    | lazard Ratio |         |

DFMO=eflornithine; EFS=event free survival; INRC=International Neuroblastoma Response Criteria; MICE=multiple-imputation-by-chained equation; PR=partial response per 1993 INRC; PSM=propensity score matching; VGPR=very good partial response per 1993 INRC

Note: Descriptions of analyses and rationales for selection are discussed in Table 15.

#### 1.6.1.6 Blinded Independent Central Review

To confirm lack of bias in EFS reporting from Study 3b Investigators (the local evaluators [LEs] of outcomes during the trial) and following guidance from FDA, data from all 92 patients in the DFMO group were assessed in a blinded independent central review of imaging (BICR) for outcome determination by independent radiologists. IR-determined outcomes were evaluated for alignment with LE-reported outcomes in Study 3b. BICR-determined outcomes were also used in comparative analyses to patient level data in the external control ANBL0032 database.

When compared to the LE-determined outcomes for the same 92 patients, there were 90 confirmed assessments, with only two discordant post-Baseline outcomes. In one instance, the LE reported a relapse event while the IR did not. In the other case, the IR determined a relapse event while the LE determined no event. In summary, both LEs and IRs determined 15 total EFS events, although the groups determined to have events differed by one patient. Concordance was assessed according to the SAP by the calculation of Cohen's kappa, which confirmed near-perfect agreement.

The results of the externally controlled EFS comparisons using IR-determined outcomes with the LE outcome-based analyses were as expected given near-perfect agreement between LE- and IR-determined EFS events. Overall, the BICR confirmed that little-to-no bias existed in the assessment and reporting of EFS events by Study 3b Investigators.

#### 1.6.2 Confirmatory Efficacy Data

#### 1.6.2.1 Overview of Confirmatory Efficacy Data

The NDA contains several components of confirmatory data, which support an assessment of efficacy primarily determined from the externally controlled Study 3b analyses. Confirmatory data include (1) evidence directly supporting the relapse risk reduction benefit observed in Study 3b vs ANBL0032 comparisons, (2) evidence of DFMO anti-tumor activity in patients with active disease, and (3) confirmation of expected pharmacodynamic response in patients receiving the recommended dose. These clinical data are further supported by a foundation of preclinical mechanistic and animal model research, which has elucidated the effects of DFMO in neuroblastoma. The totality of the supporting data is illustrated in Table 2.

| Table 2:     | Summary of Confirmatory Evidence Supporting DFMO Benefit for |
|--------------|--|
| Patients wit | th HRNB  |

|   |   | Pharmacodynamic   |
|---|---|---|
| Maintenance Efficacy  | Anti-tumor Activity   | Response  |
| <ul> <li>BCC001, second source for<br/>externally controlled analysis of<br/>Study 3b outcomes,<br/>comparisons show consistent<br/>results to pivotal (vs ANBL0032)<br/>analyses (Section 6.4.1.1)</li> <li>Cohort of patients receiving<br/>DFMO maintenance after<br/>European (SIOPEN) upfront<br/>SoC show similar EFS as Study<br/>3b (Section 6.4.1.2)</li> <li>Study 3b patients in remission<br/>after R/R therapy report 46%<br/>EFS at 4 years (Section 6.4.1.3)</li> <li>Expanded access study patients<br/>report similar EFS trends<br/>(Section 6.4.1.4)</li> <li>Overall, EFS curves show<br/>consistently durable remission<br/>after 2 years</li> </ul> | <ul> <li>Phase 1 study (NMTRC002)<br/>in patients with active R/R<br/>disease and short survival<br/>expectations showed longer<br/>than expected PFS and 3 of<br/>18 long-term survivors<br/>(Section 6.4.2.1)</li> <li>Expanded access study in<br/>patients with active HRNB<br/>showed ~50% with disease<br/>improvement (Section 6.4.2.2)</li> </ul> | <ul> <li>NMTRC002 and Study 3b demonstrated decreasing trends in urinary polyamines following treatment with DFMO patients with active R/R disease and patients in remission<sup>2</sup> (Section 6.4.3.1)</li> <li>NMTRC012 demonstrated increasing trends in Let-7 microRNA expression following treatment with DFMO (Section 6.4.3.2)</li> </ul> |

DFMO=eflornithine; EFS=event free survival; HRNB=high-risk neuroblastoma; R/R=relapsed/refractory;

SIOPEN=Society For Paediatric Oncology European Neuroblastoma.

1. (Lewis 2020); 2. (Sholler 2015).

The individual components of confirmatory data supporting DFMO benefit each have important limitations which are important to acknowledge. However, the strength of the supporting research is based on the quantity, variety, and consistency of the evidence rather than emphasis on any single data component. The totality of the evidence contributes to the assessment, attributability, and understanding of the magnitude of relapse risk reduction benefit concluded from the pivotal study comparisons. Together with the pivotal Study 3b vs. ANBL0032 externally controlled study, the confirmatory data is sufficient to meet FDA's threshold for demonstrating substantial evidence of effectiveness.

#### 1.7 Safety Findings

The safety of DFMO has been studied in a safety population of 311 patients with HRNB treated with the to-be-marketed DFMO drug product at the recommended dose level for a duration of up to 2 years. This safety population adequately reflects the intended patient population. The safety profile of DFMO supports that the therapy is generally well tolerated. Risks of myelosuppression, hepatotoxicity, and hearing loss were identified but rarely resulted in treatment discontinuation and are considered manageable with appropriate monitoring through periodic assessments.

The safety population comprises patients with HRNB enrolled in either Study 3b (specifically, those patients enrolling after the protocol amendment from NMTRC003 to 3b; n=52) or in the similarly designed, actively enrolling, prospective, single-arm, open-label study, NMTRC014 ("Study 14"; n=259). The safety profile of DFMO was characterized across studies by reporting of AEs as well as protocol-specified audiograms and laboratory assessments. In addition electrocardiograms (ECGs) were done in Study 14 only.

Within the pooled safety population (n=311), 216 patients (69.5%) received treatment for at least one year at the time of the data cutoff, with many Study 14 patients continuing on DFMO therapy at the time of the data cutoff for the NDA. The median duration of exposure was 2 years (interquartile range [IQR] 280 - 731 days).

Regarding safety results:

- Grade 3 or 4 AEs were reported in 43.7% of the pooled safety population.
  - Grade 3 or 4 AEs reported in ≥ 3% of the pooled safety population were hypoacusis (11.9%), alanine aminotransferase (ALT) increased (11.9%), aspartate aminotransferase (AST) increased (6.8%), pyrexia (4.2%), anemia (3.9%), and neutrophil count decreased (3.5%).
- Most AEs resolved without the need for discontinuation or dose modification.
  - AEs resulted in dose modification (temporary interruption or dose reduction) in 11.9% of patients.
  - Study drug was discontinued due to an AE in 5.1% of patients.
  - The most common AE leading to dose modification or discontinuation was hypoacusis.
- Serious AEs (SAEs) occurred in 16% of patients.
- There were no deaths due to AEs.

- DFMO has an established ototoxicity risk, and progressive hearing loss is a common longterm effect in patients with pediatric cancer caused by exposure to platinum-based chemotherapies, so audiograms were required.
  - Baseline audiograms confirmed expected pre-treatment hearing loss in 82.7% of patients.
  - Within the pooled safety population, 12.9% of patients had hearing loss that worsened by at least 1 grade from baseline (per the Common Terminology Criteria for Adverse Events; CTCAE v4.0), and 12.2% had hearing loss that worsened by at least 1 grade from baseline and worsened to Grade 3.
  - Among patients with dose modification or discontinuation due to hearing loss, 63% improved or resolved to baseline.
- Hepatic abnormalities and myelosuppression-related AEs are established risks and can be managed with standard interventions or dose modifications.

Periodic monitoring is recommended as part of routine follow-up care to monitor for late effects after completion of upfront treatment. The frequency of long-term monitoring can vary based on the therapy administered during upfront treatment (COG 2018). Audiograms and laboratory assessments performed during routine long-term monitoring can support safety monitoring and implementation of recommendations for management and mitigation of side effects through dose interruption and/or reduction, when indicated.

#### 1.8 Benefit-Risk Summary

HRNB is a deadly disease, with a dramatic impact on patients and their families who must endure a year and a half of upfront treatment associated with physical, emotional, and psychological pain to potentially reach a state of remission. Even after achieving remission, the journey is not over for many patients because 30% or more will relapse.

DFMO was developed to improve long-term outcomes in patients who achieve remission upon completion of HRNB SoC. The unexpectedly high EFS and OS results observed in Study 3b compared to published historical controls prompted BCC, together with USWM, to work to expedite the availability of DFMO for patients in the US. The promising survival improvement observed in Study 3b and the expected timeline required to conduct a follow-on RCT factored into discussions with FDA to identify a viable alternative registration pathway in alignment with existing regulatory framework.

USWM and BCC collaborated with the FDA to identify and implement an appropriate external control using propensity score matching to provide a more objective analysis and help limit bias. Given the high similarity in demographics, disease characteristics, and treatment patterns, patients participating in ANBL0032 offered a unique opportunity for a comparison population. The robustness as an external control is further augmented by the fact that 95% of Study 3b patients included in the PSM received upfront SoC therapy as part of their participation in ANBL0032. A detailed overview of PSM methodology and analyses are provided in Appendix 10.1.

With the robust comparisons to an appropriate external control database, Study 3b is an adequate and well controlled study that establishes meaningful benefits of DFMO in the treatment of HRNB.

DFMO treatment following upfront therapy resulted in extended remission and a lower rate of relapse, with a hazard ratio indicating approximately 50% reduction in the risk of an EFS event

compared to propensity score matched external control patients who did not receive DFMO (Table 3). The improvement in the relapse rate was supported by an improvement in survival; and EFS and OS results were consistent across a large number and variety of sensitivity analyses.

# Table 3:Event Free Survival (primary) and Overall Survival (secondary)Comparison of Propensity Score-Matched Study 3b DFMO vs ANBL0032 NODFMO Populations

| Survival Hazard Ratio: | Study 3b<br>DFMO-Matched<br>(n = 90) | ANBL0032<br>NO DFMO-Matched<br>(n = 270) |  |
|------------------------|--------------------------------------|--|--|
| EFS HR (95% CI)        | 0.48 (0.27, 0.85)                    |  |  |
| p-value                | p = 0.0114                           |  |  |
| OS HR (95% CI)         | 0.32 (0.15, 0.70)                    |  |  |
| p-value                | p = 0.0045                           |  |  |

EFS=event free survival; HR=hazard ratio; OS=overall survival.

The risk of death for patients receiving DFMO maintenance treatment was approximately one-third of that to patients who did not receive DFMO, supporting the role of DFMO in reducing the risk of relapse.

The conclusions from the study are supported by extensive and robust analyses, with multiple approaches to address potential biases. The most relevant analyses are provided in Section 6.3.3, and other analyses all support a consistent conclusion that DFMO maintenance improves EFS and OS. Additionally, the results are reinforced by evidence that further supports the benefit of DFMO. The totality of these data — both in quantity and quality — underscores the consistent and compelling role of DFMO as a maintenance therapy to improve long-term outcomes in patients with HRNB achieving remission from upfront therapy.

Prospective safety evaluations in patients with HRNB support characterization of the DFMO safety profile. Common Grade  $\geq$  3 events included hearing loss, increased ALT and AST, and potentially clinically significant anemia and blood cell count changes. These findings warrant monitoring with audiograms and laboratory assessments to identify potentially important changes and to adjust or temporarily suspend dosing when clinically warranted. Audiograms and laboratory testing, recommended as part of routine follow-up care in patients with HRNB, can support safety monitoring and implementation of recommendations for management and mitigation of side effects.

DFMO has a strongly favorable benefit-risk profile. DFMO improves treatment outcomes in patients with HRNB following the completion of multiagent, multimodality high-risk neuroblastoma therapy, during the highest risk period for a patient to relapse, with good tolerability that permits chronic dosing and risks that can be monitored and managed. This treatment addresses an unmet medical need for which no therapies currently exist.

#### 2 BACKGROUND ON HIGH-RISK NEUROBLASTOMA

#### Summary 3 1

- Neuroblastoma is a rare pediatric cancer with approximately 800 patients per year diagnosed in North America
- Approximately half of children diagnosed with neuroblastoma are classified as having high-risk neuroblastoma (HRNB)
- Available data suggest 5-year OS probabilities of only 50% 60% for HRNB children from initial diagnosis (Bagatell 2023; Park 2013; Park, Eggert and Caron 2008; Yu 2010)
- The current Children's Oncology Group (COG) SoC for HRNB includes three phases of treatment: induction, consolidation, and post-consolidation
- The efficacy of available treatments varies, and current treatment options place a high burden on the patient, including both acute side effects and long-term risks
- One-third of patients achieving remission at completion of standard of care upfront therapy are at risk of relapse
- The majority of patients that relapse will not survive 5 years, indicating a clear need for additional therapies to help patients maintain remission

#### 2.1 Overview of High-Risk Neuroblastoma

Neuroblastoma is a rare pediatric cancer affecting approximately 800 patients per year in North America, qualifying it as an orphan disease. Although rare, neuroblastoma is the most common extracranial solid tumor in children, accounting for approximately 8% of all childhood cancers and 15% of childhood cancer mortality (Brodeur 2003; Johnson 2009; Maris 2010; Park, Eggert and Caron 2010).

Neuroblastoma is a solid cancerous tumor that begins in the nerve cells outside the brain of infants and young children. Neuroblastoma can start in the nerve tissue near the spine in the neck, chest, abdomen, or pelvis, but it most often begins in the adrenal glands. Neuroblastoma typically develops in infants and young children, with 90% of diagnoses occurring by age 5.

Staging of neuroblastoma is determined by the internationally recognized criteria which have been developed by the International Neuroblastoma Staging System (INSS) and the International Neuroblastoma Risk Group Staging System (INRGSS). INSS staging categories were reported for COG and BCC trials during the DFMO program and range from Stage 1 through 4S. Stage is determined based on the location of the tumor, the extent to which it can be excised, and if and to which parts of the body the cancer has spread. Stages 1 - 3 indicate localized disease whereas Stage 4 indicates disease with distant metastases into other areas of the body.

#### 2.1.1 Risk Stratification

Recommended treatment for HRNB involves an intense, multimodal approach discussed in greater detail in Section 2.2. Risk stratification is extremely important in neuroblastoma because patients with versions of the disease associated with more favorable prognosis with less extreme treatment should not be subjected to the highly toxic therapies reserved for high-risk disease.

Patients are stratified by several factors that define the risk of relapse, including age, disease stage, and other tumor attributes, according to criteria developed by the International Neuroblastoma Risk Group (Cohn 2009) and largely adopted by COG in a recent revision to their risk stratification criteria (Irwin 2021). These criteria include a combination of clinical, pathologic, and genetic markers used to predict the clinical behavior of the tumor, how it will respond to treatment, and the risk that the disease will relapse, including:

• Stage of disease

- Age at time of diagnosis
- MYCN gene status
- Tumor ploidy
- Tumor histopathology

Based on these factors, patients are diagnosed with low-, intermediate-, and high-risk disease.

Children with low- or intermediate-risk neuroblastoma have a good prognosis, with 5-year OS probabilities of greater than 90% with less aggressive treatment, which ranges from monitoring alone to surgery with limited exposure to anticancer interventions.

However, 50% of diagnosed children will be classified as having HRNB. High-risk stratification is assigned according to objective criteria defined through international research group guidelines. The International Neuroblastoma Risk Group definitions of high-risk disease as adopted by COG and used in the era of the DFMO clinical program and ANBL0032 are outlined in (Table 4). Ongoing review and revision of risk and outcome data by international research groups can inform periodic changes in risk stratification, with the latest version in 2021.

Patients with HRNB have a much poorer prognosis than those with low- or intermediate-risk disease, despite a far more aggressive and toxic series of treatments. Various sources suggest 5-year OS probabilities of only 50% – 60% from initial diagnosis for children with HRNB (Bagatell 2023; Park 2013; Park, Eggert and Caron 2008; Yu 2010).

## Table 4:Summary of Criteria for High Risk Neuroblastoma at Time of DFMOClinical Program and ANBL0032

#### High-Risk Neuroblastoma Stratification Criteria

- Stage 2A or 2B disease and MYCN amplification
- Stage 3 disease and MYCN amplification
- Stage 3 disease in children aged 18 months or older, no *MYCN* amplification, and unfavorable histopathology
- Stage 4 disease in children younger than 12 months and MYCN amplification
- Stage 4 disease in children between 12 months and 18 months old with *MYCN* amplification, and/or diploidy, and/or unfavorable histology
- Stage 4 disease in children 18 months or older
- Stage 4S disease and MYCN amplification

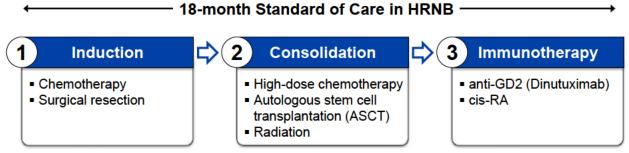
Source: 2006 COG neuroblastoma risk stratification criteria summarized in (Liang 2020).

#### 2.2 HRNB Upfront Standard of Care

The COG SoC for HRNB includes three phases of treatment: induction, consolidation, and postconsolidation immunotherapy (Figure 5). Treatment, over approximately 15-18 months, includes chemotherapy and surgical resection (induction), high dose chemotherapy with ASCT and radiation (consolidation), followed by anti-GD2 immunotherapy and 13-cis-retinoic acid (also known as isotretinoin, cis-RA) (post-consolidation immunotherapy).

The consolidation phase currently recommended by COG includes tandem ASCT, although practices vary based on individual institution practices and individual patient considerations. In all cases, SoC incorporates post-consolidation immunotherapy.

#### Figure 5: Children's Oncology Group Standard of Care in HRNB



ASCT=autologous stem cell transplant; RA=retinoic acid.

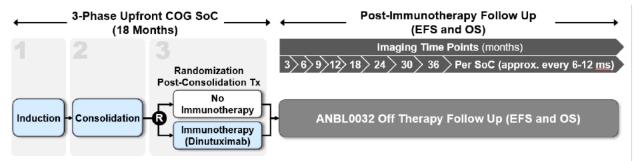
#### 2.2.1 Immunotherapy Addition to Standard of Care: Study ANBL0032

The most recent evolution of the SoC resulted from the landmark trial, ANBL0032, which established efficacy of post-consolidation immunotherapy. ANBL0032 was a large Phase 3 randomized open-label trial in patients with HRNB investigating anti-GD2 antibody, ch14.18 (dinutuximab, Unituxin<sup>®</sup>) which supported improved EFS when added to then-current maintenance therapy (Yu 2010).

Patients who had completed induction and consolidation were randomized to a post-consolidation regimen of cis-RA (Regimen A), or cis-RA plus sargramostim, dinutuximab and aldesleukin (Regimen B). Patients were assessed for disease response consistent with the 1993 International Neuroblastoma Response Criteria (INRC) prior to study enrollment (end of consolidation), optionally at Cycle 3, and at end of immunotherapy (Cycle 6) (Brodeur 1993).

After completion of the last cycle of cis-RA (Cycle 6), disease status was evaluated every 3 months during the first year off treatment, every 6 months for the next two years, then only if relapse was suspected. Patients were followed long-term based on SoC for a total of up to 10 years from enrollment (Figure 6).

#### Figure 6: Study ANBL0032 Design



COG=Children's Oncology Group; EFS=event free survival; ms=months; OS=overall survival; R=randomization; SoC=standard of care; Tx=therapy.

Patients with HRNB who met the key eligibility criteria in Table 5 were enrolled in study ANBL0032.

| I/E Category                                 | Study ANBL0032 Eligibility Criteria   |
|--|---|
| Diagnosis                                    | HRNB at time of original diagnosis (patients not originally diagnosed as high-risk but later determined to be high-risk were eligible)  |
| Age at diagnosis                             | < 31 years  |
| Previous<br>treatments                       | Completed induction chemotherapy, followed by stem cell transplant and radiation therapy  |
| Timing from<br>previous<br>treatment(s)      | <ul> <li>ASCT performed within 12 months after starting induction therapy</li> <li>Enrollment preferably between Day 56 and Day 85 (but no later than Day 200) after</li> </ul>   |
| Pre-ASCT<br>disease<br>status                | <ul> <li>final ASCT</li> <li>Met International Neuroblastoma Response Criteria (INRC) for CR, VGPR, or PR for primary site, soft tissue metastases, and bone metastases</li> <li>Bone marrow ≤ 10% tumor (of total nucleated cellular content), seen on any bilateral aspirate/biopsy specimens collected pre-ASCT and/or pre-enrollment</li> </ul>   |
| End of<br>consolidation<br>disease<br>status | <ul> <li>A determination of mandatory disease staging must be performed within 4 weeks before enrollment (tumor imaging studies including CT or MRI, MIBG scan, bone marrow aspiration &amp; biopsy)</li> <li>For those with residual disease before radiotherapy, re-evaluation of irradiated residual tumors is preferably performed at the earliest 5 days after completing radiotherapy. Patients with residual disease are eligible. Biopsy is not required. Patients who have biopsy proven residual disease after ASCT will be enrolled on Stratum 07</li> <li>Patients must not have progressive disease at the time of study enrollment except for protocol-specified bone marrow response, as defined in the details of the pre-ASCT disease status criteria</li> </ul> |

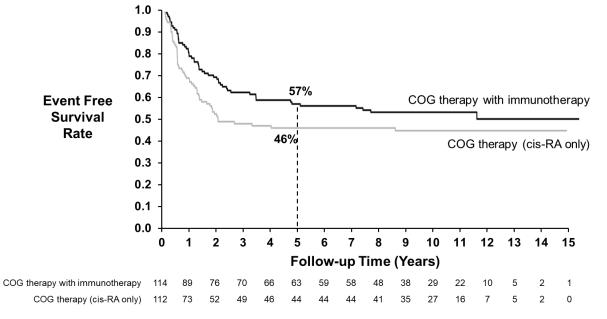
#### Table 5: Study ANBL0032 Key Inclusion/Exclusion Criteria

ASCT=autologous stem cell transplant; CR=complete response; CT=computed tomography; HRNB=high-risk neuroblastoma; I/E=inclusion/exclusion; INRC=International Neuroblastoma Research Consortium; MIBG=metaiodobenzylguanidine; MRI=magnetic resonance imaging; PR=partial response; VGPR=very good partial response.

The ANBL0032 study design included a randomization period (from 18 October 2001 to 16 April 2009), during which patients were randomized to receive either cis-RA alone (Regimen A), or cis-RA in combination with dinutuximab, aldeslukin, and sargramostim (Regimen B), as part of their maintenance therapy.

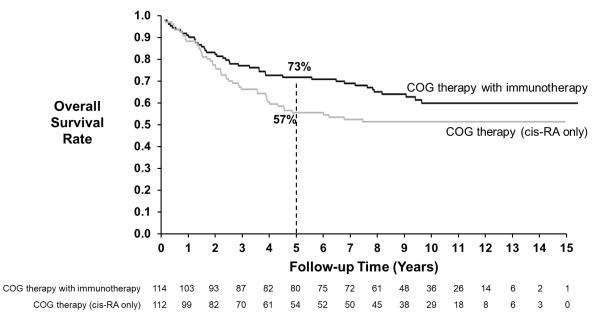
Following an interim analysis, which favored the immunotherapy + cis-RA treatment arm, the randomized phase of the study was concluded in April 2009. The results of the interim analysis were published (Yu 2010) demonstrating a significant improvement in both EFS and OS. The interim results supported registration of dinutuximab (approved in 2015) and continuation of the study with an expanded cohort in which all patients received dinutuximab therapy. More recent reporting of long-term outcomes from the randomized phase continue to demonstrate the dinutuximab treated patients experience improved EFS (Figure 7) and OS (Figure 8), but the more mature data showed a further decline in outcomes compared to the 2-year results reported in 2010.

#### Figure 7: Study ANBL0032 Randomized Phase Results – Event Free Survival



COG=Children's Oncology Group; SoC=standard of care; w/o=without. Adapted from (Yu 2021).

#### Figure 8: Study ANBL0032 Randomized Phase Results – Overall Survival



COG=Children's Oncology Group; SoC=standard of care w/o=without. Adapted from (Yu 2021).

Results from the ANBL0032 expansion cohort enrolling an additional 1,183 non-randomized patients were recently published (Desai 2022). Demographic and disease characteristic

distribution were highly similar to the randomized group of patients, and long-term EFS and OS outcomes were also highly consistent, as shown in Table 6.

### Table 6:Published ANBL0032 5-Year Event Free Survival and Overall Survivalin Randomized and Non-Randomized Phases

| ANBL0032 Patients Assigned to Immunotherapy | Randomized<br>COG SoC Therapy<br>[with Immunotherapy]<br>(N=114) <sup>1</sup> | Non-Randomized<br>COG SoC Therapy<br>[with Immunotherapy]<br>(N=1183) <sup>2</sup> |
|---|---|--|
| Event Free Survival at 5 years              | 57%   | 61%  |
| Overall Survival at 5 years                 | 73%   | 72%  |

COG=Children's Oncology Group; SoC=standard of care.

Note: 1328 patients were assigned to dinutuximab treatment, including 114 randomly assigned to dinutuximab in the randomized phase, 1183 non-randomly assigned to dinutuximab in the extension phase, and an additional 31 of whom 27 were non-randomly assigned to dinutuximab in ANBL0032 Stratum 7 (patients with biopsy confirmedactive disease or new bone marrow involvement) during the randomized phase, and 4 patients assigned to dinutuximab but did not receive treatment. The additional 31 patients are not represented in the table as outcomes have not been reported for these patients, although they were included in the data transfer from COG. 1. (Yu 2021); 2. (Desai 2022).

ANBL0032 is the largest prospective study of HRNB in the last two decades and is a recognized contemporary source of data on long-term outcomes for patients with HRNB who receive all phases of upfront treatment. Between patients randomly and non-randomly assigned to treatment with dinutuximab, the study evaluated outcomes for a total of 1328 patients receiving induction, consolidation and immunotherapy, providing a large database from which current demography, disease attributes, and long-term outcomes for the HRNB population receiving current SoC can be characterized.

#### 2.2.2 Current Upfront Treatment SoC Phases

#### 2.2.2.1 Induction

The goal of induction therapy is to obtain maximal reduction in tumor burden.

- The induction phase typically consists of 5 6 cycles of chemotherapy, stem cell harvest, and surgery.
- The dose and timing during the induction cycle of chemotherapy agents have been finetuned over time, but the list of particular agents has largely remained unchanged since the late 1990s/early 2000s.
- Chemotherapy agents used during induction include cyclophosphamide, platinum equivalents (cisplatin or carboplatin), vincristine, doxorubicin and etoposide. More recently, topotecan in combination with cyclophosphamide have been added to early induction cycles.

Patients with an adequate response after induction treatment move to the next phase of treatment, consolidation.

#### 2.2.2.2 <u>Consolidation</u>

Consolidation includes high dose chemotherapy, stem cell transplant, and radiation therapy.

- Patients will undergo single or tandem transplants in the US, with current COG SoC recommending tandem.
- Conditioning chemotherapy agents differ depending on the approach.
  - Single transplants are typically performed with high dose conditioning agents of either busulfan and melphalan (Bu/Mel) or carboplatin, etoposide and melphalan (CEM).
  - Tandem transplants typically employ cyclophosphamide and thiotepa (C&T), then CEM.
- High dose chemotherapy and radiation therapies employed during the consolidation phase are meant to destroy cancer cells; but as a result, they also destroy the patient's bone marrow tissue, the source of new blood cell generation.
- In follow-up to the high dose chemotherapy, patients receive a stem cell transplant to support bone marrow recovery.

A recent study by COG concluded that tandem transplant using CEM/C&T resulted in improved EFS compared with single CEM transplant in patients with HRNB (Park 2019). The results of this study resulted in the COG upfront SoC incorporating recommendations for tandem transplant. Another study compared CEM to Bu/Mel for ASCT and found improved outcomes with Bu/Mel of similar magnitude to those achieved with tandem ASCT in COG's study (Ladenstein 2017). As a result of these studies, both single (more commonly with Bu/Mel) and tandem ASCT remain part of the HRNB standard consolidation regimen, as practices vary by US institution and also by individual patient (e.g., those experiencing significant side effects or requiring extended recovery time for the first ASCT may not be considered for tandem). A study comparing Bu/Mel and C&T/CEM tandem transplants are in progress but have not yet been reported (COG trial ANBL1531, NCT03126916).

Consolidation therapy also involves post-stem cell transplant localized radiation which can be directed at the primary tumor bed and/or metastatic sites.

Because residual disease may remain and the risk of relapse remains high despite intensive induction and consolidation treatment regimens, the post-consolidation immunotherapy phase was developed.

#### 2.2.2.3 <u>Post-Consolidation</u>

Following the ANBL0032 protocol, post-consolidation treatment comprises six cycles of treatment. Dinutuximab is administered in the first five cycles along with granulocyte-macrophage colony-stimulating factor (GM-CSF) and cis-RA. Aldesleukin (IL-2), which augments antibody-dependent cell-mediated cytotoxicity, was administered with anti-GD2 antibody at alternating cycles until 2019 when IL-2 was removed from SoC due to benefit-risk considerations (Ladenstein 2018). The sixth cycle of immunotherapy is a course of cis-RA alone.

The most common post-consolidation anti-GD2 immunotherapy in the US is dinutuximab as applied in the COG recommended upfront treatment paradigm; however, other standard upfront

treatment protocols have been developed by Memorial Sloan Kettering and SIOPEN, utilizing alternate anti-GD2 immunotherapies 3F8 and dinutuximab-beta, respectively.

#### 2.2.3 Evaluation of Disease Response During Upfront Treatment

Response to treatment following each phase of upfront therapy is commonly assessed in clinical trials according to the INRC. At the time of the conduct for both Study 3b and ANBL0032, the 1993 response criteria were used. The INRC published updated response criteria in 2017. Response categories from the 1993 version include objective requirements to assess disease response to treatment in the following categories: Complete Response (Henderson), Very good partial response (VGPR), partial response (Molenaar), mixed response (MR), no response (NR, sometimes also recorded as stable disease [SD]), and progressive disease (PD).

At the end of immunotherapy, patients will routinely undergo imaging studies and bone marrow assessment to determine disease status. Metaiodobenzylguanidine (MIBG) and MRI/CT are the most commonly used imaging modalities, although PET imaging is sometimes used. Patients who adequately respond to therapy without progression through the completion of upfront SoC are considered to be in remission, do not receive further pharmacotherapy, and are monitored for signs of relapse.

#### 2.2.4 Surveillance

Following the completion of all three phases of upfront treatment, patients are followed closely to assess for potential recurrence of disease.

- Follow-up care generally includes clinic visits, laboratory assessments, and imaging.
- Choice of imaging studies depends primarily on the imaging techniques used during initial treatment to monitor treatment response.
  - Most often, MIBG and MRI/CT scans will be utilized to monitor for disease recurrence.
  - The INRG does not provide specific recommendations for end of treatment imaging intervals; however, typical frequency of imaging studies to monitor for relapse is at approximately 3, 6, 9, 12, 18, and 24 months, with some hospitals continuing imaging on 6-to-12-month intervals for an additional 1 to 3 years. Since the risk of relapse is lower after 5 years from the completion of upfront therapy, many institutional HRNB policies include routine scanning for up to 5 years postupfront therapy, and then only as clinically indicated thereafter.
- Bone marrow aspiration and biopsy are generally only performed if relapse is suspected (Kembhavi 2015).
- General follow-up clinic visits remain a part of HRNB survivorship treatment plans for many years even after imaging studies are no longer routinely performed.

#### 2.2.5 Treatment Burden with Standard of Care Therapy

Despite advancements in treatment, high-risk neuroblastoma remains a formidable disease with poor success rates. The efficacy of available treatments varies, and not all children respond equally to therapy. Many children experience disease progression or relapse, indicating the need for more effective interventions.

Regarding patient burden with current treatment options:

- Chemotherapy, a cornerstone of neuroblastoma treatment, can cause side effects such as nausea, vomiting, hair loss, susceptibility to potentially deadly infections, and hearing loss.
- Surgery, while essential for removing tumors, may not always be feasible due to the tumor's location or the extent of disease spread. All surgical interventions carry serious risks related to anesthesia and complications.
- Transplant, which involves high doses of chemotherapy, carry even higher risks than induction chemotherapy, with complications and/or infections being fatal in some cases.
- Immunotherapy risks include infusion-related reactions, neurotoxicity, hematologic toxicity, widespread pain, hypersensitivity at the infusion site, rare cases of capillary leak syndrome, and other complications.

Late effects of upfront therapy create significant additional burden on children and their families. These effects can include cardiotoxicities, hearing loss, endocrine dysfunction, kidney and liver damage, increased risk of secondary malignancy, neurological effects, psychological and emotional problems, and infertility. However, these risks are considered acceptable given they offer a chance to achieve remission from this fatal disease.

#### 2.3 Patient Unmet Medical Need

The prognosis of HRNB has improved through the evolution of treatment; however, EFS rates which characterize the proportion of the patient population that are able to achieve and maintain durable remission even with current, optimized upfront therapy show a significant portion of patients will experience relapse following diagnosis (Bagatell 2023). Long-term remission was only achieved in approximately 60% of patients 4 to 5 years from the beginning of immunotherapy (Bagatell 2023; Smith and Foster 2018) in ANBL0032, and similar outcomes are observed with alternate SoC incorporating immunotherapy (e.g., dinutuximab-beta by SIOPEN (Ladenstein, 2020) or 3F8 by Memorial Sloan Kettering (Cheung 2012). As a result, OS remains only at 50% – 60% from diagnosis (Bagatell 2023; Smith and Foster 2018)). This outlook improves for patients who are able to complete upfront treatment, but still approximately 30% will relapse within 2 years from the end of immunotherapy (Yu 2021). This reinforces the need for additional therapies that can further improve EFS or maintain remission because avoiding relapse is key to survival in HRNB.

Relapsed or refractory patients face an even greater challenge of overcoming disease recurrence or treatment resistance to achieve or re-achieve lasting remission. Patients who experience relapse are referred to second-line therapy to try to treat their disease back into remission, but even when remission is attained, such patients are at high-risk for subsequent, multiple relapses and have a very poor long-term prognosis. Based on a recent COG meta-analysis of relapsed HRNB studies, 94% of high-risk patients treated in relapse studies between 2002 and 2014 experienced further disease progression and 85% died within 4 years of relapsing (London 2017). These outcomes remain largely unchanged from survival outcomes reported a decade earlier by Santana (2008) for patients treated in relapse therapy studies between 1991 and 2002.

Today's standard relapse therapy evolved from the preliminary published findings of ANBL1221 (Mody 2017; Mody 2020), which showed a chemoimmunotherapy regimen comprising

dinutuximab, irinotecan, temozolomide, and GM-CSF achieved encouraging preliminary outcomes. Outcomes beyond 1-year estimates have not been reported due to the immaturity of the data. However, the preliminary curves reported show continued decline in survival beyond the first year of follow-up.

Because of the significant differences in expected outcomes, patients with relapsed or refractory disease are studied separately from those with newly diagnosed neuroblastoma. While treatments for relapsed neuroblastoma vary from upfront treatment, the risks of these treatments are similar, with risks of further treatment compounding late effects the patient may already have experienced from upfront treatment.

The limitations in efficacy and acute and late effects of current treatments, as well as the risk of compounding toxicity for patients who experience relapse, underly the urgency for improved therapeutic strategies that can enable patients to retain remission while minimizing incremental risks.

There is a need to further improve long-term survival rates in HRNB by introducing therapies that can minimize the risk of relapse that is associated with extremely high mortality. The DFMO clinical program was specifically designed to investigate if maintenance with single-agent DFMO for two years following immunotherapy could further improve EFS and OS beyond the rates reported from ANBL0032.

## 3 PRODUCT DESCRIPTION

## Summary

- DFMO (difluoromethylornithine, eflornithine) is a specific, enzyme-activated, irreversible inhibitor of ornithine decarboxylase (ODC), a key enzyme in mammalian polyamine biosynthesis
- *In vivo* models have shown efficacy for DFMO as an inhibitor of bladder, colon, esophagus, small and large intestine, liver, mammary gland, glandular stomach, skin, pancreas, and tongue carcinogenesis in *in vivo* animal models (Meyskens 2008)
- Recent work utilizing *in vivo* and *in vitro* models of neuroblastoma suggest that cancer stem cells (CSCs) may be selectively targeted by DFMO via its inhibition of ODC and associated downstream effects
- The recommended dose of oral DFMO is 576  $\pm$  192 mg/m<sup>2</sup> (equivalent to salt-based doses of effornithine HCl 750  $\pm$  250 mg/m<sup>2</sup>) BID for two years

## 3.1 Proposed Indication

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

## 3.2 Product Overview

DFMO (difluoromethylornithine, effornithine) is a specific, enzyme-activated, irreversible inhibitor of ornithine decarboxylase (ODC), a key enzyme in mammalian polyamine biosynthesis. Polyamines are also essential for neoplastic transformation, making inhibition of ODC activity an attractive target for cancer chemoprevention. Inhibition of polyamine synthesis by DFMO results in growth arrest of a number of malignant and non-malignant mammalian cells and has been shown to inhibit the promotion and progression phases of carcinogenesis in neuroblastoma. Extensive nonclinical research supports that effornithine exerts its pharmacodynamic effects through ODC inhibition, suppression of polyamine biosynthesis, inducing downstream effects on mitogenic signaling, Lin28/Let-7 pathway, and changes to the cellular microenvironment.

DFMO tablets contain effornithine (or DFMO) as the hydrochloride salt.

The DFMO drug product is a tablet for oral administration. Each tablet contains 192 mg effornithine, equivalent to 250 mg of effornithine hydrochloride, and the following inactive ingredients: 220 mg silicified microcrystalline cellulose, 25 mg partially pregelatinized maize starch, 2.5 mg colloidal silicon dioxide, and 2.5 mg vegetable source magnesium stearate.

#### 3.3 Mechanism of Action

DFMO arrests malignant cell growth by inhibiting ODC and, therefore, biosynthesis of polyamines. These small cationic molecules are essential for cellular growth and development, but polyamine upregulation has been widely implicated in tumorigenesis and tumor propagation (NowotarskiWoster and Casero 2013). DFMO's suppression of polyamine synthesis, by way of ODC inhibition, arrests growth of multiple cancer cell types, including neuroblastoma (Koomoa 2008). In neuroblastoma, ODC is frequently either over-expressed or exhibits elevated catalytic activity, which positions ODC as an attractive therapeutic target for cancer therapy.

Overabundant polyamines drive oncogenesis through multiple mechanisms. Due to their cationic/charged nature, these molecules can bind directly to nucleic acids and induce an

oncogenic shift in gene expression profiles. Additionally, polyamines can drive cells toward a hyperproliferative state by activating the MAPK pathway (MinoisCarmona-Gutierrez and Madeo 2011). Also, ODC and *MYCN* share a significant and direct relationship. In this pathway, *MYCN* hyperactivity, most commonly by amplification, leads to an overexpression of ODC and hypersynthesis of polyamines. However, upregulated ODC activity can occur independently of *MYCN*.

Direct inhibition of ODC by DFMO results in decreased production and cellular abundance of polyamines. Not only does this reverse the altered polyamine mediated transcriptome in transformed cells and rebalances mitogen-activated signaling pathways, it also results in a rebalancing of the Lin28/Let-7 signaling axis (Balzeau 2017). Among all tumor suppressor microRNAs, reduced Let-7 expression occurs most frequently in cancer and typically is associated with poorer prognosis. While MYCN amplification is present in approximately 25% of all neuroblastomas (and notably higher in HRNB cases), a genome-wide association study identified an association between several single-nucleotide polymorphisms in the Lin28 locus and the development of neuroblastoma, suggesting that Lin28 may function as a potent oncogenic driver of this cancer type independently of MYCN (Tao 2020). In this pathway, Lin28 and Let-7 work against each other, allowing the cell to guickly pivot between stable non-proliferating states to proliferation/increased metabolism states as needed by the body. When polyamine levels rise excessively in cells, the eIF5A transcription factor becomes hypusinated and activated, resulting in an increase in Lin28 expression. Lin28 inhibits the expression of Let-7. This allows Lin28 to drive growth and proliferation signaling cascades while Let-7, a tumor suppressor miRNA, loses control of gene expression of targets involved in growth and proliferation programs, allowing cells to shift to a tumorigenic phenotype. By inhibiting polyamine synthesis through ODC blockage, DFMO directly suppresses polyamine levels, which in turn restores balance the Lin28/Let-7 pathway. Thus, DFMO mediated polyamine suppression provides a multi-pronged therapeutic approach for this highly heterogeneous disease, including promoting tumor suppressive functions independent of MYCN status.

## 3.4 Efficacy in *In Vitro* and *In Vivo* Models

In neuroblastoma, polyamine metabolism is often deregulated resulting in an increase in bioavailable polyamines within the cell. The contribution of ODC activity to neuroblastoma oncogenesis was demonstrated in several murine models (Hogarty 2008). DFMO as a chemopreventative agent has shown efficacy as an inhibitor of bladder, colon, esophagus, small and large intestine, liver, mammary gland, glandular stomach, skin, pancreas, and tongue carcinogenesis in animal models, demonstrating that polyamines are required molecules for transformed cells to maintain accelerated growth and division rates (Meyskens 2008). Summarized here are preclinical studies that highlight the different mechanisms in which DFMO exerts its anti-tumor effects and the efficacy of this drug in mitigation of neuroblastoma tumors.

First, DFMO has shown selective targeting of cancer stem cells (CSCs). In neuroblastoma, the CD114+ subpopulation has been defined as CSCs, which drives tumor relapse and chemoresistance (Agarwal 2015; Hsu 2013). BCC's recent work utilizing *in vivo* and *in vitro* models of neuroblastoma suggest that CSCs may be selectively targeted by DFMO via its inhibition of ODC and associated downstream effects (polyamine suppression, mitogen-activated kinase signaling control, Lin28/Let-7 rebalancing). In this research, currently being reviewed for publication, treatment of multiple neuroblastoma cell lines demonstrated that DFMO preferentially

targets CD114+ cells at physiologically achievable doses, resulting in both loss of CD114 viability and induction of senescence.

Next, DFMO reduced neurosphere formation and tumor initiating capability in *in vivo* xenograft mice models and also caused a decrease in the prevalence of tumor initiating cells as measured by extreme limiting dilutions analysis (ELDA). These results suggest that DFMO prevents tumor initiation and relapse of neuroblastoma through targeted inhibition of CSCs and induction of senescence (Avequin 2018).

Furthermore, DFMO primes the tumor microenvironment for immune cell targeting and clearance in multiple neuroblastoma mouse models. Neuroblastomas are adept and evading immune mediated tumor-surveillance, largely achieved by downregulation of soluble immune factors. Polyamines, specifically spermine, decreases the ability of monocytes to release proinflammatory cytokines, reducing the anti-tumor response of tumor infiltrating lymphocytes (Bassiri 2015). By depleting polyamines, tumors begin recruiting natural killer and tumor infiltrating lymphocytes back to the establishing tumor, helping to mediate its destruction and clearance (Evageliou 2016).

These preclinical models provided foundational support for clinical evaluations of DFMO in the neuroblastoma patient population. The earliest work with DFMO in HRNB focused on patients with active relapsed/refractory disease (Sholler 2018), and provided initial evidence of clinical effectiveness in neuroblastoma (described further in Section 2.3). The initial efficacy and favorable tolerability supported by this early published work, along with later preclinical work establishing the potential for DFMO to prevent new tumor formation in animal models, led to the clinical program which evaluated DFMO as a therapy for patients with HRNB achieving remission to reduce the risk of relapse.

## 3.5 Dose Selection Background

Dose selection for Study 3b was guided by preclinical models focused on inhibition of neurosphere formation, published clinical trials evaluating DFMO for similar chemoprevention application in adult cancers, and BCC's Phase 1 study conducted in patients with active R/R neuroblastoma (NMTRC002, as reported by Sholler [2015]).

#### 3.5.1 Preclinical Studies Supporting Dose Selection

The majority of published preclinical proof of concept models investigated doses of DFMO able to achieve a direct anti-tumor effect (Balzeau 2017; Hogarty 2008; Kroesen 2014; Lozier 2015). In contrast, preclinical models investigating DFMO's potential to inhibit formation of new tumors offers a more direct approach to target dosing of DFMO as a maintenance therapy in patients achieving remission. Inhibition of tumorigenic potential can be assessed *in vitro* by evaluating the ability of CSCs to generate anchorage-independent spheres (neurospheres). BCC performed neurosphere inhibition experiments to assess the effect of increasing DFMO concentrations (10  $\mu$ M – 1 mM) on neuroblastoma cell lines. The results of their studies, which are currently under review for publication, showed a statistically significant reduction in neurosphere formation with clinically achievable concentrations as low at 50 – 100  $\mu$ M. Both *MYCN* amplified and non-amplified cell lines showed similar patterns of neurosphere inhibition in response to DFMO

## 3.5.2 Published Clinical Studies Supporting Dose Selection

Preclinical findings were further supported by published clinical trials in adult patients considered at risk for new or recurrent cancers, which established oral DFMO doses effective at reducing risk of new tumor formation in cancers with polyamine dependency, similar to neuroblastoma. The results of clinical trials evaluating DFMO in adult patients at risk of colorectal cancer, with history of and risk for recurrent adenomas, or at risk of skin cancer were reviewed. The studies (Bailey 2010; Love 1998; Meyskens 2008) evaluated oral DFMO doses ranging from a 500 mg fixed once daily dose (together with low dose sulindac) to 500 mg/m²/day as a single oral dose with chronic administration, with dose administration occurring for up to 5 years. Results across these studies supported that DFMO inhibited cellular ODC activity and reduced cellular polyamine levels (e.g. skin and gut cells) at the studied doses, supporting that exposures associated with these dose levels were adequate to achieve therapeutic intracellular concentrations for ODC inhibition across multiple cancer cell types. These studies also reported favorable outcomes in the clinical endpoints measured and reported safety findings (e.g., mild ototoxicity) consistent with expected pharmacology of DFMO, further supporting clinically relevant exposure at these doses.

## 3.5.3 Dose Ranging Study in Patients with HRNB

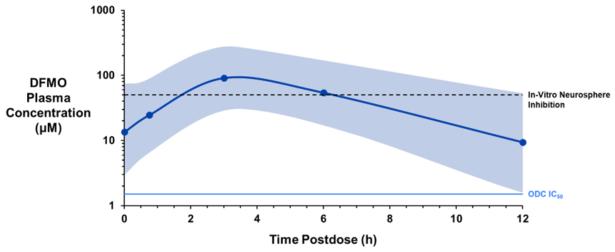
Preclinical and clinical evidence guided selection of the dose range to be evaluated in the initial DFMO clinical trial in patients with HRNB, NMTRC002 (Sholler 2015), which is described further in Section 4.2.1. NMTRC002 was a Phase 1 dose escalation study evaluating the safety and tolerability of DFMO in extensively pre-treated patients with active relapsed/refractory HRNB, considered to have no further curative options. It followed an ascending dose cohort design with patients receiving target (salt-based) doses of 500 mg/m<sup>2</sup> BID to 1500 mg/m<sup>2</sup> BID intended to advise dose selection for children with HRNB. DFMO was administered alone for the first 21-day cycle, then together with oral etoposide for 5 additional cycles. Patients completing protocol therapy were able to continue DFMO monotherapy with total dosing duration ranging up to approximately 2.4 years. A total of 21 patients were enrolled, with 18 meeting evaluable criteria for the ITT population. Preliminary signals of pharmacodynamic response and efficacy were observed across the dose range studied along with good tolerability. The published findings from this study report decreased urinary polyamines in patients treated across the dose range, as well as evidence that DFMO contributed to disease stabilization and disease improvement after the first cycle of DFMO alone and in combination with etoposide, described further in Sections 6.4.3.1 and 6.4.2 respectively. Pharmacokinetic sampling was also conducted in NMTRC002, enabling a comparison of exposures achieved from the studied dose to DFMO concentrations capable of achieving ODC inhibition. The published PK results from the study established that patients had DFMO plasma concentrations ranging from 52.24 µM to 168.10 µM for the low dose of 500 mg/m<sup>2</sup> to the high dose of 1500 mg/m<sup>2</sup> respectively, supporting that the full dose range achieved exposures exceeding the IC<sub>50</sub> for DFMO to ODC (1.5 µM) (Qu 2003), as well as DFMO concentrations associated with *in vitro* inhibition of neurosphere formation (starting at 50 µM) as concluded from BCC's more recent findings.

Together with the published adult studies and preclinical research, this study informed dose selection for Study 3b to investigate DFMO as maintenance therapy to reduce relapse, with the target (salt-based) dose level selected as 750 mg/m<sup>2</sup> BID +/- 250 mg/m<sup>2</sup> to cover the dose range providing preliminary evidence of efficacy in NMTRC002.

# 3.5.4 Comparison of Exposures Achieved with Recommended Dose to IC50 for ODC Inhibition and Concentrations Achieving in vitro Neurosphere Inhibition

Confirming observations from earlier clinical studies guiding dose selection, steady-state pharmacokinetic sampling (Day 181 of dosing) in a population of 177 patients with HRNB in remission receiving the recommended dose in Study 14, an ongoing open-label safety study of DFMO maintenance treatment for patients with HRNB in remission (see Section 4.2.3), enabled a comparison of DFMO plasma concentrations to those associated with an IC<sub>50</sub> for ODC (Qu 2003) and those associated with BCC's neurosphere inhibition model (publication pending). The reported IC<sub>50</sub> for DFMO is approximately 1.5  $\mu$ M, represented in Figure 9 by the solid blue line. The lower concentration range associated with neurosphere inhibition in BCC's research ranged from 50 to 100 µM, which is a dosing level that may be higher than what is required in vivo as this cell culture model does not have an immune response mechanism, through which DFMO activates some of its anti-tumorigenic functions. The lower bound of this range is indicated by the black dashed horizontal line. DFMO plasma concentrations across the 12-hour dosing interval are shown, with the blue shaded region representing the concentration range expected to encompase 95% of patients. Plasma concentrations remain above the reported IC<sub>50</sub> rate across the full dosing interval. The recommended dose also achieves exposures consistent with DFMO concentrations associated with in vitro inhibition of neurosphere formation for the majority of the dosing interval.





DFMO=eflornithine; h=hours; IC=inhibitory concentration; ODC=ornithine decarboxylase.

# 3.6 Dosing and Administration

The preclinical and clinical development program supported selection of the dose evaluated in Study 3b associated with efficacy and good tolerability. Consistent with the dose evaluated in Study 3b, the recommended dose of oral effornithine (DFMO) HCI monohydrate is  $576 \pm 192 \text{ mg/m}^2$  (equivalent to salt-based doses of effornithine HCI 750  $\pm 250 \text{ mg/m}^2$ ) BID for two years. BSA-defined dosing bands allow determination of the number of 192 mg effornithine tablets needed to achieve the recommended dose for each patient, ranging from 1 to 4 tablets twice daily (Table 7). Patients should be evaluated for BSA changes and dose adjustment, when applicable, approximately every 3 months given normal growth expected in the pediatric HRNB

patient population. DFMO tablets may be taken with or without food, and can be swallowed, chewed, or crushed and given in pudding.

| Table 7: | Dosage Recommendations |
|----------|------------------------|
|----------|------------------------|

| Body Surface Area (m <sup>2</sup> ): | Dosage  |  |
|--------------------------------------|---|--|
| > 1.5                                | Four tablets orally twice a day (8 tablets or 1536 mg per day)  |  |
| 0.75 to 1.5                          | Three tablets orally twice a day (6 tablets or 1152 mg per day) |  |
| 0.5 to < 0.75                        | Two tablets orally twice a day (4 tablets of 768 mg per day)    |  |
| 0.25 to < 0.5                        | One tablet orally twice a day (2 tablets or 384 mg per day)     |  |

# 4 REGULATORY AND DEVELOPMENT HISTORY

#### Summary

- DFMO has previously received FDA approval in the US as IV administration for West African sleeping sickness and topical cream for female hirsutism. No oral formulation of DFMO is commercially available for any indication in any market.
- DFMO for treatment of HRNB has received Orphan Drug Designation and Breakthrough Therapy Designation and has been granted priority review, along with participation in Real Time Oncology Review pilot programs and Project Orbis aimed at accelerating availability of promising new oncology therapies.
- Phase 1 Study NMTRC002 provided data on the safety of DFMO in patients with HRNB, informed dose selection for maintenance therapy investigations in Study 3b and provided preliminary data on efficacy.
- The core clinical program for DFMO registration includes three clinical trials, together evaluating a total of 421 patients with HRNB and 17 healthy adult volunteers.
  - NMTRC003/3b (referred to as "Study 3b") is a prospectively designed, Phase 2, multicenter, open-label, single-agent study of DFMO in children with HRNB in remission.
  - NMTRC014 (referred to as "Study 14") is an ongoing study in patients with HRNB. At the time of the data cut off for the NDA, 280 of the planned 441 patients had been enrolled. Study 14 contributes pharmacokinetics (PK) and safety data to the application.
  - USWM-FE1-1001 is a three-way cross-over PK study in healthy adult volunteers and contributes PK and safety data to the application.
- A randomized controlled trial was not performed due to promising survival results in Study 3b; externally controlling Study 3b was identified as an alternative, viable approach to registration through discussions with FDA due to the availability of ANBL0032 as an optimal source of control data.

## 4.1 Regulatory and Program History

#### 4.1.1 Prior Approvals of Eflornithine

Eflornithine (DFMO) has previously been approved by the FDA in an intravenously administered injectable formulation (Ornidyl<sup>®</sup>) for West African sleeping sickness and in a topical cream formulation (Vaniqa<sup>®</sup>) for female hirsutism. Vaniqa cream is available in the US and is actively marketed.

Ornidyl injectable was approved by the FDA but was never marketed in the US for business reasons. Ornidyl is currently manufactured strictly for humanitarian use by the World Health Organization as part of a nifurtimox-effornithine combination therapy (NECT) regimen for West African sleeping sickness. In this treatment regimen, effornithine is administered via IV infusion at 400 mg/kg/day (200 mg/kg every 12 hours) in adults and children, which is equivalent to 10,000 mg/m<sup>2</sup>/day; significantly higher than the proposed dose for the proposed indication in HRNB.

The previously approved indications for DFMO leverage the same beneficial effects of ODC inhibition established in neuroblastoma and other cancers. By blocking ODC and reducing polyamine production, DFMO can help to control the growth and division of cells, whether they are disease-causing parasites, hair follicle cells producing hair fibers, or aggressively growing tumor cells.

DFMO is not currently approved in an oral formulation for any indication and it is not approved for HRNB in any market.

## 4.1.2 History Resulting in Registration Approach without Randomized Controlled Trial

Study 3b was a single-arm Phase 2 study and was the first study to evaluate potential benefits of DFMO maintenance therapy. At the time it was initiated, the goal was that positive hypothesis testing would then be used to inform the design of a Phase 3 study following the traditional development sequence. However, preliminary reporting of outcomes from Study 3b were considerably better than predicted, both in terms of exceeding the hypothesized EFS benefit and in terms of very high OS rates. This prompted additional conversations between the Principal Investigator, Giselle Sholler MD, and FDA in 2015 and 2016. Although FDA recommended that a follow-on RCT be considered, the option of externally controlling Study 3b was discussed as a viable alternative, consistent with regulations for adequate and well controlled trials under 21 CFR 314.126. In parallel, in 2015 efforts were initiated for a RCT introducing DFMO at an earlier point in upfront therapy. The study remains ongoing today with an expected regulatory read-out and reporting target in another 7-10 years. However, by 2018, the 2-year EFS data were available for reporting on all enrolled patients, demonstrating increasingly promising EFS results as well as encouraging OS rates in DFMO-treated patients compared to published rates for patients with HRNB. These outcomes, and the availability of ANBL0032 as a uniquely optimal external control, resulted in a decision to pursue registration with Study 3b. This approach was guided by extensive FDA collaboration and executed through a BCC-USWM partnership.

A prospective RCT to evaluate 2-year EFS with DFMO as post-immunotherapy maintenance, similar to Study 3b, was considered using assumptions based on the interim results reported in Sholler (2018) and the learnings from the randomized phase of ANBL0032.

- ANBL0032 was designed to randomize 386 patients but interim analysis met early stopping rules and resulted in halting randomization after a total of 226 patients having completed induction and consolidation from 2001 to 2009, with 166 study sites listed in Yu (2010).
- A DFMO maintenance RCT would have been designed to enroll similar number of patients to detect a similar difference in EFS as reported for ANBL0032. However, the target population for a DFMO RCT would be patients completing induction, consolidation, and post-consolidation immunotherapy. This is a more limited pool of an already rare population compared to patients enrolling in ANBL0032, who were required to have completed only induction and consolidation prior to enrollment. Additionally, BCC's network of participating hospitals to conduct such a study was (and still is) much smaller than COG's network participating in ANBL0032.

Based on these considerations, the enrollment timeline, as well as the required follow-up period for accurate outcome reporting, would result in a lengthy trial. To reduce the risk of relapse sooner, the option of externally controlling Study 3b provides a pathway that would allow patients to broadly access DFMO.

The availability of the recent ANBL0032 study provided a uniquely suitable external control. This was a viable, albeit non-traditional, option for the analysis of Study 3b which fit the existing regulatory framework for adequate and well controlled studies. Consistent with the earlier discussions with FDA, the Code of Federal Regulations 21 CFR 314.126 requires that efficacy for investigational products be established by at least one adequate and well controlled study, and

further defines adequate and well controlled to incorporate an appropriate control with both historical and external controls described within these regulations. FDA has more recently issued guidance on Real World Evidence, which specifically discusses the requirements for and use of externally controlled trials, providing further support for the viability of this registration approach (FDA 2023).

Based on careful consideration of these factors, the unmet needs in the very rare disease of HRNB, and the early promising signal of benefit, the decision was made to pursue registration on the basis of an externally controlled trial, supported by continuous FDA collaboration and guidance and additional drug development and regulatory expertise through partnership between BCC and USWM.

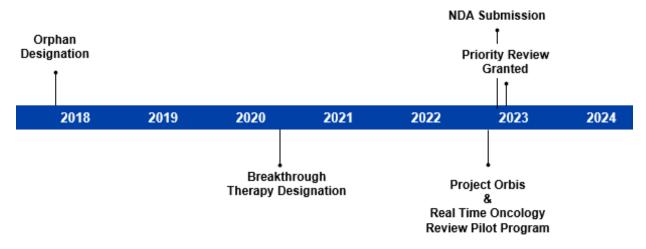
## 4.1.3 Regulatory and Development Program Milestones for the HRNB

The timeline for DFMO program milestones is illustrated in Figure 10. Details of the development program and regulatory interactions include the following:

- The development of DFMO for HRNB was initiated by Dr. Giselle Saulnier Sholler, who continues to serve as an Investigator over the clinical trials. USWM, the NDA Sponsor, licensed the rights to the clinical data package from BCC and continues to manage the development program in close collaboration with Dr. Sholler.
- Early guidance meetings relating to the design of studies and potential registration pathways were held between the FDA and Dr. Sholler, including a Type B meeting on November 18, 2015, and a Type-C meeting on February 23, 2016.
- Presentation of the interim results from Study 3b prompted discussions with FDA about the options for pursuing registration. A RCT designed in follow-up to Study 3b was considered and preferred by FDA as the traditional path for development. However, ultimately the decision was made to pursue registration by externally controlling Study 3b. Access to study level patient data to ANBL0032 enabled an approach that was considered both viable under the existing regulations and guided by ongoing interactions with FDA to ensure the most robust analysis was planned to support the NDA (Section 6.3).
- A second, supporting external control comparison was also conducted by BCC (Lewis 2020) to demonstrate reliability.
- DFMO received Orphan Drug Designation on November 22, 2017, issued to KC Pharma (the clinical trial material supply partner to Dr. Sholler prior to the Sponsor's involvement); the designation transferred to the Sponsor on September 18, 2020.
- The Sponsor's DFMO program received Breakthrough Therapy Designation on April 3, 2020.
- An initial comprehensive multidisciplinary breakthrough therapy meeting was held on September 24, 2020, and a chemistry, manufacturing, and controls (CMC)-focused Type B meeting was held on October 15, 2020. As an outcome of these meetings, Sponsor and the Agency agreed that a pre-NDA meeting should be requested in order to continue discussions on the plans for the application prior to its submission.
- Prior to the pre-NDA meeting, the Agency advised that a SAP for Sponsor's efficacy outcome comparisons for Study 3b compared to external control database ANBL0032 should be submitted for FDA review and input.

- The Sponsor submitted draft versions of the Study 3b vs ANBL0032 comparison SAP to the Agency during the first and second quarters of 2021, and the SAP was finalized.
- Topline analyses of the externally controlled study along with Sponsor's proposals for nonclinical, clinical pharmacology, biopharmaceutics, clinical efficacy and clinical safety packages for the NDA, were proposed in a Type B pre-NDA meeting held on October 25, 2021.
- As a result of the pre-NDA meeting, Sponsor agreed to conduct a BICR for the primary treated analysis population in support of the results of the pivotal Study 3b vs ANBL0032 comparison for the planned efficacy package.
- A draft charter and SAP for the BICR was reviewed by the Agency with recommendations provided in an Advice Letter dated January 13, 2022.
- Upon completion of the BICR imaging assessments for outcome determination, Sponsor submitted topline results to the Agency on August 26, 2022 to confirm the acceptability of the proposed clinical efficacy package.
- In an Advice Letter dated October 6, 2022, FDA agreed with Sponsor's planned NDA submission based on the planned efficacy package built upon the pivotal, externally controlled Study 3b vs ANBL0032, and further agreed with the Sponsor's proposals for participation in the Real Time Oncology Review (ROTR) pilot program and Project Orbis.
- The NDA was granted Priority Review, with a Prescription Drug User Fee Act (PDUFA) goal date of May 21, 2023.
- At FDA's request, teleconferences were held on April 24, 2023 and May 19, 2023 to provide Sponsor with an update on the status of the Agency's review of the application, including the Agency's decision to extend the review period in order to convene an Oncologic Drugs Advisory Committee.

# Figure 10: Timeline and Milestones of DFMO Clinical Development Program



NDA=New Drug Application.

## 4.2 Clinical Program Overview

An initial Phase 1 study supported further evaluation of DFMO for treatment of neuroblastoma. The subsequent core clinical program for DFMO registration includes three clinical trials, which together have evaluated a total of 421 patients with HRNB and 17 healthy adult volunteers (Table 8).

| Table 8:    | Summary of Clinical Studies Contributing Data to New Drug |
|-------------|---|
| Application |   |

| Study<br>Identifier:   | NMTRC002<br>(As Reported by<br>Sholler 2015*)  | Study 3b  | Study 14  | USWM-FE1-1001   |
|------------------------|--|---|---|---|
| Phase                  | Phase 1  | Phase 2   | Phase 2   | Phase 1   |
| Population             | Patients with active<br>relapsed or<br>refractory HRNB   | Patients with HRNB in<br>remission after upfront<br>(Stratum 1) or<br>relapse/refractory (Stratum<br>2) treatment | Patients with HRNB<br>in remission after<br>upfront or<br>relapse/refractory<br>treatment   | Healthy adult volunteers  |
| Dose                   | Ascending dose<br>cohorts of 500 to<br>1500 mg/m <sup>2</sup> BID (1<br>cycle DFMO alone,<br>followed by 5<br>additional cycles in<br>combination with<br>etoposide) | $750 \pm 250 \text{ mg/m}^2 \text{ BID DFMO}$<br>(27 cycles of 28-day<br>treatment periods) to total 2<br>years   | <ul> <li>750 ± 250 mg/m<sup>2</sup><br/>BID DFMO for 2<br/>years (most<br/>patients), or</li> <li>2500 mg/m<sup>2</sup> BID<br/>DFMO for 2<br/>years</li> </ul> | 1500 mg BID<br>approximately 12<br>hours apart for 10<br>consecutive days |
| Enrollment<br>(status) | N=18 evaluable   | <ul> <li>N=141<sup>1,3</sup> (complete)</li> <li>Stratum 1: n=105</li> <li>Stratum 2: n=35</li> </ul>             | N=280 of 485<br>(ongoing)   | N=17 (complete)   |

| Study<br>Identifier:                    | NMTRC002<br>(As Reported by<br>Sholler 2015*)  | Study 3b   | Study 14  | USWM-FE1-1001  |
|---|--|--|---|--|
| Primary<br>Efficacy<br>Assess-<br>ments | <ul> <li>N/A. Primary<br/>objective was<br/>safety/tolerability<br/>to identify<br/>maximum<br/>tolerated dose</li> <li>Exploratory<br/>efficacy described<br/>in published<br/>findings include<br/>PFS and long-<br/>term survivor<br/>status</li> </ul> | <ul> <li>Event free survival (EFS), defined as period from the first day of DFMO to the first occurrence of relapse, progressive disease, secondary cancer, or death, or if none occurred, until the last contact with the subject</li> <li>Imaging studies were performed to monitor disease progression and determination of efficacy of the study drug at the end of cycles 3, 6, 9, 13, 20, and at off-protocol therapy (end of cycle 27)</li> </ul> | N/A. This study<br>contributes only<br>safety and PK data<br>to the application.  | N/A. This study was<br>designed to<br>evaluate DFMO PK<br>under fed and fasted<br>conditions   |
| Safety<br>Assess-<br>ments              | Published findings<br>include CTCAE<br>Grade ≥ 2   | <ul> <li>New or worsening CTCAEs<br/>Grade ≥ 2 at each visit:</li> <li>Physical exams</li> <li>Vital signs</li> <li>Clinical labs<sup>2</sup></li> <li>Audiograms</li> </ul>   | New or worsening<br>CTCAE Grade ≥ 3<br>at each visit:<br>• Physical exams<br>• Vital signs<br>• ECG<br>• Clinical chemistry<br>• Hematology<br>• Urinalysis<br>• Audiograms | New or worsening<br>adverse events:<br>• Vital signs<br>• ECG<br>• Clinical chemistry<br>• Hematology<br>• Urinalysis<br>• Physical exam<br>• Audiograms |

BID=two times a day; CTCAE=Common Terminology Criteria for Adverse Events; DFMO=eflornithine; ECG=electrocardiogram; EFS=event free survival; HRNB=high-risk neuroblastoma; ITT=intent-to-treat; N/A=not applicable; PK=pharmacokinetics.

The Sponsor obtained efficacy data from a retrospective chart review protocol, BCC001, that included efficacy data from patients who were treated on Study 3, prior to the amendment to Study 3b (n=40); safety data were not accessible to the Sponsor at the time of the original NDA submission for patients treated prior to the Study 3b amendment. One patient enrolled but was not included in either stratum and is not included in efficacy assessments.
 Although clinical safety laboratory tests (hematology, chemistry, and urinalysis) were drawn, data were not entered. Adverse events were entered for any subject with Grade 2 or higher laboratory finding.

3. Imaging visits for the patients treated on Study 3, prior to the amendment to Study 3b (n=40) and those enrolled under Study 3b Amendment 5.0, were conducted every 3 cycles for the first 2 years of DFMO therapy. Amendment 5.1 revised the timing of imaging during the second year from every 3 cycles to every 6 months (end of cycles 13, 20 and 27). Investigators are always encouraged to scan more frequently if necessary for best patient care per their institutional policy.

\* Source: (Sholler 2015).

# 4.2.1 Phase 1 Study NMTRC002

Study NMTRC002, titled "A Phase 1 Trial for Refractory or Relapsed Neuroblastoma With DFMO Alone and in Combination With Etoposide," was designed to evaluate DFMO for safety and to find a maximum tolerated dose in the target population; a secondary objective was to evaluate efficacy of DFMO (Sholler 2018). A total of 18 evaluable patients were enrolled with active relapsed or refractory HRNB. Patients were treated with oral DFMO alone for three weeks (cycle 1), followed by additional three-week cycles of DFMO plus daily oral etoposide. Disease status was closely

monitored with frequent imaging assessments required after Cycle 1 of DFMO alone (~Day 21), Cycle 3 (~Day 63), and Cycle 5 (Day 105) and as clinically indicated thereafter.

No dose-limiting toxicities (DLTs) were identified in patients taking doses of DFMO between 500-1500 mg/m<sup>2</sup> orally twice a day. The median time to progression (TTP) was 80 days. Six of 18 evaluable patients were progression free during the trial period, with four remaining progression free for more than 1 year and three achieving long-term remission and remaining alive today.

The primary objective of the study was safety, with no prespecified efficacy endpoint. However, studies evaluating active R/R patients with HRNB meeting similar eligibility criteria to patients in NMTRC002 in earlier and concurrent timeframes, report a median PFS of only 42-45 days. One such study evaluating ABT-751 enrolled from 2007 to 2009, with a prespecified endpoint to evaluate TTP compared to a constructed historical control TTP of 42 days based on multiple similar published studies (Fox 2014). The results of the ABT-751 study showed no difference to the historical control, with TTP of 42 and 45 days for the two strata evaluated. These similar studies provide context for the interpretation of the NMTRC002 results, suggesting that the intervention was effective in stabilizing the disease for longer than expected in this group of patients (TTP of 80 days compared to published TTP of 42-45 days in similar studies).

Etoposide is generally regarded as a palliative treatment, most often reserved as a last resort for patients failing other treatments and for whom continued intensive, inpatient treatment is not considered appropriate. A recent report on the of palliative etoposide across number of cancers including neuroblastoma concludes that there is poor support for survival benefit with this therapy (Fraser 2021). Higher number of prior therapies and administration of etoposide as the final treatment were associated with poorer outcomes. Thirteen etoposide-treated neuroblastoma patients were included in the analysis, none of whom survived beyond 2 years. In contrast with the expected outcomes with etoposide in this group of patients, 3 of the 18 NMTRC002 ITT patients achieved remission and are long-term survivors with no additional therapy after stopping DFMO, now 8-10 years later. Two of the 3 long-term survivors received the lowest studied dose level of 500 mg/m<sup>2</sup> BID and 1 survivor received the highest dose of 1500 mg/m<sup>2</sup> BID.

Results from this Phase 1 study led to informed dose selection and led to the planning and conduct of Study 3b.

## 4.2.2 Study 3b

## 4.2.2.1 Overview of Study 3b

Study NMTRC003/3b ("Study 3b"), is a prospectively designed, Phase 2, multicenter, open-label, single-agent study of DFMO in children with HRNB in remission contributing PK, safety, and efficacy data to the application. The study was prospectively designed to compare EFS outcomes in DFMO-treated patients against published rates from the COG study ANBL0032, evaluating patients with HRNB receiving consistent upfront treatment without subsequent DFMO maintenance.

Study 3b comparisons to ANBL0032 patient level-data, serving as an external control, provides the primary evidence of efficacy supporting the application.

Additional details on the Study 3b design and prospectively defined analyses of outcomes are provided in Section 6.2.1.

The methodology and results for the pivotal externally controlled Study 3b vs. ANBL0032 comparisons are detailed in Section 6.3.2.

# 4.2.2.2 Drug Supply Change

Study 3b was initiated as Study 3, with the original drug product supply produced by another pharmaceutical company. Upon sudden dissolution of the supply agreement, a new source of drug product was rapidly developed and released for uninterrupted dosing in ongoing and newly enrolled patients. Patients who transitioned to the new supply of clinical trial material were reconsented and data separately captured under the amended protocol, renamed to Study 3b. The change to Study 3b also resulted in the creation of a separate study database and separate informed consent from that of Study 3.

Bioavailability of both sources of the drug product used in Study 3/3b were evaluated in a subset of N=12 patients transitioning from Study 3 to the Study 3b amendment. The results of the crossover sub-study analysis indicated bioavailability of the drug products to be comparable, supporting combined assessment of outcomes for patients who received either or both drug products in Study 3b.

## 4.2.2.3 Data Access Limitations

Patients ongoing in treatment at the time of the drug supply change were reconsented and transitioned to Study 3b. Original baseline information was re-entered and all safety and outcome assessments from the point of the transfer were recorded in the Study 3b database. However, at the time of the NDA, the Sponsor did not have legal rights to access the data collected in the Study 3 database.

Safety assessments for ongoing patients at the time of the drug supply change were captured in Study 3b only from the point of transferring to the amended study, resulting in only partial safety data for such patients. A total of 40 patients had discontinued or completed therapy under Study 3 or chose not to transfer to 3b, and no safety data are available in the Study 3b database for those patients.

Outcome data for patients who enrolled prior to the amendment to Study 3b were not entered into the Study 3b database. Therefore, outcome data for these patients were sourced from BCC001, as described further in Section 4.2.2.4.

## 4.2.2.4 BCC001 As a Second Efficacy Data Source to Study NMTRC003b

Outcome data for 100 of the 140 patients in the Study 3b ITT population, comprising those patients who either transferred from Study 3 to 3b or directly enrolled in Study 3b, are reported in the Study 3b database. However, because Sponsor did not have access to the Study 3 database at the time of the NDA submission, outcome data in the application for the remaining 40 patients (those patients who enrolled only under Study 3) are sourced from BCC001, a retrospective chart review of HRNB outcomes across BCC sites, including all sites that enrolled into Study 3b.

Data collection under BCC001 included a comprehensive review of medical records enabling the capture of prior treatment history including DFMO treatment information, demographics and disease characteristics, and EFS and OS outcomes. BCC001 provided the complete data necessary for efficacy endpoint analyses as specified by both the Study 3b SAP and the comparisons to ANBL0032.

All studies, including Study 3b and BCC001, were conducted by Dr. Sholler/BCC and were routinely monitored. Extensive source record review and data cleaning were conducted by BCC and Sponsor to ensure the accuracy of the data in both databases via access to source records covering the patients' treatment history prior to, during and after completion of treatment in the

DFMO trial. Additionally, Sponsor directly supported data management activities for the Study 3b and BCC001 databases. FDA's Office of Scientific Integrity conducted audits of BCC as the Sponsor of the clinical studies, Sponsor, and clinical sites contributing data to both Study 3b and BCC001.

## 4.2.3 Study 14 — Pharmacokinetic and Safety Data

NMTRC014 (Study 14) is an ongoing Phase 2 open-label, single-agent, multicenter study assessing DFMO in patients with HRNB in remission after initial upfront treatment or after relapse/refractory therapy. At the time of the data cut off for the NDA, 280 of the planned 441 patients had been enrolled. The majority of enrolled patients are treated at the recommended dose as evaluated in Study 3b. Study 14 contributes PK results (Section 5.2) and safety data (Section 7).

## 4.2.4 Study USWM-FE1-1001 – PK Data

USWM-FE1-1001 is a Phase 1, single center, open-label, randomized, multiple-dose, three-way cross-over, PK study in healthy adult volunteers and contributes PK data (discussed in Section 5.2) as well as safety data to the application.

## 4.3 Current Data Availability

Since the NDA submission on November 21, 2022, the Sponsor completed a transaction with Panbela Therapeutics resulting in the regulatory and commercial rights to the data associated with the Phase 1 study NMTRC002 (Sholler 2015) and Study 3 (the original version of the Study 3b protocol). Due to the timing of the transaction, these data were not included in the NDA. However, the Sponsor has current access to the data to review in support of published findings.

## 5 CLINICAL PHARMACOLOGY

#### Summary

- The pharmacokinetic and pharmacodynamic properties of DFMO tablets have been well characterized
- One study in healthy adult volunteers, USWM-FE1-1001, and extensive PK analyses in the target HRNB patient population within a subset of patients in Study 3b and from an interim analysis of Study 14, have been performed

## 5.1 Introduction

The pharmacokinetic and pharmacodynamic properties of 192 mg immediate release DFMO tablets have been well characterized. The Sponsor has conducted one study in healthy adult volunteers to evaluate food effect (USWM-FE1-1001) and performed extensive PK analyses in the target HRNB patient from an interim analysis of Study 14. Study 14 is an actively enrolling, open-label, single-agent, multicenter study for patients with HRNB in remission either after initial upfront treatment or after relapse/refractory therapy. All patients enrolled have required PK assessments on Day 1, Day 91, and Day 181. An interim PK analysis has been performed for 221 patients (ranging from 1 year to 19 years of age) with the opportunity to complete all three sampling timepoints prior to January 2021 (the cutoff for the PK data in the NDA).

## 5.2 Pharmacokinetics

## 5.2.1 Pharmacokinetics in Healthy Adults

Study USWM-FE1-1001 was a 3-treatment, 4-sequence, cross-over food effect study to assess the effect of food or tablet crushing on DFMO bioavailability conducted in 16 healthy adults. The effect of food on the rate and extent of DFMO absorption was evaluated in an open-label, randomized, multiple-dose, 3-way cross-over, food effect study conducted in healthy volunteers. The study investigated the relative bioavailability of intact DFMO tablets administered orally under fed vs fasted conditions and, additionally, compared the PK of DFMO after oral intact DFMO tablets (administered under fasted conditions) vs oral crushed DFMO tablets mixed in pudding administered under fasted conditions (USWM-FE1-1001). Study results demonstrated that food does not affect the rate or extent of DFMO absorption and that tablets may therefore be administered independent of meals. Additionally, when given under fasted conditions, DFMO bioavailability after administration of crushed tablets on standard pudding was similar to that after oral administration of intact tablets. Exploratory PK analyses in pediatric patients taking intact tablets compared to patients taking crushed (in pudding) tablets during Study 14 supported the USWM-FE1-1001 findings as summarized below.

## 5.2.2 Pharmacokinetics in Patients with HRNB

The interim PK analysis of 221 patients with HRNB receiving DFMO at the recommended dose in Study 14 supports the following conclusions:

 Mean plasma concentration-time profiles showed peak concentrations generally occurred in the PK sample collected at 3 hours post dose consistent with the other clinical studies and published studies.

- Dose proportionality for DFMO exposure was observed for the 2-fold range in dose/m<sup>2</sup> (500 to 1000 mg/m<sup>2</sup>) resulting from the evaluated target dose level of 750 mg/m<sup>2</sup> ± 250 mg/m<sup>2</sup>.
- An approximately 21% to 25% increase in maximum exposure and total exposure was observed between the first dose and steady-state. Once the DFMO concentrations reached steady-state there was little subsequent change in the DFMO PK.
- Bioavailability of DFMO was not affected by whether the tablets were administered whole (intact) or crushed and mixed in a tablespoon of pudding in patients with HRNB.
- Median DFMO elimination half-life (t<sub>1/2</sub>) was estimated at 2.7 hours to 2.8 hours in the HRNB population. The short t<sub>1/2</sub> of DFMO (between 2 and 4 hours in more than 70% of the pediatric patients) means that with BID dosing, near steady-state concentrations are achieved by the second day of treatment.
- Clearance of DFMO from plasma was consistent with elimination being renal and associated with glomerular filtration rate (GFR).
- Covariates of sex and race did not appear to have systematic effects on DFMO PK parameters.
- Both DFMO CL/F and Vz/F increased with increasing age. The effect appeared to coincide with the increase in body size that generally accompanies increasing age.
- Increases in DFMO exposure were observed with increasing creatinine and blood urea nitrogen (BUN), consistent with the apparent importance of renal clearance for DFMO elimination in healthy adults. While few patients with HRNB appear to have impaired renal function, despite harsh upfront treatments prior to starting maintenance treatments with DFMO, the drug should be used with caution in a patient that has moderate or severe renal impairment.
- A dependence of DFMO exposure on indicators of hepatic function was not observed.
- Within-patient variability for the PK parameters was approximately 40% to 50% of that observed between patients. Between-patient coefficient of variations (CVs) for PK parameters were generally large, at 39% to 88%.

## 5.2.3 Drug-Drug Interactions

DFMO has little-to-no potential to cause cytochrome P450 (CYP)-mediated drug-drug interactions (DDIs). Comprehensive testing of CYP and transporter interactions found that DFMO did not induce CYP1A2, CYP2B6, or CYP3A4 mRNA expression in primary hepatocyte cultures and DFMO was not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at concentrations well above clinically relevant concentrations (Sponsor Studies 2011RXP-UWM-001, 2011IND-UWM-002, and 2011INH-UWM-003). DFMO was not a substrate nor affected transport of P-gp, BRCP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K (Sponsor studies OPT-2020-168, OPT-2020-169). Accordingly, no DDIs are anticipated with DFMO.

# 5.3 Pharmacodynamics

The interim PK analysis of Study 14 evaluated exposure-QTc relationships in patients with HRNB. Increasing DFMO concentrations did not appear to affect QTc intervals assessed at the time point coincident with  $C_{max}$ .

## 5.3.1 Exposure and Dose Response

A limited analysis of exposure response was performed with the interim data from Study 14 which did not identify any apparent trends.

A post hoc analysis was performed to investigate the association between BSA-normalized prescribed dose and outcomes in Study 3b; however, no apparent dose relationships were identified within the approximate 2-fold range of BSA-normalized doses resulting from the target BSA-based dose level (750  $\pm$  250 mg/m<sup>2</sup>) evaluated in the study.

## 6 CLINICAL EFFICACY

## Summary

- Study 3b was a single-arm, Phase 2 study of DFMO maintenance in children with HRNB in remission
  - Patients were stratified into two cohorts: those who achieved remission after upfront SoC (Upfront Remission, Stratum 1) and those who achieved remission after treatment for relapsed or refractory (R/R) disease (Remission After R/R Therapy, Stratum 2)
  - Prespecified analyses compared EFS and OS in Study 3b Upfront Remission patients to published historical control rates from the Children's Oncology Group landmark registrationquality Study ANBL0032
- Study 3b achieved its prospectively defined endpoints for Upfront Remission patients compared to a historical rate, based on published outcomes from ANBL0032.
- Patient-level data obtained from ANBL0032 enabled statistically robust, externally controlled comparisons of outcomes. Prospectively described selection criteria, defined with FDA input, identified patients from Study 3b who received DFMO maintenance (DFMO) and Study ANBL0032 who did not receive DFMO (NO DFMO)
- Propensity score matching of patients in the DFMO and NO DFMO-All Covariates groups, performed at request of FDA and designed as a separate comparison study with Agency input, provide the pivotal efficacy results for Study 3b:
  - Primary endpoint: EFS HR=0.48; p=0.0114 with a 4-year EFS was 84% for DFMO vs 73% for NO DFMO
  - Secondary endpoint: HR=0.32; p=0.0045 with a 4-year OS was 96% for DFMO vs 84% for NO DFMO
- Multiple sensitivity analyses that challenged the matching comparisons all showed similar magnitude of benefit with statistical significance.
- A blinded, independent review of imaging for DFMO patients in the externally controlled analysis identified little-to-no bias in outcome reporting in Study 3b, confirming reliability of EFS results.
- Supportive efficacy findings further characterized the benefit of DFMO:
  - Additional cohorts of Upfront Remission and Remission After R/R Therapy from other BCC studies show similar EFS trends to those observed in Study 3b, with similar curves showing lack of relapse events following the 2-year treatment period
  - Evidence of anti-tumor effects across multiple studies of DFMO in active HRNB, and pharmacodynamic effects further supported attributability of relapse reduction benefit to DFMO in Study 3b and pivotal comparisons of 3b with ANBL0032

#### 6.1 Background Information for Establishing Efficacy

DFMO has demonstrated potential therapeutic benefits in various cancers (Alexiou 2017; LoGiudice 2018), including HRNB (Sholler 2015), based on its mechanism of action (Marton and Pegg 1995; Metcalf 1978; Meyskens and Gerner 1999; Poulin 1992). In HRNB, DFMO has been shown to restore balance of the LIN28/Let-7 signaling axis (Lozier 2015; Ma 2021; Molenaar 2012), which regulates cancer stemness, and downregulate *MYCN* expression, a known HRNB oncogene (Brodeur 2016; Seeger 1985). Results from the prospective, Phase 2, single-arm Study 3b suggested DFMO had the potential to reduce the risk of relapse with 2-year EFS rates lower than those in ANBL0032 (85% vs 70%, respectively) (Sholler 2018). Additionally, a supporting externally controlled comparison using retrospective HRNB patient data from BCC Research Consortium hospitals showed similarly promising results (Lewis 2020).

However, the single-arm design of Study 3b required further comparison against similar patients who did not receive DFMO maintenance in order to draw more robust conclusions on efficacy and safety. Patient-level data from ANBL0032 served as an optimal external control database from which to identify similarly pre-treated patients who could be compared to Study 3b patients taking DFMO. A PSM analysis, which was requested by FDA, is a widely published method for comparing cohorts (Chu 2022; Granger 2020; Rosenbaum and Rubin 1983; Yao 2017) and provided a population against which to assess results from Study 3b.

# 6.2 Study NMTRC003b (Study 3b)

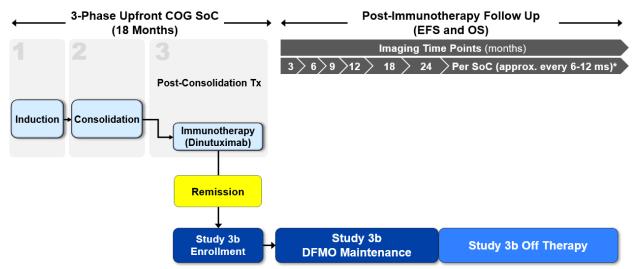
# 6.2.1 Study 3b Design

# 6.2.1.1 <u>Overall Design</u>

Study 3b is a prospectively designed, Phase 2, multicenter, open-label, single-agent study of DFMO in children with HRNB in remission. Two cohorts of patients were planned for the study as described in Section 6.2.1.2.

However, the primary objective was to compare EFS with the addition of DFMO maintenance following upfront SoC that included anti-GD2 immunotherapy (Upfront Remission Patients, Stratum 1) to the EFS rates reported from ANBL0032. Accordingly, the study was designed to enroll Upfront Remission Patients that had completed all three phases of upfront therapy including immunotherapy. Figure 11 illustrates the design for Study 3b relative to the COG SoC established in ANBL0032. Key eligibility criteria are presented in Table 9.





\*Study ANBL0032 mandated imaging at 30 and 36 months

COG=Children's Oncology Group; DFMO=eflornithine; EFS=event free survival; ms=months; OS=overall survival; SoC=standard of care; Tx=treatment.

| I/E Category                            | Study 3b Criteria   |  |  |
|---|---|--|--|
| Diagnosis                               | Histologic verification at the time of original diagnosis or previous relapse of HRNB   |  |  |
| Age at diagnosis                        | < 22 years  |  |  |
| Previous<br>treatments                  | Stratum 1 patients were required to have received upfront high-risk induction, consolidation, and immunotherapy with anti-GD2 antibody.<br>There were no specific prior treatment requirements for Stratum 2.   |  |  |
| Timing from<br>previous<br>treatment(s) | <ul> <li>&gt; 30 days from completion of cytotoxic and antibody therapy</li> <li>&lt; 120 days from previous therapy</li> </ul>   |  |  |
| Baseline disease<br>status              | Eligible patients were required to be in remission at enrollment. Remission was operationally defined as achieving 1993 INRC PR or better based on imaging disease response evaluation with no evidence of disease in the bone marrow. Patients with residual MIBG lesions were required to have biopsy or PET imaging to confirm the lesion was metabolically inactive Only 4% of patients required PET to confirm eligibility and no patient was excluded by PET. |  |  |

# Table 9: Study 3b Key Eligibility Criteria

HRNB=high-risk neuroblastoma; I/E=inclusion/exclusion; INRC=International Neuroblastoma Response Category; MIBG=metaiodobenzylguanidine; PET=positron emission tomography; PR=partial response.

## 6.2.1.2 <u>Cohort Definitions</u>

Patients in Study 3b were stratified into one of two cohorts:

- **Upfront Remission Patients (Stratum 1)**: Represents the cohort evaluated for the primary objective of the study. Patients were in remission at the end of upfront treatment, composed of induction, consolidation, and immunotherapy maintenance treatment phases (Section 6.2.1.2.1).
- **Remission After R/R Therapy Patients (Stratum 2)**: Represents a poorer-risk group of patients planned for separate outcome analyses in Study 3b. Patients either relapsed or had primary refractory disease but subsequently achieved remission after additional treatment (Section 6.4.1.3.1).

The remainder of this section will focus on Upfront Remission patient cohort (Stratum 1). Remission After R/R Therapy Patients (Stratum 2) is presented in Section 6.4.1.1.

#### 6.2.1.2.1 Upfront Remission Patients

Patients were considered in remission at the end of upfront therapy if they met the following requirements:

- Completed upfront treatment ending with immunotherapy (e.g., anti-GD2 antibody treatment and cis-RA, when applicable)
- Enrolled within 120 days of the end of immunotherapy (i.e., within 120 days of the last reported cycle of antibody or cis-RA, as applicable), which ensures immunotherapy was the last treatment received prior to enrollment
- Had upfront treatment durations that did not exceed limits defined for ANBL0032 eligibility (patients who exceeded these durations were classified as refractory patients (see Stratum 2 description in Section 6.4.1.3.1).

# 6.2.1.3 <u>Study Treatments</u>

All patients received up to 27 cycles of oral DFMO at a dose of  $750 \pm 250 \text{ mg/m}^2$  BID. Each cycle consisted of 28 days of treatment. Per protocol, patients were required to visit the clinic at least once during each 28-day cycle throughout the 2 years of DFMO treatment. Patients were followed for EFS and OS for an additional 5 years after DFMO treatment, totaling 7 years of follow-up.

# 6.2.1.4 Efficacy Endpoints

The prospectively defined endpoints for the Upfront Remission patients (Stratum 1) are presented in Table 10.

# Table 10:Prospective Endpoints for Patients with Upfront Remission (Stratum1) in Study 3b

| Endpoint: | Upfront Remission Patients (Stratum 1)   |
|-----------|--|
| Primary   | Event free survival (EFS) at 2 years post-immunotherapy compared to a 70%, historical control rate. (EFS was measured from the first day of administration of DFMO until the first occurrence of relapse, progressive disease, secondary cancer, or death, or, if none of these events occurred, until the last contact with the patient.) |
| Secondary | Overall survival (OS) at 2 years. (OS was measured from the first day of administration of DFMO until death or censored at the last contact with the patient, if death did not occur during the study.)  |

DFMO=eflornithine; EFS=event free survival; OS=overall survival; R/R=relapsed/refractory.

## 6.2.1.4.1 <u>Rationale for Primary Endpoint — Upfront Remission Patients (Stratum 1)</u>

(Yu 2010) reported a 2-year EFS of  $66\% \pm 5\%$  from the beginning of immunotherapy. However, review of the published survival curve enabled extrapolation of these data to estimate a 2-year EFS rate of 70% from the end of immunotherapy (Yu 2010). The rate of 70% was estimated by removing the first 6 months of the published curve (which presented EFS from the start of immunotherapy) to approximate the patients that remained at risk from the end of immunotherapy, which was the time period of interest for assessing EFS with DFMO as a post-immunotherapy maintenance.

The primary efficacy hypothesis was that DFMO would increase the 2-year EFS rate to 80%, representing an approximate 10 percentage point increase in the proportion of patients alive and free of disease at 2-years following the completion of immunotherapy compared to the extrapolated historical control rate of 70%.

## 6.2.1.5 Assessments Used in Study 3b

## 6.2.1.5.1 Imaging Assessments

Patients were evaluated by either MIBG (which may have been either 123I-MIBG or 131I-MIBG scans which were either planar scintigraphy or SPECT or SPECT/CT images of specific anatomy or the whole body) and/or FDG-PET (if MIBG-nonavid) and anatomical imaging (MRI and/or CT) at Baseline and at specified intervals of approximately 3, 6, 9, 12, 18, and 24 months/end of DFMO treatment. The required imaging was consistent with SoC surveillance and the first two years of monitoring specified by the ANBL0032 protocol. Unscheduled imaging (including imaging beyond the minimum requirements, e.g., FDG-PET scan for MIBG-nonavid patients, or imaging at intervening timepoints) and/or additional clinical measures relevant to outcome determination may have occurred at any time in the 2-year on-therapy period at the local Investigator's discretion. In addition, patients were followed per local SoC which may or may not have involved

additional imaging studies for up to an additional 5-years after DFMO administration had stopped (7 years of total possible follow-up). No minimum requirements for imaging frequency or modality were defined for the long-term follow-up period.

#### 6.2.1.5.2 Bone Marrow Aspirate/Biopsy

Bone marrow aspirate/biopsy evaluation was required at Baseline. Bone marrow evaluation was not required per study protocol after Baseline but may have been performed at any evaluation timepoint or unscheduled timepoints at the discretion of the Investigator.

#### 6.2.1.5.3 <u>Soft Tissue/Bone Biopsy</u>

Soft tissue/bone biopsies were not specified per protocol but may have been done at any timepoint at the discretion of the Investigator.

#### 6.2.1.5.4 Outcome Definitions

Event free survival was defined as the time from first administration of DFMO to the first occurrence of PD, relapse, secondary malignancy or death due to any cause, or if none of those occurred, until the last contact with the patient. Progressive disease was defined consistent with 1993 INRC criteria. Progressive disease and relapse were synonymous in Study 3b because enrolled patients were determined to be in remission.

Overall survival was the time from first administration of DFMO to the date of death due to any cause, or if death did not occur, until the last contact with the patient.

## 6.2.1.6 <u>Statistical Analysis</u>

The primary efficacy analysis population in Study 3b was based on the ITT population, defined as patients who received at least one dose of DFMO and did not have important eligibility deviations. A total of 141 patients are in the Study 3b database, including 106 in Stratum 1 and 35 in Stratum 2. One Stratum 1 patient had a documented eligibility waiver for inclusion as a compassionate use case and was prospectively planned for exclusion from the efficacy analyses. This patient was removed from the Study 3b database ITT population (n=140), resulting in a Stratum 1 ITT population of N=105.

## 6.2.2 Study 3b Prospective Results — Upfront Remission Patients (Stratum 1)

#### 6.2.2.1 <u>Demographics and Disease Characteristics</u>

A summary of demographics and disease characteristics for patients with Upfront Remission (Stratum 1) is presented in Table 11.

Consistent with HRNB diagnosis, most patients had Stage 4 disease (88.6%) and had unfavorable histology (78.1%), and approximately half had *MYCN* amplification. Approximately 43% achieved a CR at the pre-ASCT evaluation, and most patients had a complete response or VGPR after immunotherapy.

# Table 11:Study 3b Demographics and Disease Characteristics (ITT Population,Upfront Remission)

| Parameter, n (%): | Upfront Remission<br>(N=105) |
|-------------------|------------------------------|
| Sex               |                              |
| Female            | 43 (41.0)                    |
| Male              | 62 (59.0)                    |

| Parameter, n (%):                | Upfront Remission<br>(N=105) |
|----------------------------------|------------------------------|
| Race                             |                              |
| Asian                            | 1 (1.0)                      |
| Black or African American        | 7 (6.7)                      |
| White                            | 90 (85.7)                    |
| Unknown                          | 2 (1.9)                      |
| Multiple <sup>a</sup>            | 5 (4.8)                      |
| Age at HRNB Diagnosis            |                              |
| < 18 months                      | 15 (14.3)                    |
| ≥ 18 months                      | 76 (72.4)                    |
| ≥ 6 years                        | 14 (13.3)                    |
| Stage at HRNB Diagnosis          |                              |
| 2                                | 3 (2.9)                      |
| 3                                | 7 (6.7)                      |
| 4                                | 93 (88.6)                    |
| 4s                               | 2 (1.9)                      |
| Histology                        |                              |
| Favorable                        | 8 (7.6)                      |
| Unfavorable                      | 82 (78.1)                    |
| Not available                    | 15 (14.3)                    |
| MYCN Amplification               |                              |
| Amplified                        | 47 (44.8)                    |
| Non-amplified                    | 56 (53.3)                    |
| Unknown                          | 2 (1.9)                      |
| Overall Response Pre-ASCT        |                              |
| CR                               | 46 (43.8)                    |
| VGPR                             | 34 (32.4)                    |
| PR                               | 22 (21.0)                    |
| Missing                          | 3 (2.9)                      |
| Response at End of Immunotherapy |                              |
| CR/VGPR                          | 103 (90.5)                   |
| PR                               | 2 (1.9)                      |

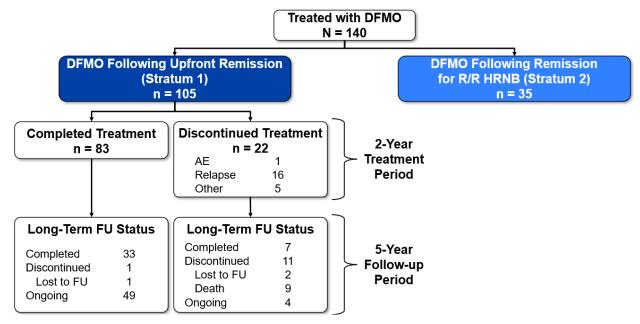
ASCT=autologous stem cell transplant; BSA=body surface area; CR=complete response; Ex-US=outside the US; HRNB=high-risk neuroblastoma; PD=progressive disease; PR=partial response; SD=standard deviation; US=United States; VGPR=very good partial response.

a. Multiple includes 1 patient each: Asian and Black or African American; Asian and White; Black or African American and White; Native Hawaiian or other Pacific Islander and White; and unknown. Upfront Remission = Stratum 1

## 6.2.2.2 Disposition

The majority of Stratum 1 ITT patients completed 2 years of treatment with DFMO (83/105, 79%; Figure 12). Of patients completing DFMO treatment, 33 (31.4%) completed the 5-year follow-up period, 49 (46.7%) were ongoing at the time of data cut off, and one was lost to follow-up. A total of 23/105 patients (21.9%) discontinued treatment early, with relapse as the leading cause. Of

the relapsed patients, 10 had died before completing the 5-year follow-up at the time of the data cutoff.



# Figure 12: Disposition of Study 3b Stratum 1, Upfront Remission Patients (ITT)

AE=adverse event; FU=follow-up; R/R=relapsed/refractory.

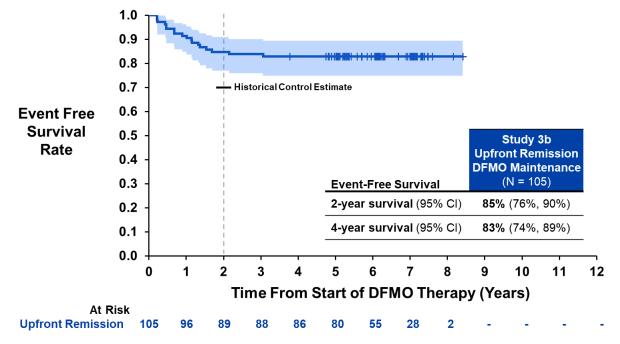
#### 6.2.2.3 Study 3b Prospective Survival Outcomes — Upfront Remission Patients (Stratum 1)

## 6.2.2.3.1 <u>Study 3b Event Free Survival — Upfront Remission Patients (Stratum 1)</u>

Figure 13 shows the EFS results for patients who achieved Upfront Remission (Stratum 1) against the prespecified historical control.

The 2-year EFS estimate was 85%, with the lower bound of the confidence interval exceeding the historical rate of 70%. Notably, the 4-year rate is comparable because very few events occurred following the 2-year DFMO therapy period.

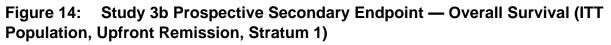
# Figure 13: Study 3b Prospective Primary Endpoint — Event Free Survival (ITT Population, Upfront Remission, Stratum 1)

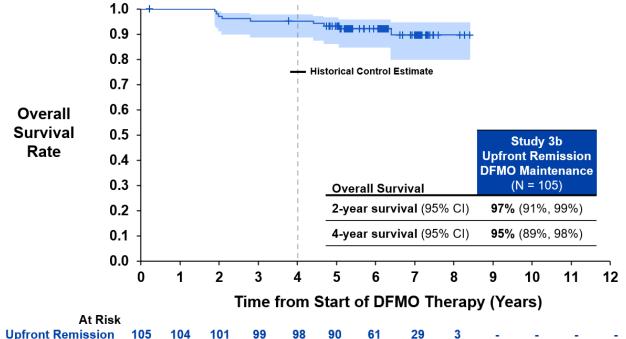


CI=confidence interval; DFMO=eflornithine; ITT=intent-to-treat. Note: Upfront Remission = Stratum 1.

6.2.2.3.2 Study 3b Overall Survival (Upfront Remission Patients, Stratum 1)

Figure 14 shows the OS results for Stratum 1 against a historical control rate estimated, like the EFS historical control rate, from the published results of ANBL0032. Both the 2- and 4-year OS estimates are > 95%, significantly higher than the historical rates of 85% and 75%, respectively.





CI=confidence interval; DFMO=eflornithine; ITT=intent-to-treat. Note: Upfront Remission = Stratum 1.

# 6.3 Externally Controlled Comparisons of Pivotal Study 3b to ANBL0032

In order to support the objectively favorable findings from Study 3b, the Sponsor and FDA agreed to perform a series of analyses comparing outcomes of DFMO-treated patients in Study 3b to patient level data from ANBL0032, which was obtained through the nonprofit COG.

## 6.3.1 Selection of External Control

The positive prospective endpoint results of Study 3b led to discussions with FDA about registration plans. Given the interpretation limitations of a single-arm study, the ANBL0032 patient-level data were identified as an appropriate external control to Study 3b, which was provided through a data transfer request from COG.

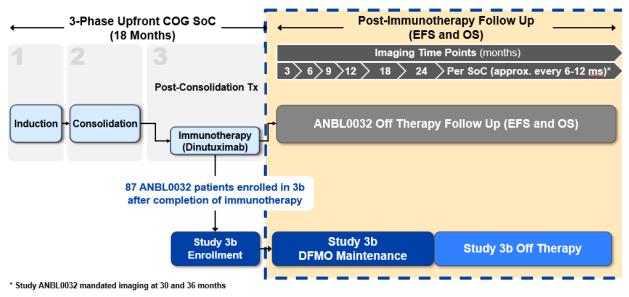
ANBL0032 was identified as an optimal external control for Study 3b, considering the following:

- Both studies exclusively enrolled patients with HRNB.
- Study 3b was prospectively designed to compare EFS outcomes with those reported in ANBL0032. Externally controlled analyses from the same study database provided an opportunity to extend testing of the prospectively defined primary endpoint.
- ANBL0032 established the current post-consolidation immunotherapy phase for US SoC for HRNB.
- The enrollment timelines for the two studies support upfront care practice similarity between treated and control patients. The randomized phase of ANBL0032 was open from 2001 to April 2009; however the majority of patients were enrolled in the expansion cohort

from May 2009 to July 2015, largely overlapping with the enrollment timeline of Study 3b from June 2012 to February 2016.

- EFS and OS outcomes for both studies were based on identical event criteria, were monitored with highly similar imaging modalities and frequencies, and included comparable long-term follow-up practices. Required imaging frequencies were identical through 2 years. ANBL0032 required imaging visits at 2.5 and 3 years; and while these visits were not required per Study 3b, the majority of patients in Study 3b were monitored at these approximate intervals and/or at later timepoints than required by the control study.
- Given that (1) enrollment into Stratum 1 of Study 3b required patients to have completed upfront therapy with anti-GD2 immunotherapy, (2) the majority of ANBL0032 enrollment occurred during an overlapping timeline with Study 3b, and (3) enrollment in ANBL0032 was the primary way to obtain dinutuximab in the enrollment timeline for Study 3b, the majority of Stratum 1 patients directly participated in ANBL0032 prior to receiving DFMO. This provides a unique opportunity to compare groups of patients who received treatment in ANBL0032 that either did or did not receive subsequent DFMO maintenance, illustrated in Figure 15.

# Figure 15: Schematic for ANBL0032 as External Control to Study 3b Supporting Comparisons of Patients With and Without Post-Immunotherapy DFMO Maintenance



COG=Children's Oncology Group; DFMO=eflornithine; EFS=event free survival; ms=months; OS=overall survival; SoC=standard of care; Tx=treatment

\* Study ANBL0032 mandated imaging at 30 and 36 months.

## 6.3.2 Methods

The plan for the externally controlled comparison was developed in collaboration with FDA through a series of informal and formal meetings. The SAP (Section 6.3.2.4) incorporated FDA recommendations and was executed prior to receipt of the final data transfer from COG, containing an additional 18 months of follow-up for outcome reporting, in comparison to an earlier cut of data used for preliminary analyses.

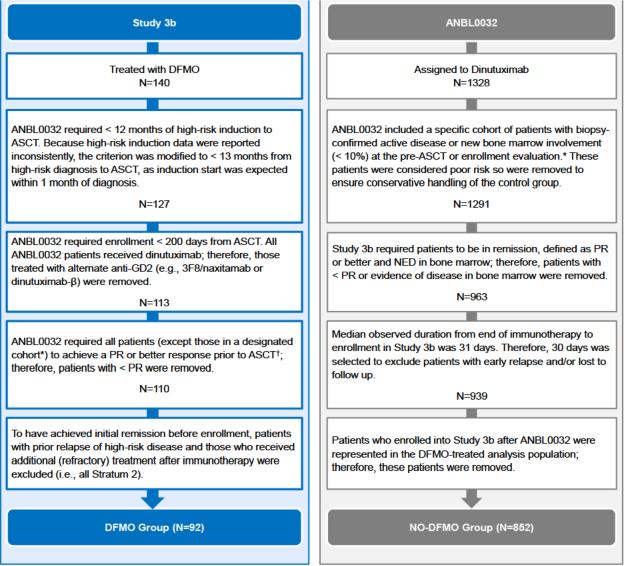
## 6.3.2.1 Study 3b and ANBL0032 Patient Selection Criteria for Use As Comparators

In accordance with the FDA-negotiated SAP, a series of selection rules were applied to the ITT population in Study 3b to identify a group of patients who received upfront therapy on, or consistent with, ANBL0032 before achieving remission and being eligible to enroll on DFMO therapy.

This treated population is the DFMO group from Study 3b (N=92; Figure 16). Within the DFMO group, 87/92 (94.5%) patients had participated directly in ANBL0032. The remaining 5 patients would have met eligibility criteria and received dinutuximab, consistent with the study protocol, but did not receive dinutuximab through the study (e.g., represent the earliest patients receiving commercial therapy following dinutuximab commercial launch in the third quarter of 2015).

Selection criteria were similarly applied to the ANBL0032 database of 1328 patients who were assigned to dinutuximab therapy. This identified patients who would have met the Study 3b eligibility criteria but did not receive DFMO. This control group population is the NO DFMO group (N=852).

# Figure 16: Patient Selection for Comparison of Outcomes in Study 3b and ANBL0032



ASCT=autologous stem cell transplant; DFMO=eflornithine; NED=no evidence of disease; PR=partial response. \* ANBL0032 Stratum 7.

† Pre-ASCT overall response, excluding bone marrow.

## 6.3.2.2 Selected DFMO and NO DFMO Population Demographics

The SAP-defined selection rules resulted in groups of 92 and 852 patients in the treated DFMO and NO DFMO populations, respectively, from which externally controlled outcome comparisons could be conducted. The groups were well balanced on key demographic and disease characteristics as shown in Table 12. The majority of patients in both studies received single transplant, consistent with COG consolidation practices at the time of the studies; however, both groups have tandem transplant representation as expected given the concurrent timeframe of research evaluating this practice.

Also notably, although ANBL0032 required follow-up for a total of 10 years, compared to required follow-up for only 7 years in Study 3b, the median follow-up time for the DFMO group is 1 year greater than for the NO DFMO--All Covariates group as a result of the later data cut off for Study 3b.

| Population with Non-missing Data, n (%):                              | Study 3b<br>DFMO Maintenance<br>(N=92) | ANBL0032<br>NO DFMO<br>(N=852)ª |
|---|--|---------------------------------|
| Sex   |  | (N=688)                         |
| Female  | 37 (40.2)                              | 298 (43.3)                      |
| Male  | 55 (59.8)                              | 390 (56.7)                      |
| Race  |  | (N=616)                         |
| American Indian or Alaska Native                                      | 0                                      | 2 (0.3)                         |
| Asian   | 1 (1.1)                                | 28 (4.5)                        |
| Black or African American   | 7 (7.6)                                | 92 (14.9)                       |
| Multiple  | 3 (3.3)                                | 0                               |
| Native Hawaiian or Pacific Islander                                   | 0                                      | 1 (0.2)                         |
| White   | 81 (88.0)                              | 493 (80.0)                      |
| Age at HRNB diagnosis ≥ 18 months                                     |  | (N=688)                         |
| < 18 months   | 12 (13.0)                              | 93 (13.5)                       |
| 18 months to < 6 years  | 68 (73.9)                              | 497 (72.2)                      |
| ≥ 6 years   | 12 (13.0)                              | 98 (14.2)                       |
| INSS Stage 4  | 80 (87.0)                              | 565/688 (82.1)                  |
| MYCN amplified  | 40/91 (44.0)b                          | 250/595 (42.0)                  |
| Pre-ASCT Response <sup>c</sup>  |  | (N=852)                         |
| CR/VGPR   | 70 (76.1)                              | 564 (66.2)                      |
| PR  | 22 (23.9)                              | 288 (33.8)                      |
| End of immunotherapy response   |  | (N=852)                         |
| CR/VGPR   | 88 (95.7)                              | 797 (93.5)                      |
| PR  | 4 (4.3)                                | 55 (6.5)                        |
| Single transplant type  | 84 (91.3)                              | 748/852 (87.8)                  |
| Median (IQR) follow-up <sup>d</sup> (years) from end of immunotherapy | 6.1 (5.2–7.2)                          | 5.0 (3.5–7.0)                   |

# Table 12:Overall Study 3b DFMO and ANBL0032 NO DFMO PopulationDemographics and Disease Characteristics

ASCT=autologous stem cell transplant; CR=complete response; HRNB=high-risk neuroblastoma;

INSS=International Neuroblastoma Staging System; IQR=interquartile range; PR=partial response; VGPR=very good partial response

a. Number of patients with non-missing data in Study ANBL0032 are presented for each category.

b. One patient in Study 3b was missing MYCN amplification data.

c. Response assessment included primary tumor, soft tissue metastases, and bone metastases (excludes bone marrow), consistent with ANBL0032 protocol.

d. Follow-up was calculated from the end of immunotherapy until the patient died, withdrew consent or was lost to follow-up, or if none occurred, until last contact with the patient.

## 6.3.2.3 <u>FDA-Recommended Propensity Score Matching Used for Primary Analysis of Study 3b</u> <u>Results vs ANBL0032</u>

Although the overall selected populations were comparable, FDA advised that the primary analysis for the external control comparison apply a PSM approach in order to optimize balance in important demographics and disease characteristics of the populations to be compared. The PSM model incorporated 11 covariates, including a required exact matching on *MYCN* because of its prognostic significance in risk stratification.

Covariates were:

- Age at high-risk diagnosis
- Sex
- Race
- Stage at HRNB diagnosis per 1993 INSS (categories of 4 or < 4, including 4S)
- Pre-ASCT response
- Transplant type
- Time from ASCT to start of immunotherapy
- Duration of immunotherapy
- Overall response at immunotherapy end
- Time from diagnosis to immunotherapy end
- *MYCN* (categories of amplified or non-amplified), exact match required.

(See Appendix 10.1 for a detailed justification of covariates used.)

For PSM analyses, only patients with complete covariate data were eligible for the analysis, which further restricted the Study 3b treated group to N=91 and the ANBL0032 control group to N=516. These groups were referred to as the DFMO-All Covariates (from Study 3b) and NO DFMO-All Covariates (from ANBL0032) populations.

The propensity score (Santana), which is the conditional probability of receiving DFMO given the observed covariates, was estimated from a logistic regression controlling for 10 of the 11 covariates excluding *MYCN* since it is used for exact matching (Rosenbaum and Rubin 1983).

First, all patients in the All Covariate population are assigned a propensity score. Next, patients were discarded if their PS was outside the overlapping range between treated and control. This step removes patients in both groups, but only one in the DFMO group leaving a total of 90 eligible to be matched.

Then, three available patients with closest PS in the NO DFMO group were selected for comparison to each DFMO patient within the same *MYCN* category. For example, a DFMO-treated patient from Study 3b with *MYCN* amplification would be matched with 3 *MYCN*-amplified NO DFMO patients from ANBL0032 who had the nearest propensity scores. Once a NO DFMO patient was matched to a DFMO patient, that patient could not be matched with another DFMO patient.

The resulting 3:1 matched populations (270 NO DFMO-MATCHED to 90 DFMO-MATCHED) were then compared for EFS (primary) and OS (secondary) outcomes.

## 6.3.2.4 Statistical Methods Used in Comparison

The SAP for the external control comparison defined primary and secondary endpoints for the external control analyses as EFS and Overall Survival as presented in Table 13.

# Table 13:EFS and OS Definitions for Externally Controlled Comparisons ofStudy 3b DFMO and ANBL0032 NO DFMO Populations

| Endpoint:                    | Definition   |  |  |
|------------------------------|--|--|--|
| Event Free<br>Survival (EFS) | EFS was defined as the period from the last day of immunotherapy until the first occurrence of relapse, progressive disease, secondary cancer, or death for any cause. If none of these events occurred, the patient was censored using the last day of contact. Last day of immunotherapy was defined as end date of the last cycle of immunotherapy (completion of Cycle 6 or last cycle completed). |  |  |
| Overall Survival<br>(OS)     | OS was defined as the period from the last day immunotherapy until death for any cause. If death did not occur, the patient was censored using the last day of contact. Last day of immunotherapy was defined as end date of the last cycle of immunotherapy (completion of Cycle 6 or last cycle completed).  |  |  |

Although each individual study used a different index date, all sources of data contain the end of immunotherapy date allowing harmonization of the index date for the comparative analyses. The end of immunotherapy was selected as the index date because this is the common point in treatment before introduction of DFMO maintenance in the treated group compared to continued follow-up without DFMO in the control group.

- All available follow-up data through the data cutoff for each study were used in the analyses
- The data cutoff for Study 3b was June 30, 2021
- The data cutoff for ANBL0032 was June 30, 2019

The primary analysis is an unadjusted Cox Proportional Hazards (CPH) model controlling only for treatment (DFMO versus NO DFMO) for the primary outcome, EFS, and secondary outcome, OS comparing the DFMO-MATCHED and NO DFMO-MATCHED populations.

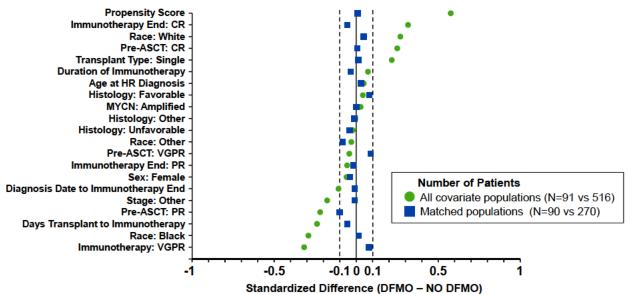
Estimated hazard ratio, two-sided 95% confidence interval, and two-sided p-value testing against a value of 1 for the treatment effect comparing DFMO to the control are reported.

## 6.3.3 Study 3b vs ANBL0032 Propensity Score Matched Results

#### 6.3.3.1 <u>Demographics and Baseline Medical Characteristics</u>

Figure 17 further illustrates the effectiveness of PSM. The love plot shows green circles for the standardized differences on the x-axis for each covariate on the y-axis considering all patients in the All Covariates populations. The blue squares show the standardized differences for the PS-MATCHED populations, with the post-matching (blue) standardized differences being minimized to the target range of  $\pm$  0.1 compared to the pre-matching population SDs(Pinto), which are much more widely distributed.

# Figure 17: Standardized Differences in Study 3b DFMO and ANBL0032 NO DFMO Analysis Populations Pre- and Post-Propensity Score Matching



ASCT=autologous stem cell transplant; CR=complete response; HR=high-risk; PR=partial response; VGPR=very good partial response. Histology was not used as a covariate in the propensity score model given the amount of missing data, but included here to evaluate balance for those patients where histology was reported.

The matched populations resulting from the PSM model are shown in Table 14, illustrating the excellent balance in key demographic and disease characteristics achieved from this methodology.

 Table 14:
 Demographics and Disease Characteristics for Study 3b DFMO vs

 ANBL0032NO DFMO Propensity Score Matched Populations

| % of population with non-missing data:    | Study 3b<br>DFMO-MATCHED<br>(N=90) | ANBL0032<br>NO DFMO-MATCHED<br>(N=270) |
|---|------------------------------------|--|
| Sex                                       |                                    |  |
| Female                                    | 36 (40.0)                          | 113 (41.9)                             |
| Male                                      | 54 (60.0)                          | 157 (58.1)                             |
| Race                                      |                                    |  |
| American Indian or Alaska Native          | 0                                  | 1 (0.4)                                |
| Asian                                     | 1 (1.1)                            | 15 (5.6)                               |
| Black or African American                 | 6 (6.7)                            | 17 (6.3)                               |
| Multiple                                  | 3 (3.3)                            | 0                                      |
| Native Hawaiian or Other Pacific Islander | 0                                  | 1 (0.4)                                |
| White                                     | 80 (88.9)                          | 236 (87.4)                             |
| Age at HRNB diagnosis                     |                                    |  |
| < 18 months                               | 46 (17.0)                          | 12 (13.3)                              |
| 18 months to < 6 years                    | 190 (70.4)                         | 67 (74.4)                              |
| ≥ 6 years                                 | 34 (12.6)                          | 11 (12.2)                              |
| INSS Stage 4                              | 78 (86.7)                          | 233 (86.3)                             |
| MYCN amplified                            | 40 (44.4)                          | 120 (44.4)                             |
| Pre-ASCT                                  |                                    |  |

| % of population with non-missing data:                        | Study 3b<br>DFMO-MATCHED<br>(N=90) | ANBL0032<br>NO DFMO-MATCHED<br>(N=270) |
|---|------------------------------------|--|
| CR/VGPR   | 69 (76.7)                          | 195 (72.2)                             |
| PR  | 21 (23.3)                          | 75 (27.8)                              |
| End of immunotherapy response                                 |                                    |  |
| CR/VGPR   | 86 (95.6)                          | 257 (95.2)                             |
| PR  | 4 (4.4)                            | 13 (4.8)                               |
| Single transplant type  | 82 (91.1)                          | 245 (90.7)                             |
| Median (IQR) follow-up from end of immunotherapy <sup>b</sup> | 6.1 (5.2-7.2)                      | 5.0 (3.7-6.8)                          |

ASCT=autologous stem cell transplant; CR=complete response; HRNB=high-risk neuroblastoma;

INSS=International Neuroblastoma Staging System; IQR=interquartile range; PR=partial response; VGPR=very good partial response.

a. Response assessment included primary tumor, soft tissue metastases, and bone marrow.

b. Follow-up was calculated from the end of immunotherapy until the patient died, withdrew consent or was lost to follow-up, or if none occurred, until last contact with the patient.

#### 6.3.3.2 <u>Evaluation of Potential Population Differences Beyond PSM</u>

PSM is an effective tool to achieve baseline attribute balance between two populations for covariates included in the algorithm, but it cannot directly address other potential differences that may be associated with underlying biases impacting outcomes. The 11 covariates used in the model were selected based on i) a review of published risk factors identified through univariate and multivariate analyses in recent studies to ensures the most prognostic attributes were incorporated, ii) availability of the data across both study sources, and iii) FDA guidance.

Some additional covariates were considered, in particular histology. Histology was not incorporated due to higher levels of missing data in both databases (a result of actual missing data and the fact that histology may only be reported in patients with disease that can be resected), which would have limited power for the analysis. However, good balance is nonetheless achieved on this potentially prognostic attribute following matching, as illustrated on the love plot in Figure 17. Socioeconomic status indicators were also considered due to their potential influence on outcome; however, such data were not provided in the ANBL0032 database and could not be incorporated in the PSM model.

While not all potential differences could be evaluated, effort was made to characterize the populations in areas of interest that could be assessed within the available data. These evaluations included characterizing geographic distributions of patients and evaluations aimed at understanding potential differences in supportive care based on enrolling site information.

Additionally, groups of control patients that did and did not have missing covariate data were compared to understand if missing covariates indicated a potential underlying difference that could introduce bias in the comparisons given only those patients with all covariates could be considered for the PSM.

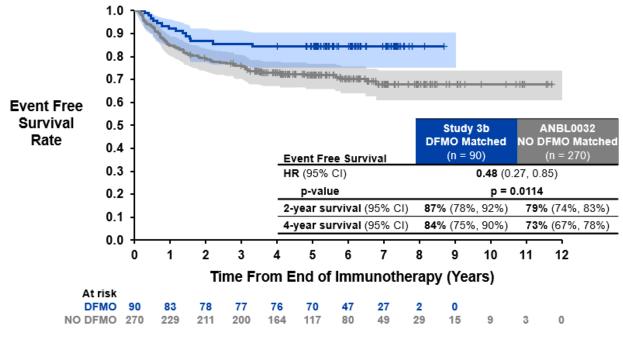
These evaluations and others along with related sensitivity analyses are described in Appendix 10.2. No clear differences were identified based on these additional evaluations. Additional sensitivity analyses performed to address potential differences beyond those that could be directly considered in the PSM analyses continued to be consistent with the primary comparison, lending further confidence to the interpretation of the results shown in the following sections.

# 6.3.3.3 <u>Study 3b vs ANBL0032 Propensity Score Matched Populations Survival Outcomes</u> <u>Results</u>

## 6.3.3.3.1 Event Free Survival in Study 3b vs ANBL0032 Matched Population

Figure 18 displays the Kaplan-Meier curves with 2-year and 4-year KM estimates, along with the 95% confidence interval for the SAP-defined primary PSM comparison of matched populations. The 4-year EFS rates are 84% and 73% for the DFMO and NO DFMO population, respectively (HR=0.48, 95% CI: 0.27, 0.85; p=0.0114).

# Figure 18: Event Free Survival Comparison in Study 3b DFMO vs ANBL0032 NO DFMO-Matched Populations



CI=confidence interval; DFMO=eflornithine; HR=hazard ratio.

## 6.3.3.3.2 Overall Survival in Study 3b vs ANBL0032 Matched Population

Figure 19 presents the results of the OS comparison in the same primary matched groups (HR=0.32; 95% CI: 0.145, 0.702; p=0.0045).

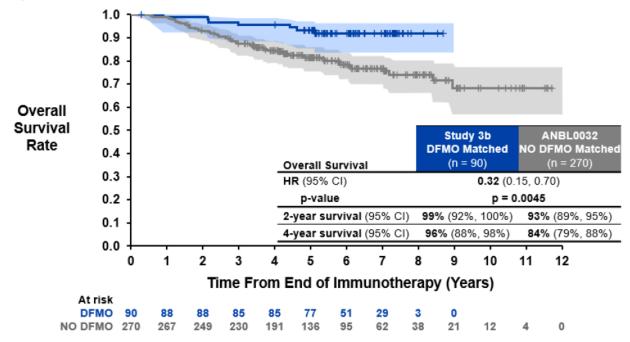


Figure 19: Overall Survival in Study 3b DFMO vs ANBL0032 NO DFMO-Matched Populations

CI=confidence interval; DFMO=eflornithine; HR=hazard ratio.

More censoring is observed in the NO DFMO group for both EFS and OS analyses. Reasons for censoring were further characterized for both populations as detailed in Appendix 10.3.

### 6.3.3.3.3 <u>Sensitivity Analyses of Survival Outcomes in Study 3b vs ANBL0032 Propensity</u> <u>Score Matched Populations</u>

Extensive sensitivity analyses were performed based on FDA input during SAP development and further investigation by the Sponsor during the review. Notable sensitivity analyses include those that applied more conservative selection rules designed to favor the control group, analyses that restricted the control population to those in the same era as the treated patients, and analyses to address missing data.

A summary of sensitivity analyses conducted to address clinical and statistical topics considered to be of highest interest/relevance is presented in Table 15. These analyses were performed on both the primary (EFS; Figure 20) and secondary (OS; Figure 21) endpoints in the comparison of Study 3b vs ANBL0032.

### Table 15:Summary of Select Sensitivity Analyses on Survival Outcomes forStudy 3b DFMO vs ANBL0032 NO DFMO Populations

| Sensitivity<br>Analysis | Rationale   |
|-------------------------|---|
| Primary Analysis        |   |
| Fixed ratio 1:1         | The primary analysis uses a fixed 3:1 ratio which was selected to increase power in the comparison. This sensitivity analysis reduces the ratio to 1:1, resulting in inclusion of only the single best control match for each DFMO patient. |

| Sensitivity<br>Analysis  | Rationale   |  |  |  |
|--|---|--|--|--|
| Change Patient Selection   |   |  |  |  |
| Remove NO DFMO<br>patients with EFS ≤<br>123 days                          | The selection rules employed to construct the NO DFMO group for the primary analysis excluded patients with EFS dates < 31 days from the end of immunotherapy. This rule was defined based on the median time of 30 days from end of immunotherapy to enrollment for the DFMO group. However, the maximum observed duration was 123 days for the DFMO group. Accordingly, this sensitivity analysis conservatively applies the extreme lead-in time advantage to the control group. By excluding patients with EFS dates < 123 days, patients that relapsed or were censored within 4 months of their last disease evaluation in ANBL0032 are removed from the analysis as patients relapsing or being lost to follow-up in this time could have theoretically relapsed before they could have been evaluated for Study 3b eligibility. A sensitivity analysis restricting the control patients eligible for matching to only those with EFS dates >123 days was performed. The end of immunotherapy date in ANBL0032 is generally reported as the date of the end of treatment visit when end of immunotherapy scans would have been conducted. Notably, ANBL0032 required imaging at 3 months from the end of the ANBL0032 reported date of end of immunotherapy is expected to remove any control patients who were determined to have relapsed based on 3-month imaging with a further 1 month window to account for possible scheduling or reporting delays. |  |  |  |
| Remove NO DFMO<br>patients with a<br>VGPR or PR at End<br>of Immunotherapy | The selection rules employed to construct the NO DFMO group for the primary analysis required patients to have achieved at least a PR at the end of immunotherapy disease evaluation. This criteria was consistent with the eligibility for Study 3b. However, PR or VGPR patients at the end of immunotherapy could be considered at an increased risk of relapse compared to CR patients. Additionally patients in <cr "best="" (including="" (this="" 3b="" 3b.="" 4%="" a="" additional="" analysis="" analysis,="" and="" as="" at="" be="" because="" biopsy="" but="" confirm="" conservatively="" control="" could="" covariate="" cr="" create="" dfmo="" disease="" due="" eligible="" end="" enhance="" for="" from="" full="" group="" group).="" group.<="" had="" have="" imaging="" imbalance="" immunotherapy="" in="" inactivity="" it="" lesions="" maintains="" match="" metabolic="" mibg="" no="" of="" only="" or="" order="" patients="" patients)="" pet="" players"="" pr="" remaining="" removed="" removes="" required="" residual="" response="" study="" td="" that="" the="" this="" to="" vgpr="" was="" which="" would=""></cr>   |  |  |  |
| Landmark < 120<br>days with matched<br>patients                            | Landmark analyses remove both early relapse events and censored patients to the specified landmark timepoint in both treated and control groups to further evaluate treatment differences. Using the 120-day landmark, the most conservative analysis, events are removed in both the treated and control groups and outcomes for the remaining patients in both groups are compared.   |  |  |  |
| Remove 5 DFMO<br>patients not treated<br>on 0032                           | The DFMO group includes 87 patients with verified participation in ANBL0032 and 5 early commercial dinutuximab patients who would have been eligible and received immunotherapy consistent with ANBL0032. A sensitivity analysis was performed to limit the DFMO group to only those with verified ANBL0032 study participation.  |  |  |  |
| Keep Only<br>NO DFMO<br>Contemporary<br>Patients (2:1)                     | The Contemporary population is a subset of the NO DFMO group in ANBL0032 who enrolled in 2011 or later (N=599). This was the timeframe of ANBL0032 that overlapped with possible enrollment into Study 3b. The NO DFMO selection rules did not exclude patients based on treatment era given induction and consolidation regimen variations did not evolve considerably over the full enrollment timeframe for ANBL0032. Nonetheless, the Contemporary analysis permits a matched analysis of only those patients treated in the same era to assess any potential impact of upfront treatment evolution over the course of ANBL0032. Given the reduction in available patients with All Covariate data in the NO DFMO (n=516) to the NO DFMO Contemporary population (n=370) requiring approximately 270 patients resulted in insufficient balance after the match (e.g., the standardized differences of the PS scores did not fall within the prespecified $\pm$ 0.1 as illustrated for the primary population in Table 12). As a result, a 2:1 fixed ratio was used in the analysis, which did achieve good balance.   |  |  |  |

| Sensitivity<br>Analysis                         | Rationale  |
|---|--|
| MICE imputation of                              | missing covariate data   |
| MICE Imputation of<br>Missing Covariate<br>Data | A sensitivity analysis was performed to explore how the choice of using complete data and excluding patients with missing covariate information influences the propensity score matched analysis. Multiple-imputation-by-chained-equations (MICE) algorithm as described in van Buuren is a commonly used approach for imputation (van Buuren 2011). MICE was used to impute any missing value for any covariate used in the propensity score model separately for the NO DFMO and DFMO patients. This approach assumed the data were missing at random. Once the data were imputed, the propensity score matched analysis as performed for the primary endpoint was repeated. |
| Stratification of the                           | propensity score   |
| Stratification on the<br>Propensity Score       | All patients from the NO DFMO control and DFMO populations were used in the stratified propensity score analysis, where four equal sized groups were formed based on quartiles of PS scores, each quartile was compared, and the weighted results (equal to the proportion of treated patients within each quartile) pooled to calculate and overall average treated effect.   |
| Inverse probability                             | weighting  |
| Inverse Probability<br>Weighting                | Inverse probability weighting was utilized to weigh individuals by the inverse of the probability of that unit being assigned to the observed group, resulting in a modified population with balanced covariates between treated and control patients.   |
| CR=complete respon                              | se; DFMO=eflornithine; EFS=event free survival; MICE=multivariate imputation by chained  |

CR=complete response; DFMO=eflornithine; EFS=event free survival; MICE=multivariate imputation by chain equations; PR=partial response.

### Sensitivity Analyses of Event Free Survival

The results of these sensitivity analyses for the primary endpoint of EFS are shown in Figure 20, with the primary analysis presented in the top row for reference. All analyses produced hazard ratios ranging from 0.4 to 0.6, similar to the primary result of approximately 0.5, all with statistical significance.

|  | # Events | / # Patients |                                   |            |            |         |
|--|----------|--------------|-----------------------------------|------------|------------|---------|
|  | DFMO     | NO DFMO      | Favors treated with DFMC          |            |            | p-value |
| Primary Analysis (DFMO vs NO DFMO 3:1)                               | 14 / 90  | 79 / 270     |                                   | 1          |            | 0.0114  |
| Change PSM Model   |          |              |                                   |            |            |         |
| Ratio 1:1  | 14 / 90  | 31 / 90      | │ <b>⊢●</b> ───┥                  |            |            | 0.0038  |
| Change Patient Selection   |          |              |                                   |            |            |         |
| Remove NO DFMO patients with EFS ≤ 123 days                          | 14 / 90  | 72 / 270     |                                   | -i         |            | 0.0363  |
| Remove NO DFMO patients with a VGPR or PR at<br>end of Immunotherapy | 14 / 88  | 76 / 264     | • • • • • • • • • • • • • • • • • |            |            | 0.0164  |
| Landmark < 120 days with matched patients                            | 13 / 89  | 64 / 255     | │ ⊢ ● ───                         |            |            | 0.0440  |
| Remove 5 DFMO patients not treated on 0032                           | 13 / 84  | 74 / 252     | │ ⊢_●                             | ⊣i         |            | 0.0125  |
| Keep only NO DFMO Contemporary patients (2:1)                        | 15/91    | 55 / 182     |                                   | 1          |            | 0.0124  |
| MICE imputation of missing covariate data                            | 15/92    | 82 / 275     |                                   |            |            | 0.0140  |
| Stratification of the propensity score                               | 15/91    | 150 / 516    | │ ⊢ ● ──── ┥                      | 1          |            | 0.0125  |
| Inverse probability weighting  | 14 / 90  | 141 / 494    |                                   |            |            | 0.0377  |
|  |          | 0            | .0 0.5                            | 1.0        | 1.5        | 2.0     |
|  |          |              | Event Free Su                     | rvival Haz | zard Ratio |         |

### Figure 20: Selected Sensitivity Analyses of Event Free Survival in Study 3b DFMO vs ANBL0032 NO DFMO-Matched Population

DFMO=eflornithine; EFS=event free survival; INRC=International Neuroblastoma Response Criteria; MICE=multipleimputation-by-chained equation; PR=partial response per 1993 INRC; PSM=propensity score matching; VGPR=very good partial response per 1993 INRC.

Note: Descriptions of analyses and rationales for selection are discussed in Table 15.

The results across this wide array of sensitivity analyses were highly consistent with the primary EFS result, both in terms of magnitude of effect (HR values generally ranged 0.4 to 0.6) and in terms of statistical significance.

#### Sensitivity Analyses of Overall Survival

The full complement of sensitivity analyses for the primary EFS analysis were also applied to the OS analysis. Results of the OS sensitivity analyses were consistent with the secondary endpoint results in terms of hazard ratio and statistical significance, shown in Figure 21, with primary population analysis of OS presented in the top row for reference.

|  | # Events / # Patients |          |                               |
|--|-----------------------|----------|-------------------------------|
|  | DFMO                  | NO DFMO  | Favors treated with DFMO      |
| Primary Analysis (DFMO vs NO DFMO 3:1)                               | 7 / 90                | 57 / 270 | ·◆                            |
| Change PSM Model   |                       |          |                               |
| Ratio 1:1  | 7 / 90                | 24 / 90  | 0.00                          |
| Change Patient Selection   |                       |          |                               |
| Remove NO DFMO patients with EFS ≤ 123 days                          | 7 / 90                | 45 / 270 | 0.03                          |
| Remove NO DFMO patients with a VGPR or PR at<br>end of Immunotherapy | 7 / 88                | 50 / 264 | 0.01                          |
| Landmark < 120 days with matched patients                            | 7 / 89                | 57 / 270 | 0.004                         |
| Remove 5 DFMO patients not treated on 0032                           | 7 / 84                | 48 / 252 | 0.020                         |
| Keep only NO DFMO Contemporary patients (2:1)                        | 8 / 91                | 37 / 182 | 0.004                         |
| MICE imputation of missing covariate data                            | 8 / 92                | 55 / 275 | 0.012                         |
| Stratification of the propensity score                               | 8 / 91                | 97 / 516 | 0.024                         |
| Inverse probability weighting  | 7 / 90                | 93 / 494 | 0.03                          |
|  |                       | C        | 0.0 0.5 1.0 1.5 2.0           |
|  |                       |          | Overall Survival Hazard Ratio |

### Figure 21: Selected Sensitivity Analyses of Overall Survival in Study 3b DFMO vs ANBL0032 NO DFMO-Matched Populations

DFMO=eflornithine; EFS=event free survival; INRC=International Neuroblastoma Response Criteria; MICE=multipleimputation-by-chained equation; PR=partial response per 1993 INRC; PSM=propensity score matching; VGPR=very good partial response per 1993 INRC.

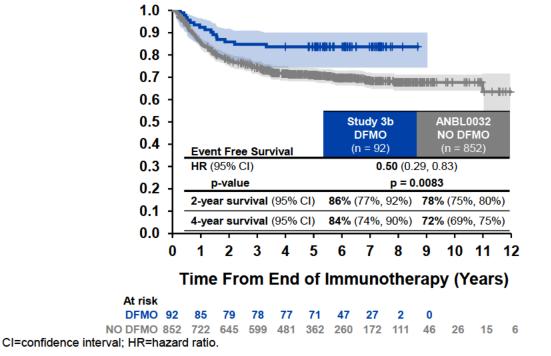
Note: Descriptions of analyses and rationales for selection are discussed in Table 15.

#### Sensitivity Analyses of Overall DFMO vs NO DFMO Comparisons Without Matching

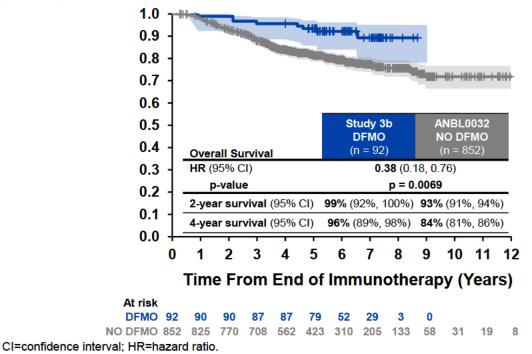
The primary comparative analyses employed PSM to address potential sources of bias; however, missing covariate data, primarily in the control database, have the potential to introduce their own sources of bias by restricting the eligible matches to those with all covariates reported. Missing covariate data in some patients could theoretically be associated with some underlying difference in that group of patients that is not able to be compared with PSM. To address this, additional missing data sensitivity analyses were conducted with similar results to the primary analysis, and event rates in NO DFMO patients with complete vs missing covariate data were compared and confirmed to have very similar EFS event rates (approximately 30% in each group).

In addition, the overall DFMO and NO DFMO populations were compared given that all patients in these groups had available data to apply the population selection rules and disease characteristics and demographics of these overall groups were very similar (see Table 12). The EFS and OS comparisons for the overall selected DFMO and NO DFMO populations are presented in Figure 22 and Figure 23, respectively.

### Figure 22: Event Free Survival in Study 3b DFMO (N=92) vs. ANBL0032 NO DFMO (N=852) Overall Populations



### Figure 23: Overall Survival in Study 3b DFMO (N=92) vs. ANBL0032 NO DFMO (N=852) Overall Populations



### 6.3.3.4 <u>Blinded Independent Central Review (BICR) of Imaging for DFMO Patients to Evaluate</u> <u>Study 3b Investigator EFS Reporting Bias</u>

Following guidance from FDA, all 92 patients in the DFMO group were further assessed in a blinded independent central review of imaging (BICR) for outcome determination by independent radiologists (Mody). Outcomes as determined by IRs were evaluated for concordance with Study 3b reported outcomes by the Study 3b site Investigator who served as the LEs for outcome determinations during the trial. IR-determined outcomes were also used in comparative analyses to patient level data in the external control ANBL0032 database.

When compared to the LE-determined outcomes for the same 92 patients, there were two discordant post-Baseline outcomes. In one instance, the LE reported a relapse event while the IR did not. In the other case, the IR-determined relapse event, while the LE determined no event. In summary, both LEs and IRs called 15 total EFS events, although the groups determined to have events differed by one patient. Concordance was assessed according to the SAP by the calculation of Cohen's kappa, which confirmed near-perfect agreement.

The results of the externally controlled EFS comparisons using IR-determined outcomes from the BICR matched the LE outcome-based analyses, as expected given near-perfect agreement between LE- and IR-determined EFS events. Overall, the BICR data confirmed that little-to-no bias existed in the assessment and reporting of EFS event by Study 3b site Investigators.

### 6.3.4 Conclusions from Pivotal Study 3b Externally Controlled Comparisons

ANBL0032 is a fit-for-purpose external reference for Upfront Remission patients in Study 3b who received COG SoC. Patient populations, prior therapies, and outcome assessments frequencies, and definitions were highly consistent between the studies as illustrated in Table 16. Careful patient selection from these two prospective clinical trials enables EFS and OS comparisons in similar groups of patients with HRNB receiving induction, consolidation, and post-consolidation immunotherapy with dinutuximab that either do or do not go on to receive DFMO maintenance.

### Table 16:Key Similarities in Patient Populations and Designs of Study 3b andExternal Control ANBL0032

| Key Attributes for Optimal External Control | Study 3b<br>Upfront Remission<br>DFMO Maintenance | ANBL0032<br>Assigned Immunotherapy<br>No DFMO    |
|---|---|--|
| Demographics                                | Highly similar                                    | Highly similar                                   |
| Disease Characteristics                     | Highly similar                                    | Highly similar                                   |
| Upfront treatments                          | Induction, consolidation, anti-GD2 immunotherapy  | Induction, consolidation, anti-GD2 immunotherapy |
| Objective, Clinically Meaningful Endpoints  | EFS, OS   | EFS, OS  |
| LTFU measures and frequencies               | Highly similar                                    | Highly similar                                   |

DFMO=eflornithine; EFS=event free survival; LTFU=long-term follow-up; OS=overall survival.

The similarity of the patient populations, assessments and outcomes make the ANBL0032 a uniquely suited control arm for Study 3b; however, to address common challenges with robust, reliable external controls, FDA recommendations through frequent Sponsor interactions were implemented to enhance precision in the comparison and reduce potential biases as illustrated in Table 17.

### Table 17:Recommendations to Address Common Challenges with Use ofExternal Control Study

| Common challenges with external controls  | Advice to Optimize Control Robustness   |
|---|---|
| Lack of data granularity in published point<br>estimates to understand and account for potential<br>patient populations differences | Access detailed patient-level data from registration-quality Study ANBL0032   |
| No randomization in study, needed to<br>mimic randomized, controlled trial-like balance for<br>comparisons                          | Implement propensity score matched analyses to<br>ensure similarity of patient characteristics,<br>treatment patterns and prognosis   |
| Known and unknown sources of potential biases in comparator data  | Conduct multiple sensitivity analyses to explore<br>various potential sources of bias<br>Use BICR to confirm reliability of Investigator EFS<br>event reporting for DFMO-treated patients |

BICR=blinded independent central review; EFS=event free survival; FDA=Food and Drug Administration.

The careful characterization of the patient populations, application of PSM to mimic the effects of randomization, consistency of the results across exhaustive comparisons, and independent outcome verification through the BICR, allow the Study 3b vs ANBL0032 externally controlled study to meet the requirements of an adequate and well controlled study to support DFMO efficacy for registration.

### 6.4 Confirmatory Clinical Data Supporting DFMO Efficacy

The NDA contains several components of confirmatory data which support an assessment of efficacy that is primarily determined from the adequate and well controlled Study 3b vs ANBL0032 analyses. Confirmatory data include (1) supporting evidence of the maintenance benefits for HRNB, (2) evidence supporting the anti-tumor effects of DFMO in patients with HRNB with active disease, (3) analysis of pharmacodynamic effects which confirm expected pharmacodynamic activity of DFMO in patients with HRNB receiving the recommended dose. The clinical data summarized here are further supported by extensive nonclinical mechanistic and disease model research, which has elucidated the role of DFMO in preventing tumor pathogenesis detailed in Section 5.3.

Each element of confirmatory data presented herein is associated with important limitations recognized by the Sponsor. However, the strength of the supporting data is derived from the quantity and variety of the evidence available along with the consistency of the efficacy trends observed across the data package. The quantity and quality of data provides confirmation of the pivotal study benefits based on the totality of evidence as opposed to emphasis on any one aspect of the supporting research.

### 6.4.1 Supporting Evidence of DFMO Maintenance Benefit

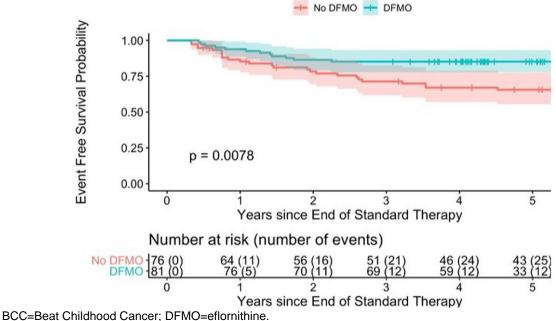
### 6.4.1.1 Separate Externally Controlled Analysis of Study 3b Patients Enrolled After COG SoC

When the decision was made to externally control Study 3b, informal FDA discussions and familiarity with similar development programs prompted work to identify two sources of suitable external control data on the basis that reproducibility of results across two control groups could increase confidence and reliability of the registrational approach. Discussions with COG related to the ANBL0032 database initiated in follow-up to those early guidance discussions with FDA;

however, in parallel BCC initiated efforts to identify an appropriate secondary control for Study 3b comparisons.

BCC conducted BCC001, a large retrospective chart review study of patients diagnosed with HRNB from 2003 to 2018 that were treated across BCC network institutions. A total of 378 patients with HRNB were included in the study, for which demographics, disease characteristics, treatment history, and outcomes were reported. The database was reviewed to identify a group of 76 BCC001 control patients with HRNB that achieved and maintained Upfront Remission for at least 120 days after completing induction, consolidation and post-consolidation immunotherapy with dinutuximab. Outcomes for these patients were compared to Study 3b a group of Stratum 1 (Upfront Remission) patients having received consistent upfront therapy, with results reported by (Lewis 2020). The results of this separately developed, published external control comparison were highly similar to the results of the pivotal Study 3b vs ANBL0032 comparison, favoring DFMO with statistical significance (p=0.0078; Figure 24).





Source: Lewis (2020).

The work reported by Lewis (2020) shows reproducibility of the results of Study 3b comparisons using a separate source of control data. This comparison was specifically designed to evaluate potential study-site effects given both Study 3b and BCC001 patients received treatment across the smaller network of BCC affiliated hospitals as compared to the larger network of hospitals participating in ANBL0032.

### 6.4.1.2 DFMO Maintenance in Upfront Remission SIOPEN Patients

The majority of Stratum 1 Upfront Remission patients in Study 3b were treated with standard COG upfront therapy, including dinutuximab immunotherapy. However, patients in remission after upfront therapy including any anti-GD2 antibody were eligible for Stratum 1, and a small proportion of Upfront Remission patients received treatment with the standard European protocol

by SIOPEN with dinutuximab-beta as the anti-GD2 antibody used in the immunotherapy phase. Likewise, such patients are also eligible for the actively enrolling, similarly designed study by BCC, Study 14.

Published event free survival rates are similar between ANBL0032, evaluating outcomes with post-consolidation immunotherapy with dinutuximab, and HRNBL-1, evaluating outcomes with post-consolidation immunotherapy with dinutuximab-beta. Both studies report a 4-year rate of approximately 60% from the start of immunotherapy (Desai 2022; Ladenstein 2020; Yu 2021).

Based on the similarity of outcomes across these two standards of care, a preliminary evaluation of patients receiving DFMO maintenance following SIOPEN upfront therapy was conducted to explore if similar trends are observed in EFS outcomes compared to the primary analysis population receiving DFMO following COG SoC (DFMO group of N=92 evaluated in the pivotal externally controlled analysis to ANBL0032).

Criteria for defining a group of patients treated per SIOPEN SoC were informed by the publication of HRNBL-1 study conducted by SIOPEN (Ladenstein 2020). As a result of the findings of the HRNBL-1 study, SIOPEN upfront treatment evolved to incorporate dinutuximab-beta immunotherapy following induction and consolidation treatment.

To maximize the sample size for this cohort of DFMO patients, both Study 3b and Study 14 were reviewed to identify all patients receiving dinutuximab-beta and preceding upfront therapy that was on (N=40) or consistent with (N=7) requirements of SIOPEN's protocol, HRNBL-1 (this group is referred to as DFMO Per SIOPEN, N=47). Patients were considered to have been treated consistent with HRNBL-1 if they received Rapid COJEC<sup>1</sup> or similar induction, comparable consolidation treatment, and dinutuximab-beta immunotherapy. The majority of the DFMO Per SIOPEN cohort received Bu/Mel transplant. However, consolidation was considered comparable if the patient received any single transplant or tandem transplant with C&T/CEM. Recent studies have shown similarly improved outcomes with tandem transplant vs single CEM (Park 2019) and with Bu/Mel vs CEM (Ladenstein 2017). However, there are no completed studies comparing tandem and Bu/Mel, and these approaches are both used in US clinical practice depending on specific institutions and patient considerations.

Table 18 shows key demographic and disease characteristics of the resulting DFMO Per SIOPEN population side by, along with the primary Study 3b DFMO (N=92) analysis population used in the externally controlled comparisons to ANBL0032.

# Table 18:Key Demographic and Disease Characteristics of DFMO Per SIOPENand Study 3b DFMO Primary Analysis Population (for Externally ControlledAnalysis)

| Parameter: | DFMO<br>Per SIOPEN<br>(N=47) | DFMO Primary Analysis<br>Population<br>(N=92) |
|------------|------------------------------|---|
| Sex, n (%) |                              |   |
| Female     | 46.8%                        | 40.2%   |
| Male       | 53.2%                        | 59.8%   |

<sup>&</sup>lt;sup>1</sup> Rapid COJEC: cisplatin [C], vincristine [O], carboplatin [J], etoposide [E], and cyclophosphamide [C]).

| Parameter:                         | DFMO<br>Per SIOPEN<br>(N=47) | DFMO Primary Analysis<br>Population<br>(N=92) |
|------------------------------------|------------------------------|---|
| Age at high-risk diagnosis (years) |                              |   |
| < 1.5                              | 14.9%                        | 13.0%   |
| ≥ 1.5 to < 6                       | 76.6%                        | 73.9%   |
| ≥6                                 | 8.5%                         | 13.0%   |
| Stage 4                            | 85.1%                        | 87.0%   |
| MYCN amplified                     | 46.8%                        | 43.5%   |
| Pre-ASCT <sup>1</sup>              |                              |   |
| Not Reported                       | 4.3%                         | 0%  |
| CR/VGPR                            | 61.7%                        | 76.1%   |
| PR                                 | 34.0%                        | 23.9%   |

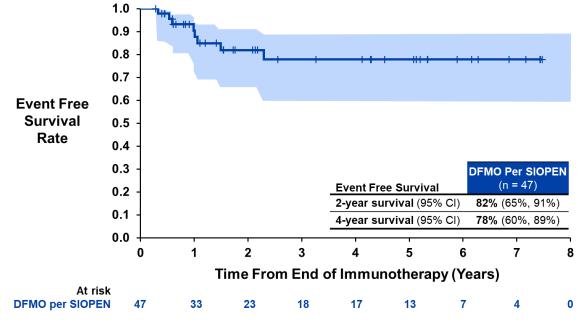
CR=complete response; PR=partial response; SIOPEN=European Association Involved in the Research and Care of Children with Neuroblastoma; VGPR=very good partial response.

1. Overall pre-ASCT response reported for DFMO Per SIOPEN, but overall response without bone marrow reported for DFMO Primary Analysis Population

Key demographic and disease characteristics were similar between the two groups of DFMO Upfront Remission patients. Further characterization of demographic and disease characteristics of the DFMO Per SIOPEN group compared to published characteristics of dinutuximab-beta patients in the HRNBL-1 study (Ladenstein 2020) is presented in Appendix 10.4.

Analysis of interim EFS data for the DFMO Per SIOPEN group is presented in Figure 25.

### Figure 25: Event Free Survival in DFMO Per SIOPEN Cohort



DFMO=eflornithine; CI=confidence interval.

The 2- and 4-year EFS estimates for the DFMO Per SIOPEN group reflect higher levels of early censoring but are generally similar to those reported for the primary analysis DFMO group (Upfront Remission following COG SoC) in the externally controlled comparison. This provides preliminary support for consistency of outcomes with DFMO maintenance after upfront treatment across two similar upfront treatment paradigms (COG and SIOPEN). Also, the shape of the DFMO curve, with most patients achieving durable remission beyond 2 years, is similar to Study 3b DFMO group for the externally controlled comparison (Figure 18).

### 6.4.1.3 <u>Relapse Risk Reduction in Study 3b Patients in Remission After R/R Therapy</u> (Stratum 2)

As described in Section 6.2.1.2, Study 3b enrolled two cohorts of patients. While the primary study objective was to evaluate outcomes for Upfront Remission (Stratum 1) patients, an analysis of EFS was also prospectively planned for the poorer risk group of Remission after R/R Therapy Patients (Stratum 2).

#### 6.4.1.3.1 Definition of Patient Population for Remission After R/R Therapy

Patients were considered to have relapsed if they had a confirmed relapse of high-risk neuroblastoma prior to enrollment to Study 3b. Per protocol, these patients were required to achieve a subsequent remission prior to participation on DFMO treatment. Remission was operationally defined identically for patients as in Stratum 1 (achieving at least a PR at conclusion of R/R therapy with no evidence of disease in the bone marrow and, for patients with residual MIBG lesions, PET or biopsy to confirm metabolic inactivity). Although refractory HRNB lacks a consensus definition, for purposes of the Study 3b analysis and reporting, patients were considered refractory if they met either of the following two objective criteria. These criteria were defined based on ANBL0032 eligibility criteria, thus ensuring that all patients that could have been eligible for ANBL0032 were maintained in the Upfront Remission cohort (Stratum 1) of Study 3b:

- Patients were considered refractory if they exceeded high-normal upfront treatment durations, which were defined in relation to whether patients received ASCT.
  - Patients who received ASCT were considered refractory if either of the following were true: there were > 13 months from high-risk diagnosis to ASCT or > 205 days from ASCT to start of immunotherapy.
  - Patients who did not receive ASCT were considered refractory if there was
     > 13 months from diagnosis to start of immunotherapy.
- Patients were considered refractory if they required additional treatment after immunotherapy (i.e., patients who did not relapse during standard upfront treatment but required further treatment to achieve initial remission). Such patients would also be expected to fail the Stratum 1 criteria to enroll on DFMO within 120 days of completion of immunotherapy.

Patients who met both refractory and relapsed criteria were considered relapsed for the purposes of Stratum 2 cohort placement.

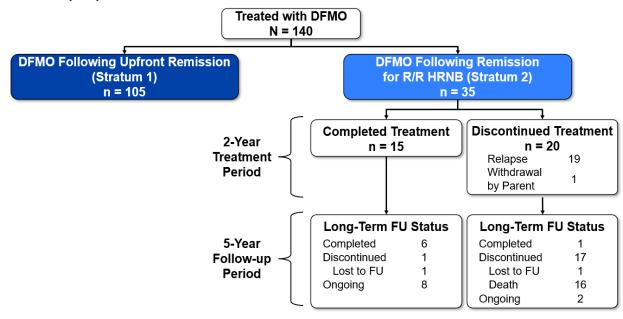
### 6.4.1.3.2 <u>Endpoint Definitions for Patients In Remission After R/R Therapy (Stratum 2)</u> The prospective endpoint for patients who achieved remission only after treatment for R/R disease (Stratum 2) was to compare EFS at 2 years vs a 10% historical control rate.

Based upon median EFS times at 2 years, as presented by Santana (2008), a median of 8.7 months from first-to-second recurrence is equivalent to a 14.8% EFS rate, and a median 3.8 months from second-to-third recurrence is equivalent to a 1.3% EFS rate, assuming an

exponential time-to-event model. Assuming (1) two-thirds of the relapsed patient population will have one relapse and the other one-third will have  $\geq$  2 relapses, a weighted average of these two EFS rates (14.8% and 1.3%) equals 10.3%. A 10% historical 2-year EFS rate was assumed for simplicity.

6.4.1.3.3 <u>Study 3b Results for Patients In Remission After R/R Therapy (Stratum 2)</u> An overview of the disposition of patients who had been treated for relapsed/refractory disease prior to receiving DFMO maintenance is presented in Figure 26.

### Figure 26: Disposition of Study 3b Stratum 2, Remission After R/R Therapy Patients (ITT)



FU=follow-up; ITT=intent-to-treat; R/R=relapsed/refractory.

Note: Patients in remission after relapse/refractory therapy = Stratum 2.

In Stratum 2, 15/35 patients (42.9%) completed 2 years of DFMO treatment and 20/35 patients (57.1%) discontinued treatment early with relapse being the leading cause (19 patients). This result is expected as the Stratum 2 patients had already experienced a previous relapse or refractory disease. Sixteen/19 patients (84.2%) who discontinued DFMO treatment due to relapse died before completing the 5-year follow-up period of the study.

### Disease Characteristics of Patients In Remission After R/R Therapy (Stratum 2)

A total of 35 patients who achieved remission after R/R therapy were enrolled in the Stratum 2 cohort, including 28 patients in remission after one or more prior relapses and 7 patients in remission after refractory therapy. Of the relapsed patients, 23 patients had one prior relapse while 5 patients had two or more relapses prior to enrollment (Table 19).

Notably, the Stratum 2 relapsed patient who was included in the DFMO group for the pivotal, externally controlled study is also conservatively included in the Stratum 2 analysis as prospectively planned. Therefore, this patient contributes a relapse event to both the pivotal Upfront Remission patient outcome comparisons and the supporting Remission After R/R Therapy patient outcome comparisons which establish DFMO maintenance benefits.

Table 19 summarizes demographic, disease and treatment history information for each of the refractory and relapsed patient groups, and for the overall Stratum 2 population.

| Table 19:   | Demographics and Disease Characteristics for Study 3b Stratum 2, |  |  |
|---|--|--|--|
| Patients in Remission Following R/R Therapy (ITT) |  |  |  |

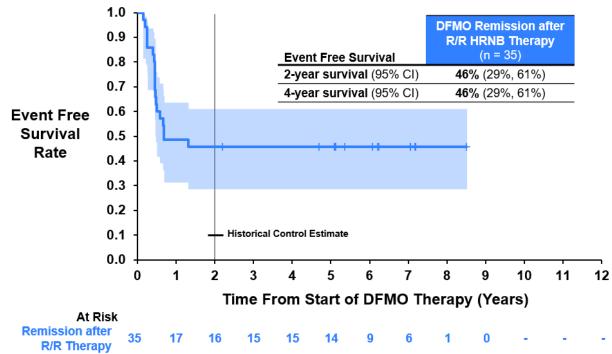
| Parameter, n (%):                 | Refractory<br>(N=7) | Relapsed<br>(N=28) | All R/R<br>(Stratum 2)<br>(N=35) |
|-----------------------------------|---------------------|--------------------|----------------------------------|
| Age at HRNB Diagnosis             |                     |                    |                                  |
| < 18 months                       | 1 (14.3)            | 2 (7.1)            | 3 (8.6)                          |
| ≥ 18 months and < 6 years         | 4 (57.1)            | 25 (89.3)          | 29 (82.9)                        |
| ≥ 6 years                         | 2 (28.6)            | 1 (3.6)            | 3 (8.6)                          |
| Stage at HRNB Diagnosis           |                     |                    |                                  |
| 3                                 | 0                   | 1 (3.6)            | 1 (2.9)                          |
| 4                                 | 6 (85.7)            | 26 (92.9)          | 32 (91.4)                        |
| 4s                                | 1 (14.3)            | 1 (3.6)            | 2 (5.7)                          |
| Histology                         |                     |                    |                                  |
| Favorable                         | 2 (28.6)            | 3 (10.7)           | 5 (14.3)                         |
| Unfavorable                       | 2 (28.6)            | 20 (71.4)          | 22 (62.9)                        |
| Not available                     | 3 (42.8)            | 5 (17.9)           | 8 (22.9)                         |
| MYCN Amplification                |                     |                    |                                  |
| Amplified                         | 1 (14.3)            | 9 (32.1)           | 10 (28.6)                        |
| Non-amplified                     | 4 (57.1)            | 18 (64.3)          | 22 (62.9)                        |
| Unknown                           | 2 (28.6)            | 1 ( 3.6)           | 3 (8.6)                          |
| Time to First Relapse (months)    |                     |                    |                                  |
| > 6 to ≤ 18                       | -                   | 22 (78.6)          | -                                |
| > 18                              | -                   | 6 (21.4)           | -                                |
| Number of Prior Relapses          |                     |                    |                                  |
| 1 Prior Relapse                   | -                   | 23 (82.1)          | -                                |
| ≥ 2 Prior Relapses                | -                   | 5 (17.9)           | -                                |
| Received Chemoimmunotherapy (yes) | 0                   | 1 (3.6)            | 1 (2.9)                          |

HRNB=high-risk neuroblastoma, ITT=intent-to-treat

Note: Chemoimmunotherapy defined as a combination regimen of irinotecan, temozolomide, and dinutuximab. Patients in remission after relapse/refractory therapy = Stratum 2

### Prospective Survival Results in Patients In Remission After R/R Therapy (Stratum 2)

The Kaplan-Meier estimated EFS at 2 years was 46% (95% CI: 29%, 61%) (Figure 27). This was improved (p < 0.0001) compared to prespecified historical control EFS rate of 10%.



## Figure 27: Event Free Survival in Study 3b Remission Following R/R Therapy Patients (Stratum 2, ITT)

CI=confidence interval; DFMO=eflornithine; EFS=event free survival; HRNB=high-risk neuroblastoma; R/R=relapsed or refractory.

Notably, no events are observed after the 2 year treatment period, consistent with the curve for the Upfront Remission (Stratum 1) patients in Study 3b.

The prespecified analyses consider the combined group of refractory and relapsed patients. Further characterization and discussion of the two subgroups is presented in Appendix 10.5.

#### 6.4.1.4 Expanded Access Study 6b (NMTRC006b) Remission Patients

BCC has an actively enrolling intermediate population expanded access study for DFMO, NMTRC006b (Study 6b). The study aims to provide access to patients who do not meet eligibility criteria for enrolling prospective, interventional studies of DFMO. A total of 97 patients have been enrolled to date, including 28 neuroblastoma patients (all HRNB except 1 intermediate-risk patient) in remission at the time enrollment. Within this group of patients, 13 were Upfront Remission patients and 15 were Remission After R/R Therapy patients.

Of the 13 Upfront Remission patients, 12 (92.3%) remain in remission with 8 completing 2 years of DFMO therapy and 4 continuing on DFMO therapy (duration of DFMO therapy range: 180 to 629 days) (Table 20). One patient (7.7%) relapsed after 453 days on DFMO therapy.

Of the 15 Remission After R/R Therapy Patients, 10 patients (66.6%) remain in remission with 6 patients completing 2 years of DFMO therapy (5 HRNB, 1 intermediate-risk neuroblastoma), 1 patient stopped DFMO (duration of DFMO therapy: 86 days), and 3 patients with HRNB continuing on DFMO therapy (duration of DFMO therapy range: 285 to 685 days). Five patients with HRNB (33.3%) relapsed during DFMO therapy (start of DFMO therapy to relapse: 49 to 170 days).

A summary of EFS outcomes for both cohorts of patients is presented in Table 20.

| Table 20: | Summary of Event Free Survival in Expanded Access Study 6b |  |
|-----------|--|--|
|-----------|--|--|

| EFS Outcome, n (%):                        | Upfront Remission<br>(N=13) | <b>Rem</b> ission after R/R<br>(N=15) |
|--|-----------------------------|---------------------------------------|
| Remain in remission                        | 12 (92.3%)                  | 10 (66.6%)                            |
| Completed treatment                        | 8 (66.6%)                   | 6 (60%)                               |
| Treatment ongoing                          | 4 (33.3%)                   | 3 (30%)                               |
| Treatment stopped                          | -                           | 1 (10%)                               |
| Relapse                                    | 1 (7.7%)                    | 5 (33.3%)                             |
| Days (Range) to relapse from start of DFMO | 453 days                    | 49-170 days                           |

DFMO=eflornithine; EFS=event free survival; R/R=relapsed or refractory.

While these preliminary results are based on small groups of patients and do not reflect fully matured data, the current trends again are consistent with the reported rates of the completed pivotal Study 3b for both Strata 1 (Upfront Remission) and 2 (Remission After R/R Therapy) DFMO-treated patients.

### 6.4.2 Anti-Tumor Effects

DFMO has been developed as a maintenance therapy to reduce the risk of relapse in patients achieving remission. This use is well aligned with the preclinical evidence and mechanistic attributes of DFMO to reduce cellular levels of polyamines and reverse the tumorigenic phenotype. However, DFMO's inhibition of ODC and its downstream impact on polyamines, the Lin28/Let-7 balance, and changes to the microenvironment associated with immune response all indicate the potential for DFMO to contribute to direct anti-tumor effects in active disease patients. More recent research showed that DFMO reduces tumor growth and drives distinct and reproducible alterations in the cellular composition of the neuroblastoma tumor microenvironment. At the center of this observation, DFMO mediated decreases in polyamines results in an increase in frequency and abundance of natural killer (NK) cells in tumor areas. Furthermore, there was an increase in tumor cells expressing NK cell ligands. Consistent with the current DFMO hypothesis that this drug drives its anti-tumor effect by a polyamine blockade, it appears that DFMO primes the tumor microenvironment to be more efficient at immune mediated cancer cell clearance (McNerney 2020).

The utility of DFMO in the treatment of active disease has been mostly studied at higher doses than those evaluated for maintenance and has most commonly been evaluated in combination with other cytotoxic agents, based on hypothesized synergistic effects for improved disease response. Clinical data from some studies evaluating DFMO in the setting of active disease are described further below.

### 6.4.2.1 <u>Published and Sponsor-acquired Studies in R/R Active Disease HRNB</u>

DFMO research for the R/R HRNB population includes trials conducted by the New Approaches to Neuroblastoma Therapy (NANT) consortium, BCC, and COG. In July 2023, Sponsor obtained regulatory rights to data for all studies conducted across these groups evaluating DFMO in HRNB active relapsed/refractory disease patients, including:

- NMTRC002, a Phase 1 study conducted by BCC (Sholler 2015)
  - Design: Open-label, single-arm, dose escalation study of DFMO alone (Cycle 1) and in combination with low dose oral etoposide (Cycles 2-5) in patients with R/R active HRNB
  - Key findings:
    - Median PFS: 80 days (range 21–1573 days at published data cutoff) [not designed for efficacy but median PFS exceeds reports from similar studies in contemporary and historical timeframe (Fox 2014)
    - 12 of 18 (66.7%) patients with response > PD after DFMO alone Cycle 1
    - 13 of 18 (72.2%) patients with response > PD after any cycle
    - 6 of 18 (33.3%) progression free during the trial period, 4 of 18 progression free >1 year
    - 3 of 18 (16.7%) patients are long-term survivors (Status: Remission, Alive)
    - Supported dose level selection for Study 3b
- NANT 2012-01, a Phase 1 study by NANT (Marachelian 2018)
  - Design: Single-arm, open-label, dose escalation study of DFMO in combination with celecoxib, cyclophosphamide/topotecan for patients with R/R active HRNB
  - Key findings:
    - Median PFS 19.8 months
    - 3 of 24 patients completed therapy (achieving CR or PR) and 2 were ongoing at time of publication, with the remaining patients discontinued for PD, doselimiting toxicity, or patient decision (e.g., withdrew consent)
    - Supported dose level selection for ANBL1821, an actively enrolling randomized controlled Phase 2 study by COG (NCT03794349) of irinotecan, temozolomide, and dinutuximab with or without DFMO in patients with R/R active HRNB

### 6.4.2.2 <u>Evaluation of Disease Improvement in HRNB Active Disease Patients In Expanded</u> <u>Access Study NMTRC006b</u>

Due to the very recent timing of the data acquisition for completed studies NANT2012-01 and BCC's NMTRC002 and the availability of published findings from these studies, the expanded access study NMTRC006b was the source of information selected for further evaluation of DFMO treatment in patients with active HRNB for presentation to the advisory committee panel.

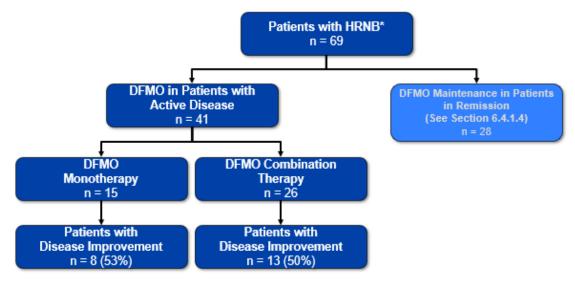
A total of 97 patients have been enrolled in the expanded access study, including a total of 69 neuroblastoma patients. Twenty-eight patients were in remission at the time of enrollment on 6b (described in Section 6.4.1.4), and 41 had active disease at the time of enrollment (Figure 28). Per the study protocol, patients were permitted to receive one combination therapeutic regimen with DFMO. In the active disease group, 15 received DFMO monotherapy and 26 received DFMO combination therapy with other agents.

This study did not prospectively define objective response; however a retrospective review of imaging impressions was conducted to characterize findings consistent with anti-tumor effects. Source records for all 41 patients with active disease were reviewed, including imaging reports and pathology findings from Baseline through study discontinuation/completion to assess for evidence of disease improvement. Disease improvement for this review was defined as imaging impressions which noted reduced tumor size or count on anatomical imaging, reduction or resolution of MIBG or PET signal intensity in Baseline lesions, or bone marrow change from

positive to negative. Evidence of improvement was observed in approximately half of all treated patients, including 8/15 DFMO monotherapy patients and 13/26 DFMO combination therapy patients.

Imaging for a subset of patients with evidence of improvement were subsequently independently reviewed by a radiologist to provide further evaluation and confirmation of post-DFMO disease changes.

### Figure 28: Expanded Access Study 6b – Disease Improvement in Patients with Active HRNB



<sup>\* 1</sup> patients with intermediate risk neuroblastoma

### 6.4.3 Measurable Pharmacodynamic Response in Patients Treated with Recommended Dose

#### 6.4.3.1 Urinary Polyamines

#### Decreasing urinary polyamine trend in DFMO-treated patients with active R/R disease

DFMO inhibits ODC, and in turn, reduces synthesis of polyamines. Polyamines are excreted in the urine, with urinary levels reflecting blood concentrations. Therefore, analysis of urinary polyamines provides an opportunity to detect changes in systemic polyamine levels through noninvasive sampling. The Phase 1 study of DFMO in patients with active R/R HRNB, NMTRC002 (Sholler 2015), included protocol-specified urine collections at pre-dose Cycle 1, Day 1 (Baseline), Day 8 and Day 15 and for subsequent DFMO + etoposide Cycles at Day 1 and/or Day 15. The findings of the polyamine analyses were reported by (Sholler 2015); and the Sponsor recently acquired the polyamine data enabling verification of the published results.

The published findings supported a relationship between DFMO treatment within the evaluated dose range of  $500 - 1500 \text{ mg/m}^2$  BID (covering the recommended dose level of  $750 \pm 250 \text{ mg/m}^2$  BID) and decreased urinary polyamines. Greater decreases from Baseline were observed within Cycle 1 (when patients received DFMO alone) in patients with a particular ODC genotype and in patients that remained progression free for at least 100 days. Baseline polyamines and change from Baseline levels were highly variable, which is expected given the

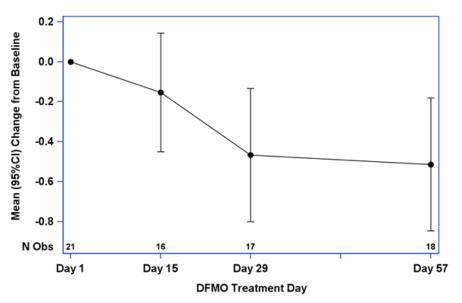
heterogeneity of enrolled patient population which included both relapsed and refractory patients having active disease considered either stable or progressing at the time of enrollment.

Decreasing urinary polyamine trend in DFMO-treated patients in remission

To further evaluate pharmacodynamic effects for the target patient population, urinary polyamine data were recently obtained for a small subgroup of N=21 Study 3b patients, including both Upfront Remission and Remission After R/R Therapy patients. Additional analyses of urine samples were originally planned but were halted during the study due to funding limitations at the time. These preliminary data were originally generated but only recently became available to the Sponsor as part of a data acquisition. Additional sample analysis has resumed but remains ongoing.

Consistent with the published findings in (Sholler 2015), the analysis focuses on acetylated polyamines. Urine samples contained very low levels of unmodified polyamines (putrescine, spermine, and spermidine), but had measurable and quantifiable levels of acetylated polyamines, including diacetylspermine, N8-acetylspermidine, and N1-acetylspermine, which are marked for excretion in the urine. Analyzing their sum provides insight into the body's polyamine production status. As shown in Figure 29, treatment with DFMO at the recommended dose evaluated in Study 3b causes a reduction in excreted polyamines (Mean [95% CI] of N1+N8+DAS change from baseline [log-transformed values]) found in the urine.

### Figure 29: Log-Transformed Mean (with 95% CI) Change from Baseline in Summed Acetylated Polymanines<sup>1</sup> in Urine Samples During DFMO Treatment in Study 3b (N=21) Patients in Remission



<sup>1</sup>Summed Acetylated Polyamines include diacetylspermine, N8-acetylspermidine, N1-acetylspermine

### 6.4.3.2 Plasma Let-7 microRNA Expression

As described in Section 6.4.3.1, ODC inhibition and reduced polyamine synthesis supports restored balance of Let-7 microRNA expression, a tumor suppressor involved in cellular regulatory feedback loops important to normal cell function. Thus, DFMO treatment would be

expected to result in increased levels of Let-7 which can be quantified by real-time reverse transcribed polymerase chain reaction (Real Time RT-PCR) analysis in plasma. BCC's Study NMTRC012 (described above in Section 1.6.2.1; Table 2) included plasma sample collection for analysis of biomarkers.

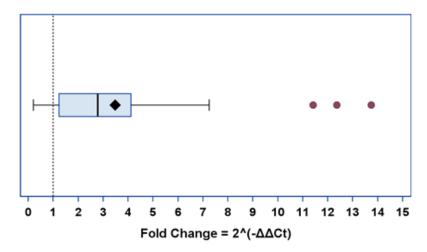
DFMO dosing in NMTRC012 was at the recommended dose, both for patients randomized to receive DFMO during immunotherapy (Arm B) and for all patients that received DFMO maintenance after immunotherapy (Arm A and Arm B).

A total of 33 patients met the minimum sampling requirements for inclusion in a preliminary PCR analysis of Let-7. Due to the small sample size, pre- and post-DFMO samples are compared for all patients regardless of arm assignment in order to assess DFMO treatment related changes for Let-7. Pre-DFMO samples for Arm A patients include samples collected through the end of immunotherapy given these patients were assigned to receive immunotherapy alone, whereas pre-DFMO samples for Arm B are samples collected prior to immunotherapy given these patients receive DFMO in combination with immunotherapy. Additionally, some patients have samples collected during induction and consolidation when patients generally have higher disease burden and could theoretically have reduced Let-7 expression compared to later treatment phases where the patient has lower disease burden. Thus, the pre-DFMO Let-7 mean calculation for each patient considered only samples collected after consolidation or later in order to limit the influence of Let-7 levels during early treatment on the pre-DFMO Let-7 expression value. Thus, for inclusion in the analysis, patients were required to have at least one pre-DFMO plasma sample that was collected after consolidation therapy and at least one post-DFMO sample.

Cycle threshold data was calculated using relative threshold analysis algorithms. Each target miR assay was normalized against a standardization miRNA to determine Delta Ct ( $\Delta$ Ct) values for each sample set and experimental condition. Delta Ct is the difference in Ct values between the target gene and the standardization miRNA calculated as  $\Delta$ Ct = Ct\_target - Ct\_reference. Delta Cts are averaged separately for the pre-DFMO samples and the post-DFMO samples for each patient. The change between pre and post-DFMO sample means are calculated as Delta Delta Cts ( $\Delta$ ACt). It is calculated as follows:  $\Delta$ ACt =  $\Delta$ Ct\_postDFMO -  $\Delta$ Ct\_pre-DFMO. Delta Delta Ct values allow calculation of a relative fold change between the preDFMO expression level and the post-DFMO expression level using the following formula:  $2^{(-\Delta\Delta$ Ct)}. The calculation is based on the principle that each Ct value represents a 2-fold change in the amount of target nucleic acid. So, raising 2 to the power of the negative  $\Delta$ ACt gives you the fold change. For example, if the  $\Delta$ ACt value is -3, the fold change would be  $2^{-(-3)} = 8$ , which means the gene expression has increased by 8-fold in the experimental sample (in this case the post-DFMO sample mean) compared to the control (in this case the pre-DFMO sample mean). A fold change of 1 would indicate no change between the samples being compared.

The resulting fold change values for all patients included in the analysis were then averaged and presented in the box and whisker plot in Figure 30.

### Figure 30: Post vs Pre-DFMO Fold Changes in Serum Levels of Let-7 miRNA in Study NMTRC012 (n=33)



The results identify a trend for increased Let-7 expression in patients with HRNB treated with DFMO at the recommended dose, with an average increase from pre-DFMO to post-DFMO samples of approximately 3-fold across the evaluated patients. The trends for increased Let-7 expression with DFMO treatment are consistent with literature characterizing interactions between reduced polyamine and Let-7 balance restoration expected to occur with adequate ODC inhibition. There are limitations to this analysis as it is an exploratory analysis in a small sample size. However, these preliminary results are complimentary and supportive to reduced urinary polyamine levels observed in NMTRC002 and with the clinical outcomes observed in the pivotal Study 3b external control comparison and other supporting analyses of relapse risk reduction benefit with DFMO at the recommended dose.

### 6.4.4 Conclusions from Confirmatory Data

Supportive evidence, including additional analyses supporting maintenance benefit, anti-tumor activity, and pharmacodynamic effects of DFMO in HRNB, contributes to the efficacy package of DFMO. Further, these clinical data are consistent with the extensive nonclinical mechanistic and animal model research (Section 3.4), which has long supported the biological plausibility of DFMO benefit in patients with HRNB.

The confirmatory data supporting DFMO as an effective maintenance treatment for HRNB is summarized in Table 2. While each component of the confirmatory data package has limitations, together the quantity and quality of the evidence provides support for the interpretation of the EFS improvement from the pivotal comparisons, adding confidence to the attributability and magnitude of DFMO's relapse risk reduction benefit.

### 6.5 Efficacy Conclusions

DFMO treatment produced meaningful improvement in EFS rates in pediatric HRNB patients who have completed multiagent multimodality therapy. This claim is supported by the prospective evaluations in Study 3b, the patient-level comparisons to the external control database, ANBL0032, and independent evaluation of the outcomes for treated patients based on a BICR of imaging. Overall survival is also improved in patients receiving DFMO treatment, which is

expected given a lower rate of relapse would be expected to translate into a lower risk of death in the same group of patients.

DFMO program data meets regulatory requirements to demonstrate substantial evidence of effectiveness. The regulatory criteria for substantial evidence require that efficacy be established with either two adequate and well controlled studies, or one adequate and well controlled study that is supported by additional confirmatory data. The DFMO data package includes pivotal, externally controlled Study 3b vs ANBL0032 analysis together with multiple components of supporting evidence of sufficient quality and quantity to exceed the regulatory threshold.

The preponderance of evidence supports DFMO's efficacy for its proposed use as a maintenance therapy in the HRNB population, especially in the context of this rare, serious disease with significant unmet medical needs. The program meets stringent regulatory criteria while showcasing the potential of real-world evidence, in particular externally controlled trials, as a means to accelerate new therapies for rare diseases, consistent with current regulatory initiatives in the US and worldwide.

### 7 CLINICAL SAFETY

#### <u>Summary</u>

- DFMO was generally safe and well tolerated in clinical trials
- 311 patients with HRNB have received DFMO at the proposed 1500 mg/m<sup>2</sup> dose, including 52 patients in Study 3b and 259 in Study 14
- Grade 3 or 4 AEs were reported in 43.7% of the pooled safety population:
  - Hypoacusis (11.9%), ALT increased (11.9%), AST increased (6.8%), pyrexia (4.2%), anemia (3.9%), and neutrophil count decreased (3.5%) were the Grade 3 of 4 AEs reported in ≥ 3% of patients who received DFMO
- Most AEs resolved without the need for discontinuation or dose modification
  - AEs resulted in dose modification in 11.9% of patients and discontinuation in 5.1%.
  - o Hypoacusis led to the most dose modifications or discontinuations
- Serious AEs occurred in 16% of patients, with most consistent with normal childhood illnesses.
- There were no deaths due to AEs
- DFMO has an established ototoxicity risk, so audiograms were required
  - Baseline audiograms confirmed expected pre-study hearing loss in most patients (82.7%)
  - Within the pooled safety population, 12.9% of patients had hearing loss that worsened by ≥ 1 grade from baseline, and 12.2% had hearing loss that worsened by at least 1 grade from baseline and worsened to Grade 3
  - Among patients with dose modification or discontinuation due to hearing loss, 63% improved or resolved to baseline
- The most common laboratory parameter changes in Study 14 were consistent with anticipated potential risks of hepatotoxicity and myelosuppression

#### 7.1 Introduction

The safety of DFMO has been studied in a safety population of 311 patients with HRNB treated with the to-be-marketed DFMO drug product at the recommended dose level for a duration of up to 2 years. This safety population adequately addresses the intended patient population.

The primary pooled safety population of 311 patients comprises patients in Study 3b and a similarly designed, actively enrolling, prospective, single-arm, open-label study, Study 14 (Table 8). Study 14 was initiated following completion of accrual and initial analyses of Study 3b in order to provide continued DFMO access to patients with HRNB in remission and to further characterize the PK and safety profile of the product, including assessments to address registration requirements (e.g., ECGs).

Study 3b contributes safety data for 52 patients. As described further in Section 4.2.2.2, Study 3b was initiated as Study 3 and amended to Study 3b when the study transitioned to a new source of drug product. The amendment to Study 3b resulted in the creation of a separate database, which includes safety data from the time of the amendment to 3b. The Sponsor did not have legal rights to access safety data collected prior to the amendment to Study 3b at the time of the NDA. Therefore, only the 52 Study 3b patients enrolled after the amendment to Study 3b are included in the pooled safety population.

Safety assessments in both studies included AEs, vital signs, audiograms, and clinical labs, however, there were some differences in reporting requirements (Table 21). Specifically, Study 3b required reporting of Grade 2 and higher AEs whereas Study 14 required reporting of only

Grade 3 and higher events. Study 14 reporting included individual laboratory parameter data, whereas only laboratory abnormalities meeting the criteria for Grade 2 or higher events were reported as AEs in Study 3b. Due to these differences, analyses of non-laboratory related AE data in the pooled safety population are limited to Grade 3 and higher events. Additionally, the most comprehensive assessment of laboratory abnormalities is limited to Study 14 patients for whom parameter data can be compared against CTCAE criteria for all grades.

The majority of the pooled safety population are patients who achieved initial remission after upfront treatment and also includes patients in remission after R/R therapy. All other demographics and baseline characteristics as well as safety data were generally similar across Study 3b and Study 14 patients comprising the pooled safety population. Therefore, the following sections will focus on data for the pooled safety population, except for data that were collected more extensively in Study 14 (e.g., ECGs and laboratory parameters).

### Table 21:Adverse Event Reporting Requirements for the Pooled SafetyPopulation (Study 3b and Study 14)

| Pooled Safety (N=311) | Grade 1      | Grade 2  | Grade 3               | Grade 4               |
|-----------------------|--------------|--|-----------------------|-----------------------|
| Study 3b (n=52)       |              | Reporting Required   |                       |                       |
| Study 14 (n=259)      | Not reported | Only reported if the<br>event resulted in dose<br>modification or study<br>discontinuation | Reporting<br>Required | Reporting<br>Required |

### 7.2 Treatment Exposure

Within the pooled safety population (n=311; Table 21), 216 patients (69.5%) received treatment for at least one year at the time of the data cut, with many Study 14 patients continuing on DFMO therapy at the time of the data cutoff for the NDA. The median duration of exposure was 2 years (interquartile range: 280 - 731 days).

After completing or stopping DFMO early, patients continue in long-term follow-up for up to five years. The majority of patients (266/311; 85.5%) remained ongoing in the long-term follow-up at the time of the data cutoff for the NDA.

### 7.3 Adverse Events

Both studies captured AEs per CTCAE, Version 4. Differences in AE reporting requirements between the studies led to a higher percentage of Study 3b patients reporting AEs (80.8% in Study 3b versus 46.3% in Study 14) (Table 22). As expected, these differences are primarily driven by a higher incidence of Grade 2 AEs reported in Study 3b (42/52; 80.8%) compared to Study 14 (8/259; 3.1%).

To address differences in AE collection between the two studies, AE tables include one column containing all AEs reported for Study 3b and then a column of Grade 3 or higher AEs in Study 3b to enable appropriate comparison to Study 14 AE rates. The pooled 1500 mg/m<sup>2</sup> group does not include Study 3b AEs < Grade 3.

Severe AEs (Grade 3 or 4) were reported in 43.7% of patients in the pooled population. The incidence of severe AEs was similar between Study 3b and Study 14.

| Patients with, n (%): | Study 3b<br>(N=52) | Study 3b<br>Grade ≥ 3<br>(N=52) | Study 14<br>(N=259) | Both<br>Studies<br>Pooled<br>(N=311) |
|-----------------------|--------------------|---------------------------------|---------------------|--------------------------------------|
| Patients with any AE  | 42 (80.8)          | 21 (40.4)                       | 120 (46.3)          | 141 (45.3)                           |
| Grade 2 events        | 42 (80.8)          | -                               | 8 (3.1)             | 8 (2.6)                              |
| SAE (Grade 3 or 4)    | 21 (40.4)          | 21 (40.4)                       | 115 (44.4)          | 136 (43.7)                           |
| Highest AE of Grade 3 | 20 (38.5)          | 20 (38.5)                       | 93 (35.9)           | 113 (36.3)                           |
| Highest AE of Grade 4 | 1 (1.9)            | 1 (1.9)                         | 22 (8.5)            | 23 (7.4)                             |
| SAEs                  | 6 (11.5)           | 5 (9.6)                         | 46 (17.8)           | 51 (16.4)                            |
| AEs leading to death  | 0                  | 0                               | 0                   | 0                                    |

| Table 22: | Overall Summary of Adverse Events in the Pooled Safety Population |
|-----------|---|
|-----------|---|

AE=adverse event; SAE=serious adverse event.

### 7.3.1 Common Adverse Events

AEs reported in at least 5% of patients in any subgroup are presented in Table 23. The most common AEs in the pooled safety population were hypoacusis (12%) and ALT increased (12%), followed by AST increased (7%), pyrexia (4%), anemia (4%), and neutrophil count decreased (4%).

When considering events of all grades reported in Study 3b (first data column in Table 23), the most common AEs included otitis media, sinusitis, pyrexia, and diarrhea.

## Table 23:Overall Summary of Adverse Events Reported by $\geq$ 5% Patients inAny Subgroup by Preferred Term in Descending Incidence in the Pooled SafetyPopulation

| Preferred Term, n (%):               | Study 3b<br>(N=52) | Study 3b<br>Grade ≥ 3¹<br>(N=52) | Study 14<br>(N=259) | Both<br>Studies<br>Pooled<br>(N=311) |
|--------------------------------------|--------------------|----------------------------------|---------------------|--------------------------------------|
| Hypoacusis                           | 5 (9.6)            | 5 (9.6)                          | 32 (12.4)           | 37 (11.9)                            |
| Alanine aminotransferase increased   | 5 (9.6)            | 3 (5.8)                          | 34 (13.1)           | 37 (11.9)                            |
| Aspartate aminotransferase increased | 4 (7.7)            | 3 (5.8)                          | 18 (6.9)            | 21 (6.8)                             |
| Pyrexia                              | 10 (19.2)          | 0                                | 13 (5.0)            | 13 (4.2)                             |
| Anemia                               | 3 (5.8)            | 2 (3.8)                          | 10 (3.9)            | 12 (3.9)                             |
| Neutrophil count decreased           | 5 (9.6)            | 4 (7.7)                          | 7 (2.7)             | 11 (3.5)                             |
| Vomiting                             | 6 (11.5)           | 0                                | 8 (3.1)             | 8 (2.6)                              |
| Skin infection                       | 4 (7.7)            | 3 (5.8)                          | 3 (1.2)             | 6 (1.9)                              |
| Diarrhea                             | 9 (17.3)           | 3 (5.8)                          | 3 (1.2)             | 6 (1.9)                              |
| Blood alkaline phosphatase increased | 3 (5.8)            | 1 (1.9)                          | 4 (1.5)             | 5 (1.6)                              |
| Pneumonia                            | 8 (15.4)           | 1 (1.9)                          | 4 (1.5)             | 5 (1.6)                              |
| Platelet count decreased             | 0                  | 0                                | 4 (1.5)             | 4 (1.3)                              |

| Preferred Term, n (%):            | Study 3b<br>(N=52) | Study 3b<br>Grade ≥ 3 <sup>1</sup><br>(N=52) | Study 14<br>(N=259) | Both<br>Studies<br>Pooled<br>(N=311) |
|-----------------------------------|--------------------|--|---------------------|--------------------------------------|
| Otitis media                      | 20 (38.5)          | 1 (1.9)                                      | 3 (1.2)             | 4 (1.3)                              |
| Upper respiratory tract infection | 7 (13.5)           | 0  | 4 (1.5)             | 4 (1.3)                              |
| Urinary tract infection           | 5 (9.6)            | 1 (1.9)                                      | 3 (1.2)             | 4 (1.3)                              |
| Pain in extremity                 | 4 (7.7)            | 0  | 2 (0.8)             | 2 (0.6)                              |
| Sinusitis                         | 10 (19.2)          | 0  | 1 (0.4)             | 1 (0.3)                              |
| Rash maculo-papular               | 3 (5.8)            | 1 (1.9)                                      | 0                   | 1 (0.3)                              |
| Cough                             | 7 (13.5)           | 0  | 0                   | 0                                    |
| Rhinitis allergic                 | 6 (11.5)           | 0  | 0                   | 0                                    |
| Conjunctivitis                    | 5 (9.6)            | 0  | 0                   | 0                                    |
| Eye infection                     | 3 (5.8)            | 0  | 0                   | 0                                    |
| Constipation                      | 3 (5.8)            | 0  | 0                   | 0                                    |
| Nausea                            | 3 (5.8)            | 0  | 0                   | 0                                    |

1. CTCAE v4.0

### 7.3.2 Serious AEs

In the pooled safety population, 51 patients (16.4%) reported an SAE (Table 22). SAEs reported in more than one patient are presented in Table 24.

In the absence of a control arm, it is important to consider that these SAEs may be related to DFMO. However, many of the events are consistent with illnesses that may be expected to be observed in some children over the course of a two-year time frame.

### Table 24:Overall Summary of Serious Adverse Events Reported in More thanOne Patient in the Pooled Safety Population by System Organ Class

| System Organ Clas<br>Preferred Term n (%): | ss Study 3b<br>(N=52) | Study 14<br>(N=259) | Both Studies<br>Pooled<br>(N=311) |
|--|-----------------------|---------------------|-----------------------------------|
| Infections and infestations                | 1 (1.9)               | 23 (8.9)            | 24 (7.7)                          |
| Pneumonia                                  | 0                     | 4 (1.5)             | 4 (1.3)                           |
| Bacteremia                                 | 0                     | 3 (1.2)             | 3 (1.0)                           |
| Device related infection                   | 0                     | 3 (1.2)             | 3 (1.0)                           |
| Skin infection                             | 1 (1.9)               | 2 (0.8)             | 3 (1.0)                           |
| Upper respiratory tract infection          | 0                     | 3 (1.2)             | 3 (1.0)                           |
| Otitis media                               | 0                     | 2 (0.8)             | 2 (0.6)                           |
| Metabolism and nutrition disorders         | 2 (3.8)               | 12 (4.6)            | 14 (4.5)                          |
| Dehydration                                | 0                     | 7 (2.7)             | 7 (2.3)                           |
| Hypoglycemia                               | 1 (1.9)               | 3 (1.2)             | 4 (1.3)                           |
| Hyponatremia                               | 1 (1.9)               | 1 (0.4)             | 2 (0.6)                           |
| Gastrointestinal disorders                 | 2 (3.8)               | 8 (3.1)             | 10 (3.2)                          |

| System Organ Class<br>Preferred Term n (%):          | Study 3b<br>(N=52) | Study 14<br>(N=259) | Both Studies<br>Pooled<br>(N=311) |
|--|--------------------|---------------------|-----------------------------------|
| Vomiting   | 0                  | 6 (2.3)             | 6 (1.9)                           |
| Diarrhea   | 1 (1.9)            | 1 (0.4)             | 2 (0.6)                           |
| General disorders and administration site conditions | 1 (1.9)            | 7 (2.7)             | 8 (2.6)                           |
| Pyrexia  | 1 (1.9)            | 7 (2.7)             | 8 (2.6)                           |
| Respiratory, thoracic and mediastinal disorders      | 0                  | 5 (1.9)             | 5 (1.6)                           |
| Нурохіа  | 0                  | 3 (1.2)             | 3 (1.0)                           |
| Investigations                                       | 0                  | 4 (1.5)             | 4 (1.3)                           |
| Blood creatinine increased                           | 0                  | 2 (0.8)             | 2 (0.6)                           |

### 7.3.3 Deaths

There were no AEs leading to death in either Study 3b or Study 14.

### 7.3.4 Adverse Events Leading to Dose Modification or Discontinuation

For both Study 3b and Study 14, dose modifications due to AEs included both temporary interruptions and/or dose reductions.

In the pooled safety population, 34 patients (10.9%) had their dose temporarily interrupted due to an AE (Table 25). The most common AEs which required dose interruptions were: hypoacusis (12/311; 3.9%), ALT increased (9/311; 2.9%), and AST increased (5/311; 1.6%).

The DFMO dose was reduced due to an AE in 17 patients (5.5%) in the pooled safety population. The only AE which required a dose reduction in more than 1% of those patients was hypoacusis (8/311; 2.6%).

Very few patients permanently discontinued DFMO treatment due to AEs. In the pooled safety population, 16 patients (5.1%) discontinued DFMO due to an AE. The only AE that led to discontinuation of study drug in more than 1% of patients was hypoacusis (5/311; 1.6%).

### Table 25:Summary of Adverse Events Requiring Dose Modification or DoseDiscontinuation in the Pooled Safety Population

| Patients with AEs Leading to Discontinuation or Modification <sup>1</sup> , n (%): | Study 3b<br>(N=52) | Study 14<br>(N=259) | Both Studies<br>Pooled<br>(N=311) |
|--|--------------------|---------------------|-----------------------------------|
| Dose modification  | 9 (17.3)           | 28 (10.8)           | 37 (11.9)                         |
| Dose interruption  | 7 (13.5)           | 27 (10.4)           | 34 (10.9)                         |
| Dose reduction   | 6 (11.5)           | 11 (4.2)            | 17 (5.5)                          |
| Drug discontinuation   | 3 (5.8)            | 13 (5.0)            | 16 (5.1)                          |

1. Dose modification includes patients with an interruption and/or reduction. Patients with more than one action with study drug are counted in all applicable rows. Not all patients with a dose modification had both an interruption and a reduction.

### 7.3.5 Adverse Events of Special Interest

### 7.3.5.1 Laboratory Abnormalities

### 7.3.5.1.1 Programmatic Assessment of Laboratory Abnormalities

Because Study 3b and 14 only required reporting of Grade 2 and higher or Grade 3 and higher AEs, respectively, lower grade AEs related to laboratory parameter changes may not have been consistently reported. AE reporting is the only source of identifying laboratory abnormalities in Study 3b; however, individual laboratory parameter data were captured in the study database for Study 14. To ensure a thorough assessment of potentially clinically significant laboratory abnormalities, the individual lab parameter data for Study 14 was programmatically compared to the CTCAE criteria for all grades. Higher rates of Grade 1 and 2 laboratory parameter changes occurred as compared to Grade 3 and 4 changes observed in protocol-required AE reporting, with the most common mild/moderate abnormalities (Grade 1-2) associated with liver function tests and decreases in blood cell counts. Rates of Grade 3 to 4 abnormalities were consistent with Study 14 AE reporting as expected, given the programmatic assessment of laboratory changes was limited to the Study 14 safety population.

#### 7.3.5.2 Clinical Chemistries

Changes in liver function parameters were the most common Grade 3 and Grade 4 changes observed from the programmatic assessment of laboratory data in Study 14 safety population and the most common Grade 3 and Grade 4 AEs associated with laboratory testing in the pooled safety population. In the pooled safety population, Grade 3/Grade 4 events of ALT increased and AST increased occurred in 11.9% and 6.8% of patients, respectively (Table 23).

Across the pooled safety population, very few patients required dose modification (11/311; 3.5%) or drug discontinuation (1/311; 0.3%) due to abnormal clinical chemistries, which were mostly due to changes in liver function parameters.

AEs related to clinical chemistries generally resolved. Among patients with dose modifications due to abnormal reported clinical chemistries, 91% (10/11) resolved after dose modification. Among patients without a dose modification, the majority (87.5%) of clinical chemistry AEs resolved and only 2 patients had AEs ongoing at the 30 day follow-up off DFMO visit.

#### 7.3.5.3 <u>Hematology</u>

Hematological changes assessed form programmatic assessment of laboratory parameter data identified Grade 3 and 4 changes at rates consistent with AE reporting in Study 14. In the pooled safety population, the most commonly observed Grade 3 and 4 hematological changes were anemia (3.9%) and neutrophil count decreased (3.5%), followed by platelet count decreased (1.3%) (Table 23).

Across the pooled safety population, hematological changes resulted in dose modification in 5 patients (5/311; 1.6%) and drug discontinuation in 3 patients (3/311; 1%), all of which were due to either decreased platelet count, decreased neutrophil count, or anemia.

AEs related to hematological changes generally resolved. Among patients with dose modifications due to hematological changes, all AEs resolved after dose modifications. Among patients without a dose modification, the majority (95.2%) of hematology AEs resolved and only one patient had an event ongoing at the 30-day follow-up off DFMO visit.

### 7.3.5.3.1 <u>Summary of Laboratory Safety Findings</u>

The observed increases in liver function parameters and decreases in blood cell counts are consistent with anticipated potential risk of hepatotoxicity and myelosuppression that have been reported with administration of higher doses of DFMO for the treatment of African sleeping sickness (Steverding 2010).

### 7.3.5.4 Hearing Loss

Hearing loss is a common long-term effect in pediatric cancer patients as a result of extensive anticancer therapy. A 2014 COG report evaluating ototoxicity rates in high-risk neuroblastoma patients receiving platinum-based chemotherapy established prevalence of any hearing loss ranging from 64% to 90% across hearing scales and exposure groups (lower dose cisplatin or higher dose cisplatin and/or carboplatin) (Landier 2014). The incidence of severe hearing loss (Grade 3 and 4) by CTCAE v3 was 47% and 71%, in the low and high exposure groups, respectively. Landier and other reports note that hearing loss risk is higher based on age of exposure to platinum-based therapy, with younger patients having significantly more risk of severe hearing loss. Putting this into context for the pooled safety population, patients enrolled in Study 3b or Study 14 would have been exposed to cisplatin and/or carboplatin during induction and (when CEM condition regimen was used) consolidation therapy, approximately a year or more prior to study Baseline. The pooled safety population further includes Study 3b Stratum 2 and Study 14 patients in remission after R/R therapy and may have had either higher and/or repeated exposure to platinum-based therapy. As a result, these patients would be expected to have further time for hearing loss side effects to develop and progress between exposure and Study 3b or 14 Baseline assessment.

Given the established ototoxicity risk of DFMO (i.e., Ornidyl®) and the SoC in HRNB to continue to monitor for continued progression of hearing loss as a late effect of upfront therapy, hearing assessments via audiograms were required safety assessments in both Study 3b and Study 14.

Table 26 captures reported AEs of hearing loss (hypoacusis). However, because Study 3b and 14 only required Grade 2 or Grade 3 and higher reporting, respectively, lower-grade hearing loss events were not required to be reported as AEs. Investigators were required to report categorical assessment of changes in hearing loss for all protocol-specified audiogram timepoints. The categorical assessment included responses of Abnormal, Normal, or No Significant Change. To more thoroughly characterize rates and severity of hearing loss during DFMO treatment, including changes that did not meet protocol-required AE reporting, an independent audiologist reviewed audiograms for patients with reported changes from Baseline hearing assessments (i.e., categorical change from Normal to Abnormal) who did not have reported AEs of hypoacusis. The results of this independent review were combined with AE reporting in the pooled safety population, to provide a more comprehensive assessment of changes in hearing loss.

Baseline audiograms confirmed expected pre-study hearing loss in the majority of patients; 82.7% of the pooled patients had abnormal hearing exams prior to receiving DFMO. Within the pooled safety population, 12.9% of patients had hearing loss that worsened by at least 1 grade from baseline, and 12.2% had hearing loss that worsened by at least 1 grade from baseline and worsened to Grade 3. New or worsening hearing loss overall was infrequent, and was not considered to be a major factor in discontinuation. Among patients with dose modification or discontinuation due to hearing loss, 37.5% (6/16) showed improvement and 25.0% (4/16) resolved to baseline.

|   |                    |                     | Both<br>Studies   |
|---|--------------------|---------------------|-------------------|
| Toxicity Assessment Based on Patient-Level Audiogram Data and Adverse Event reporting, n (%):                     | Study 3b<br>(N=52) | Study 14<br>(N=259) | Pooled<br>(N=311) |
| Audiogram abnormal at baseline <sup>1</sup>   | 45 (86.5)          | 209 (80.7)          | 254 (82.7)        |
| Patients with hearing loss worsened by at least <sup>1</sup> Grade 2 from baseline                                | 7 (13.5)           | 33 (12.7)           | 40 (12.9)         |
| Patients with hearing loss that worsened by at least 1 Grade 2 from baseline and worsened to Grade 3 <sup>3</sup> | 7 (13.5)           | 31 (12.0)           | 38 (12.2)         |
| Patients with hearing loss requiring dose modification or discontinuation   | 4 (7.7)            | 12 (4.6)            | 16 (5.1)          |
| Temporary interruption <sup>4</sup>   | 3 (5.8)            | 9 (3.5)             | 12 (3.9)          |
| Dose reduction <sup>4</sup>   | 2 (3.8)            | 6 (2.3)             | 8 (2.6)           |
| Drug discontinuation <sup>4</sup>   | 1 (1.9)            | 4 (1.5)             | 5 (1.6)           |
| Among patients with dose modification or discontinuation  |                    |                     |                   |
| Improved but did not return to baseline <sup>5</sup>  | 2 (50.0)           | 4 (33.3)            | 6 (37.5)          |
| Resolved to baseline <sup>5</sup>   | 0                  | 4 (33.3)            | 4 (25.0)          |

1. Percents calculated using the number of patients with a non-missing baseline audiogram.

2. Assessed per CTCAE.

3. No patient experienced a worsening to Grade 4.

4. Patients with more than one action taken with study drug are counted in each applicable row.

5. Percents calculated using the number of patients requiring a dose modification or discontinuation as the denominator.

### 7.4 Other Safety Assessments

Additional safety assessments performed in both Study 3b and Study 14 included physical examinations and vital signs. Electrocardiograms were also performed in Study 14.

There were generally no clinically meaningful changes observed in vital signs (temperature, heart rate, resting blood pressure, height, and weight) in either study. Heart rate decreased compared to baseline during the 2-year DFMO treatment period in a manner consistent with expected changes in growing children.

ECG data collected in Study 14 indicate that the PR interval generally appeared to increase compared to baseline over the 2-year DFMO treatment period whereas no changes in the QRS duration, QTcB, QTcF, or VR were observed. Less than 1% of patients experienced QTcF interval >450 msec to ≤480 msec at each post-baseline time point, and no patients experienced a QTcF >480 msec at any post-baseline time point. Concurrent PK sampling in Study 14 allowed assessment of concentration-QTc effects with no interactions identified.

### 7.5 Safety Conclusions

The DFMO program supports a favorable safety profile, especially for a therapeutic drug in the field of oncology. Conclusions and support of safety are supported by a wide range of preclinical research and thorough assessments in the target HRNB patient population. Evaluation of changes in vital signs, and ECGs did not identify any trends in the data indicative of safety concerns at the proposed dosing level. Some patients experienced abnormal liver function tests or decreased cell counts during treatment with DFMO, however these abnormalities generally resolved without requiring dose modification or discontinuation.

New and or worsening hearing loss may occur during DFMO treatment at the proposed recommended dose, although such changes should be considered in the context of the patient's treatment history, which most often will include platinum-based chemotherapy or other toxic treatments with the potential for late effects, including ototoxicity. Among patients whose dose was modified or discontinued due to new or worsening hearing loss, many showed improvement or resolution to baseline hearing levels, suggesting that hearing changes may be managed with dose reduction or interruption.

The most common events occurring during DFMO treatment, hearing loss, abnormal liver function tests, and decreased cell counts, are expected based on the pharmacology of DFMO. In the absence of a control arm, it is important to consider that other events may also be related to DFMO. However, some AE reporting is also consistent with clinical findings that can occur in children who have recently completed upfront treatment for HRNB or associated with normal childhood illnesses that may be expected to occur during the two year reporting period, as these children return to school and family activities.

Periodic monitoring is recommended as part of routine follow-up care to monitor for late effects after completion of upfront treatment although the frequency of long-term monitoring can vary based on the therapy administered during upfront treatment (COG 2018). Audiograms and laboratory testing, recommended as part of routine follow-up care in HRNB survivors, can support monitoring for hearing changes as well as indicators of hepatotoxicity or myelosuppression and implementation of recommendations for management of side effects, including dose modifications when indicated.

### 8 BENEFIT-RISK CONCLUSIONS

#### 8.1 Introduction

Benefits and risks of DFMO must be considered in the context of the seriousness of HRNB, a devastating, deadly disease. Nearly half of patients diagnosed with HRNB will not live more than 5 years after their diagnosis. High mortality is attributed to a number of factors: some patients have particularly aggressive and refractory disease at diagnosis that can persist or progress despite treatment; lethal side effects and complications including late effects are associated with highly toxic and invasive treatments employed with upfront treatment; and, for those patients able to achieve an initial remission, relapse occurs at an unacceptable rate and most often results in death.

Relapsed HRNB increases a patient's risk of death significantly. Innovations in HRNB therapy have most recently included the addition of anti-GD2 antibody immunotherapy, most commonly dinutuximab, to post-consolidation. Unfortunately, published outcomes on patients receiving all three phases of upfront therapy (induction, consolidation, and post-consolidation with immunotherapy) establishes that 2-year EFS is approximately 66% from the beginning of immunotherapy (Yu 2010). For patients who complete immunotherapy, the two-year EFS rate improves marginally to approximately 70%. In other words, among those children who can achieve and maintain remission through the end of immunotherapy, nearly one-third will relapse thereafter — and those patients face an even poorer outlook for survival into adulthood.

New therapies are needed to improve EFS rates in patients who achieve remission. The highest risk of relapse following current upfront therapy is during the first two years. Thus, DFMO as a treatment that is well tolerated with chronic administration, providing pharmacologic defense against disease recurrence during this timeframe, would address a significant unmet medical need.

The efficacy data from Study 3b support meaningful improvements in EFS in patients with HRNB achieving remission after upfront therapy when:

- Compared to published rates from study ANBL0032 as prospectively designed;
- Externally controlled with patient level data from study ANBL0032, overall and via the application of PSM; and
- Outcomes determined by BICR used in the comparative analyses.

ANBL0032, as an external control, meets the requirements for real-world evidence to support a regulatory decision. While Study 3b was not originally intended as a registration study, the unexpectedly high EFS and OS results compared to published historical rates warranted the use of an external control to expedite the availability of DFMO to patients with HRNB.

Taken together, the prospectively defined endpoint for Study 3b, access to and exhaustive analyses of patient level data for ANBL0032 (the same study against which it was originally designed for comparison), and the independent verification of outcomes via the BICR, enable Study 3b to meet the requirements of an adequate and well controlled study. In the context of this ultra-rare disease, such alternate investigational approaches are warranted and have precedent to support characterization of benefit, given randomized studies add significant length to development programs aimed to meet the needs of patients with serious conditions, especially those like HRNB that almost exclusively affect children.

### 8.2 Benefits

The EFS outcomes for DFMO-treated Upfront Remission patients demonstrate an improvement of 15 percentage points over historical and external controls. Cox proportional model analyses demonstrate a hazard ratio of approximately 0.5 across the defined primary and extensive sensitivity analyses utilizing PSM against the ANBL0032 external control. A hazard ratio of 0.5 conveys important clinical benefit, particularly in the context of HRNB EFS, translating to patients in the DFMO group having 50% reduction in risk for an EFS event over the course of the follow-up period compared to patients in the (overall population and matched) NO DFMO group.

While the EFS curves remain separated over the full follow-up time course, it is notable that the occurrence of late events in the DFMO-treated group was extremely low compared to ANBL0032, which showed EFS continuing to decline in Year 3 and beyond. In contrast, DFMO-treated patients' EFS remained nearly unchanged from the end of Year 2 and beyond. This finding supports the durability of the effect achieved with 2-year maintenance treatment with DFMO.

OS was also improved, consistent with the observed EFS improvement and known correlation between relapse and mortality. Hazard ratios for various externally controlled OS comparisons were in the range of 0.3 - 0.5. Thus, patients in the DFMO group had approximately one-third to one-half the risk of death over the follow-up period, compared to patients in the (overall population and matched) NO DFMO groups. The externally controlled comparisons of Study 3b to ANBL0032 are further supported by a separate externally controlled analysis (Lewis 2020).

Additional supportive evidence of DFMO efficacy includes similar EFS outcomes in other cohorts of patients in Upfront Remission and patients in remission after relapsed/refractory therapy. Across all cohorts evaluated for EFS, few events occur after the 2-year DFMO therapy period, a consistent finding that is unlike published survival curves in HRNB which continue to decline even beyond 5 years. Together, supporting evaluations of patients receiving DFMO maintenance increase confidence in the magnitude of benefit reported from the pivotal, externally controlled study. Attributability of observed relapse risk reduction across multiple evaluations is also supported by evidence of anti-tumor activity, with ~50% of the expanded access active disease patients experiencing some disease improvement during DFMO treatment. These observations were consistent with findings in published preclinical models and with preliminary signals of efficacy in published early clinical investigations in patients with active disease, including BCC's Phase 1 NMTRC002. Also, pharmacodynamic effects of DFMO were measurable in patients who received DFMO at the recommended dose, providing further biological confirmation of DFMO's mechanistic impact on polyamines and Let-7 which affect important pathways for neuroblastoma survival and growth.

Many oncology programs evaluate surrogate endpoints based on tumor response or PFS, which must be carefully weighed and considered to assign true clinical value, often considering the impact on extension and quality of the patient's remaining life as its primary benefit. By contrast, the primary EFS endpoint in the DFMO program can be interpreted clearly in terms of benefits. Given that patients receiving DFMO or included in the control comparisons were considered to be in remission, the occurrence of an event (relapse associated with referral to salvage therapy and increased risk of death) vs the lack of an event (maintained remission) can be clearly interpreted as adding significant clinical value to the treatment of HRNB.

### 8.3 Risks

The DFMO program supports a favorable safety profile, particularly for therapeutics in the field of oncology. Safety conclusions in HRNB maintenance are supported by a wide range of preclinical research, safety conclusions underlying prior approval of Ornidyl (recommended for pediatric use at much higher doses), and thorough safety assessments in more than 300 pediatric patients with HRNB.

In the DFMO clinical program, there were no AEs leading to death. Overall, DFMO displays a favorable toxicity profile, with anticipated side effects and risks that can be monitored and managed during clinical follow-up, including during periodic monitoring that is recommended as part of routine follow-up care after completion of upfront treatment. Treatment-related adverse effects, including hearing loss, changes in blood cell counts, and changes in liver function tests, have been identified through the safety evaluations in the DFMO safety population.

While hearing loss is a well characterized and common long-term side-effect of chemotherapies used to treat pediatric cancers, there have been reports in other studies assessing the safety of DFMO identifying hearing loss as a DFMO-related adverse drug effect. The majority of patients in the DFMO safety population had abnormal hearing at study Baseline, and 13% of patients had new or worsening hearing loss during the study. Within this group of patients experiencing treatment emergent changes in hearing who also had dose modifications (including temporary dose holds or reductions), many had improvement or resolution to back to Baseline. Very few patients discontinued DFMO due to hearing loss.

Laboratory abnormalities were carefully characterized, with the most common changes associated with the potential risks of myelosuppression and hepatotoxicity. Most abnormalities met criteria for CTCAE Grade 1 or 2 (mild-moderate) changes; however, Grade 3 and 4 changes did occur during treatment and warrant monitoring with routine laboratory testing. Very few AEs related to hepatotoxicity and myelosuppression required dose modifications or discontinuation of treatment and events generally resolved, either with or without dose modification.

### 8.4 Benefit-Risk Conclusions

In summary, the DFMO clinical program supports meaningful benefit in the HRNB population. Treatment with DFMO for up to the first two years following contemporary standard upfront therapy reduced the risk of relapse and death compared to patients who did not receive DFMO. A relapse diagnosis carries severe implications: a return to aggressive therapy, in addition to exacerbating the emotional, physical, and financial impacts of this devastating disease. Most children who experience even one relapse will die within 5 years, and DFMO reduces the risk of relapse.

The benefits of DFMO maintenance therapy clearly outweigh the risks, which can be anticipated, monitored, and managed with routine follow-up, including laboratory assessments and audiograms, consistent with survivorship care practices in place for pediatric patients with HRNB completing multiagent, multimodality therapy.

DFMO addresses a clear unmet need for children with HRNB, who currently have no treatment options to reduce the risk of relapse once they achieve remission and therefore remain vulnerable to disease recurrence and a dramatically shortened future. DFMO offers the option of continued, home-based maintenance treatment that does not contribute significant incremental toxicities to

prior therapies and increases the chances for children to enjoy durable long-term remission and live into adulthood.

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## **10 APPENDIX**

## **10.1 Propensity Score Matching Methodology**

### 10.1.1 Overview of Propensity Score Matching Methodology

We implemented propensity score matching (PSM) in this study to improve balance between DFMO-treated patients and NO DFMO patients based on available baseline covariates that determined both the propensity for a patient to be treated with DFMO and their outcome. Each analysis population required an All Covariate subset population, defined as the patients in the analysis population with available data for all 11 covariates: age at high risk diagnosis; sex; race; INSS stage; *MYCN* status; pre-ASCT response (primary tumor, soft tissue and bone metastases); transplant type; time from transplant (ASCT) to start of immunotherapy; overall response at end of immunotherapy; time from start of immunotherapy to end of immunotherapy. These covariates were used in the PS assignment. (Detailed explanations for covariate selection is presented in Section 10.1.2.)

A multiple logistic regression model was constructed using the group assignment (1=DFMOtreated and 0=NO DFMO) as the dependent variable with the 10 covariates as the potential confounders to be adjusted for. An estimated PS was assigned to each patient from All Covariate populations since logistic regression requires that no data be missing. Patients with propensity scores outside the overlapping score range were discarded prior to matching. NO DFMO patients (ANBL0032) were subsequently matched with DFMO-treated patients (Study 3b) using a greedy nearest-neighbor approach with a fixed 3:1 NO DFMO:DFMO ratio that exactly matched on the two-level MYCN amplification status. Because of the large available control patient population, a 3:1 ratio (i.e., 3 NO DFMO patients matched to each DFMO patient without replacement) was used to improve study power. In greedy matching, a treated patient is first selected at random and subsequently paired with a patient in the NO DFMO group with the closest propensity score; this is repeated until all DFMO patients are matched to patients in the NO DFMO group. After all DFMO patients have a single match, the process is repeated twice more to identify three NO DFMO patients for every one DFMO patient. After PSM, covariate balance was assessed using standardized differences, and adjustments to the matching algorithm were planned to ensure adequate balance (standardized differences within  $\pm 0.1$ ).

### 10.1.2 Rationale for Covariates Used in Propensity Score Algorithm

Covariates for propensity scores were chosen based on data availability, the potential to influence enrollment on Study 3b, and/or for their prognostic significance in neuroblastoma outcomes.

### Age at High-Risk Diagnosis

Age at high-risk diagnosis is a prognostic factor for neuroblastoma with survival in infants better than in older children at the same disease stage (Cohn 2009; Jereb 1984) and > 90% of diagnoses occurring by age 5. Patients initially diagnosed as non-high risk, but who later converted (and/or relapsed) to high-risk neuroblastoma (HRNB) were eligible to enroll in ANBL0032. Therefore, the date and age of diagnosis pertained to their original diagnosis, rather than high-risk diagnosis. To ensure consistency for age at high-risk diagnosis for all patients, the age (years) at high-risk diagnosis for the NO DFMO group was determined and included as a continuous variable.

### Sex

Although sex does not appear to predict neuroblastoma outcomes, it does adjust for possible demographic differences between groups and so was used as a categorical variable.

### Race

Race may be a potential prognostic factor for long-term outcomes in HRNB. African American and Native American neuroblastoma patients enrolled on COG ANBL00B1, for example, had a higher prevalence of high-risk disease with poorer EFS vs White patients, and African American vs White patients had a higher prevalence of late-occurring events (> 2 years from diagnosis) (Henderson 2011). Since this variable adjusts for possible demographic differences between groups, it was used a categorical variable.

### Stage at High-Risk Diagnosis

Tumor load at the time of diagnosis is described by the disease stage at high-risk diagnosis, and is a marker of disease severity with patients at a higher disease stage considered to be at higher risk of death and progression than those at a lower stage (Cohn 2009). Stage was used as a two factor categorical variable (stage < 4 and stage = 4).

### **Pre-ASCT Response**

In HRNB, the end of induction response is an established prognostic factor for EFS and OS (Pinto 2019). Since patients transition from induction to autologous stem cell transplant (bone marrow transplant; ASCT), the pre-ASCT response (primary tumor, soft tissue metastases, and bone metastases, excluding consideration of bone marrow) and End of Induction response should be similar. ANBL0032 patients were stratified based on pre-ASCT response that, as the most important early treatment response covariate, was used as a categorical variable (partial response, PR; very good partial response, VGPR; and complete response, CR).

#### Tandem/Single Transplant

Autologous stem cell transplant (tandem/single) is SoC for patients with HRNB, and tandem vs single transplant has been associated with improved EFS (Park 2019). This variable differentiated whether ANBL0032 patients had had a single or tandem transplant so transplant type (single/tandem) was used as a categorical variable.

#### Time from Transplant to Start of Immunotherapy

ANBL0032 initially required enrollment within 100 days of ASCT that was later expanded to 200 days so time from ASCT to start of immunotherapy (Cycle 1 onset) varied. Starting immunotherapy promptly following ASCT is influenced by various factors, including recovery time post-consolidation chemotherapy and, as with ANBL0032, the time for screening and enrollment to the study (dinutuximab was not commercially available so patients may have had to transfer to another institution to participate). Thus, time from ASCT to start of immunotherapy (days) was included as a continuous variable.

#### Duration of Immunotherapy

Duration of immunotherapy [the time from start of immunotherapy (Cycle 1 onset) to end of immunotherapy (end of last Cycle), days] represented the length of time for immunotherapy completion in ANBL0032, which varied. Thus, duration of immunotherapy was included as a continuous variable.

## **Overall Response at End of Immunotherapy**

In accordance with ANBL0032, Study 3b enrollment required patients to undergo both anatomical (CT/MRI) and nuclear (MIBG) imaging and bone marrow assessment at the end of immunotherapy/end of study treatment to determine disease response, an overall response of CR, VGPR or PR without evidence of bone marrow involvement being prerequisite. Disease response at the end of immunotherapy also correlated to the index date for the comparison. Thus, overall response at end of immunotherapy was included as a categorical variable.

### Time from Original Diagnosis to End of Immunotherapy

Time from diagnosis to end of immunotherapy measures the total duration of neuroblastoma treatment from diagnosis to immunotherapy end. In ANBL0032, consistent with enrollment criteria that allowed patients with original low- or intermediate-risk disease diagnoses who subsequently relapsed/progressed to high-risk disease to be enrolled, the date of diagnosis may have corresponded to that of original diagnosis rather than high-risk diagnosis in some patients. To maintain the longer total treatment duration in the model, the date of diagnosis to the end of immunotherapy was used for all NO DFMO patients. The date of high-risk diagnosis (including when it differed from original diagnosis) was reported in Study 3b. Thus, time from original diagnosis date to end of immunotherapy (days) was included as a continuous variable.

### **MYCN** Amplification Status

Amplification of *MYCN* is the best-characterized genetic marker of risk in neuroblastoma (Cohn 2009; Huang and Weiss 2013) and, compared to non-amplified patients, *MYCN*-amplified patients experience a significantly shorter time to relapse (PD) during upfront treatment. Additionally, the biology of amplified tumors are known to be different. As a result, *MYCN* status (not amplified/amplified) was used to match exactly in analyses.

### 10.2 Additional Characterization of DFMO and NO DFMO Populations for Externally Controlled Analysis

PSM is an effective tool to achieve baseline attribute balance between two populations for covariates included in the algorithm, but it cannot directly address other potential differences that indicate underlying biases impacting outcomes.

The following sections outline some of the additional evaluations by the Sponsor to assess potential differences in the Study 3b DFMO and ANBL0032 NO DFMO populations in the pivotal, externally controlled comparisons that provide primary support for efficacy.

### 10.2.1 Assessing Additional Covariates in the PSM Algorithm

Eleven covariates were selected in consultation with FDA to represent the most prognostically significant and potentially important patient attributes with high levels of reporting across both the Study 3b and ANBL0032 databases, as described in Appendix 10.1.2. However, additional covariates were considered and were incorporated in additional sensitivity analyses as described below.

#### 10.2.1.1 Histology Added as a Covariate

Histology (favorable/unfavorable) is an established factor in neuroblastoma risk stratification and therefore is of interest as a covariate for the PSM model. However, patients missing this covariate in Study 3b were due to either lack of reporting or because histology was unavailable given tumor

resection is required to obtain histology and may not be possible in all cases. The ANBL0032 database also had a higher proportion of missing data for histology. For these reasons, it was excluded from the covariates for the primary PSM model. However, to further evaluate the impact of histology, a modified PSM comparison was conducted with histology as an additional covariate.

In the modified PSM analyses including histology, propensity scores were calculated in two ways:

Histology was treated as an independent categorical covariate in the model with valid options of Favorable, Unfavorable (referent category), and Other (combining Blank/Missing/Not Available responses) for comparison of the NO DFMO-All Covariate and DFMO-All Covariate populations (those with no missing data for the 11 covariates identified for the primary PSM).

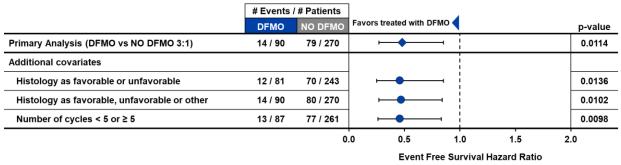
In the second analysis, histology was treated as an independent categorical variable with valid options of only Favorable and Unfavorable, and Unfavorable as the referent category. For this analysis, the NO DFMO – All Covariate and DFMO PER COG -All Covariate populations were further restricted to those patients with recorded histology findings (those with Blank/Missing, Not Available responses are excluded from patients that are eligible to be considered for propensity score calculations and subsequent matching).

#### 10.2.1.2 Dichotomized Number of Immunotherapy Cycles Added as a Covariate

Patients may discontinue immunotherapy due to adverse reactions or refusing further treatment. The first 5 cycles of immunotherapy incorporate anti-GD2 antibody whereas the 6<sup>th</sup> cycle is a cycle of cis-RA alone. The majority of patients meeting the selection criteria for both the NO DFMO and DFMO populations completed all 6 cycles of immunotherapy; however, to further consider potential differences in patients that received fewer than 5 cycles and thus theoretically did not receive the full benefit of anti-GD2 antibody, the number of immunotherapy cycles categories  $\geq$  5 or < 5 were treated as an additional independent categorical variable in the model with  $\geq$  5 as the referent category.

The results of these modified PSM analyses with additional covariates included are presented in Figure 31 with the primary PSM analysis presented at the top of the plot for reference.

# Figure 31: Forest Plot of Study 3b DFMO vs. ANBL0032 NO DFMO Primary PSM Analysis and Modified PSM Analyses with Additional Covariates



### 10.2.2 Geographic Distribution of Patients

Enrolling site IDs were not originally available in the ANBL0032 data transfer but were subsequently provided after all analyses were completed per the statistical analysis plan. The availability of the data permitted further evaluation of the geographic distribution of patients included in the NO DFMO-Matched and DFMO-Matched groups. ANBL0032 included enrolling

sites in the US, Canada, Australia, and New Zealand, whereas Study 3b enrolled patients only from the US and Canada. Distribution by country is summarized in Table 27 for the patients included in the overall DFMO and NO DFMO analysis populations as well as those included in the primary PSM matched populations.

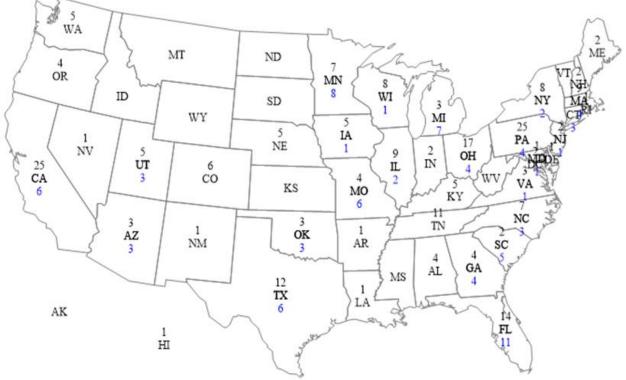
| Country:      | NO DFMO -<br>Overall (N=852) | DFMO -Overall<br>(N=92) | NO DFMO -<br>Matched<br>(N=270) | DFMO-Matched<br>(N=90) |
|---------------|------------------------------|-------------------------|---------------------------------|------------------------|
| United States | 673 (79.0%)                  | 91 (98.9%)              | 231 (85.6%)                     | 89 (98.9%)             |
| Canada        | 94 (11.0%)                   | 1 (1.1%)                | 25 (9.3%)                       | 1 (1.1%)               |
| New Zealand   | 12 (1.4%)                    | 0                       | 1 (0.4%)                        | 0                      |
| Australia     | 73 (8.5%)                    | 0                       | 13 (4.8%)                       | 0                      |

| Table 27: | NO DFMO and DFMO I | Populations | Distribution | by Country* |
|-----------|--------------------|-------------|--------------|-------------|
|-----------|--------------------|-------------|--------------|-------------|

\* Country where patients were enrolled in ANBL0032

Given the large majority of patients in both studies were enrolled in the US, enrolling site IDs and associated state locations were used to visually depict national geographic distribution of treatment location for US patients in the primary matched groups in Figure 32.

# Figure 32: Map of Primary Matched ANBL0032 NO DFMO (n=231) and Study 3b DFMO (n=89) US Enrolled Populations by State



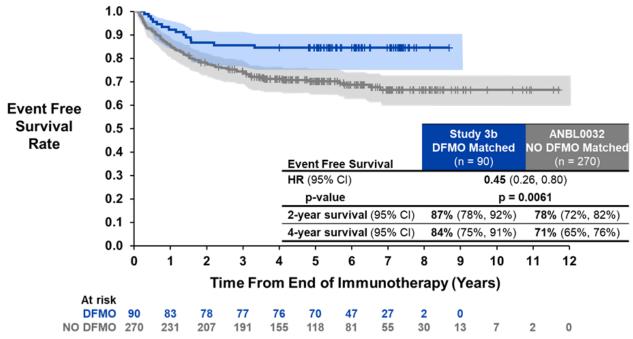
Note: Blue text represent DFMO-matched patients; black text represent NO DFMO-matched patients.

The US geographical distribution is proportionally similar between treated and control groups, and follows expected patterns based on US population distribution. Similar distributions are observed when US patients from the overall NO DFMO (N=852) and DFMO (N=92) groups are mapped.

The participation of patients outside of North America applies only to the NO DFMO group given all Study 3b patients received immunotherapy prior to DFMO in the US or Canada. Although the EFS outcomes in patients treated in vs. outside of North America were similar and all patients would have been required to have preceding upfront treatment meeting ANBL0032 protocol criteria, this was a difference that warranted further evaluation.

Within the overall NO DFMO group of N=852 patients, a total of 767 (90%, with 491 having complete covariate data) patients received dinutuximab treatment at sites located in North America while the remaining 85 (10%) of patients were treated at sites located in Australia and New Zealand. To compare outcomes in patients in common geographies (DFMO patients were strictly North American), an additional PSM sensitivity analysis was performed limiting the eligible NO DFMO pool for matching to those patients in North America with complete covariate data (N=491) using the primary PSM (3:1) methodology (Figure 33).





CI=confidence interval; HR=hazard ratio; PSM=propensity score matched.

Additional comparisons of the DFMO group (N=92) to the overall North American NO DFMO population (N=767) without matching and sensitivity analyses which further restricted the NO DFMO group to only United States patients (both with and without matching) were also performed. These additional analyses produced highly similar results in terms of hazard ratio and statistical significance.

## 10.2.3 Potential for Differences in Supportive Care to Influence Outcomes

A total of 160 sites contributed ANBL0032 patients to the NO DFMO analysis population. As a result of the large number of sites and the rarity of HRNB, the majority of sites contributed very few patients. A small number of institutions contributed 10 or more NO DFMO patients, and upon further review, those sites were consistent with larger hospitals that may be considered among US centers of excellence for pediatric oncology, such as Children's Hospital of Philadelphia,

Dana-Farber/Harvard Cancer Center, and Children's Hospital of Los Angeles, along with large pediatric hospitals in Australia and Canada. Institutions with larger patient volume could also be considered to be those with the greatest experience treating patients with HRNB, offer the highest level of supportive care, with access to greater resources than smaller hospitals, and may also attract patients from the larger surrounding region with the means or motivation to seek out subspecialized medical teams, most often associated with larger institutions.

Enrollment trends across ANBL0032 sites were investigated to identify thresholds for "higher" vs. "lower" enrolling sites. Given there was no clear delineation, two thresholds were used to explore control population differences that could be associated with institutional capabilities and supportive care: sites enrolling  $\geq$ 10 ANBL0032 patients and a slightly lower threshold of sites enrolling  $\geq$ 8 ANBL0032 patients.

These thresholds were applied to identify sites that enrolled  $\geq 10$  or  $\geq 8$  ANBL0032 patients in 2011 or later. This is the timeframe contemporary to Study 3b as patients starting immunotherapy on ANBL0032 in 2011 would have end of immunotherapy dates aligned with the time period of Study 3b enrollment (described as the "NO DFMO Contemporary" population, N=599). This timeframe was considered most appropriate to evaluate potential supportive care differences for the comparison in order to further evaluate if high enrolling ANBL0032 institutions during that time period were also those contributing patients to Study 3b.

The breakdown of the number of sites meeting the  $\geq$ 10 and  $\geq$ 8 enrollment thresholds and their total contribution to the NO DFMO Contemporary population is presented in Table 28.

## Table 28: ANBL0032 High Enrolling (≥8 or ≥10 Patients) in Contemporary Timeframe (2011 or Later) and Contribution to ANBL0032 NO DFMO or Study 3b DFMO Population

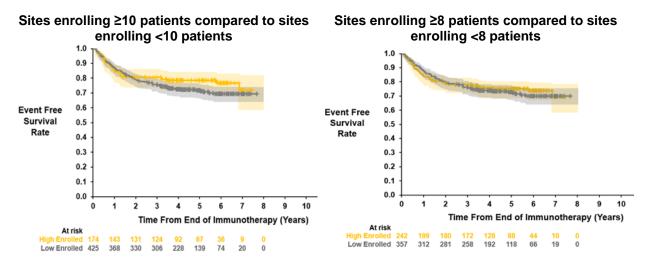
|  | ANBL0032 Sites  |   | ANBL0032 Patients  |
|--|---|---|--|
| ANBL0032 Patients<br>Enrolled Per Site, n (%): | Sites Contributing to<br>NO DFMO<br>Contemporary<br>Population<br>(N=143 total sites) | ANBL0032 Sites<br>(Patients) That<br>Enrolled Patients in<br>Study 3b | Patients Contributing<br>to NO DFMO<br>Contemporary<br>Population<br>(N=599) |
| ≥10 Patients                                   | 11 (7.7%)   | 0   | 174 (29.0%)  |
| ≥8 Patients                                    | 19 (13.3%)  | 1 site (3 patients)   | 242 (40.4%)  |

Using the 10-patient threshold, 7.7% of sites enrolled 29% of NO DFMO Contemporary patients. Using the 8-patient threshold, 13.3% of sites enrolled 40% of NO DFMO Contemporary patients. No site enrolling 10 or more NO DFMO ANBL0032 patients in the contemporary era to Study 3b contributed any patient to Study 3b; and 1 site enrolling 8 or more ANBL0032 NO DFMO patients contributed 3 patients to Study 3b.

Available demographic and disease characteristic data were reviewed for NO DFMO Contemporary populations defined by each threshold for "higher" enrolling and "lower" enrolling sites, and each subset of the NO DFMO Contemporary population was generally similar.

Comparisons of outcomes for NO DFMO Contemporary patients grouped by "higher" and "lower" enrolling sites are presented in Figure 34.

# Figure 34: Comparison of Event Free Survival in Patients at NO DFMO Contemporary "Higher" Enrolling Sites vs. "Lower" Enrolling Sites Defined by ≥10 and ≥8 Patient Enrollment Thresholds



When evaluating outcomes for patients enrolled to ANBL0032 at higher enrolling sites defined by the 10-patient threshold, a slightly higher curve is observed compared to patients treated at lower enrolling sites. Because DFMO patients did not receive prior treatment at these highest enrolling ANBL0032 institutions, any trend toward improved EFS at these sites would only benefit the control group. When the threshold is defined at 8 patients, the trend appears to diminish, and outcomes are very similar which suggests site patient volume (used in this analysis as a potential indicator of supportive care differences); is unlikely to influence outcomes in this patient population.

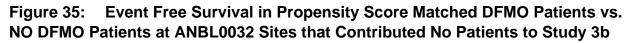
In addition to the analysis presented here, groups of NO DFMO patients that received upfront immunotherapy (enrolled in ANBL0032) at sites that did vs. did not contribute any patients to Study 3b were also compared, and outcomes were again similar supporting that there were no apparent difference in supportive care contributing to the outcomes observed in the primary comparison.

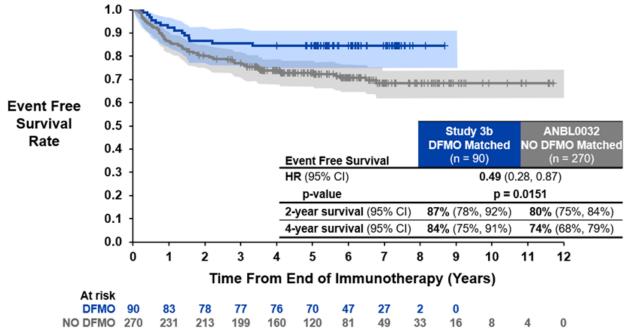
This may be expected given all patients in this analysis population have completed upfront therapy and are in remission, thus any theoretical earlier supportive care differences (during upfront treatment) may be unimpactful for patients that have reached the end of upfront therapy milestone.

### 10.2.4 Potential Differences in Patients Without Opportunity to Consider DFMO

Patients enrolled in Study 3b in the DFMO analysis population received prior immunotherapy at 45 ANBL0032 sites. This leaves a total of 120 ANBL0032 sites that had no patients who ultimately pursued DFMO treatment. The patients enrolled in ANBL0032 across these 120 sites could be considered those that, due to geography or potentially due to treating medical staff opinion or lack of familiarity, were not aware of or not realistically able (e.g., intercontinental travel) to seek out DFMO treatment. This group then provides the best look at patients that are free of the potential biases introduced by having the "choice" of DFMO because they did not have the opportunity to choose. Thus, another sensitivity analysis was performed limiting the NO DFMO group to only

those patients enrolled at ANBL0032 sites that did not contribute any patients to Study 3b. This limited the NO DFMO group to N=600 of 852, of whom 359 had complete covariate data to enable PSM analyses using the primary PSM (3:1) methodology (Figure 35).





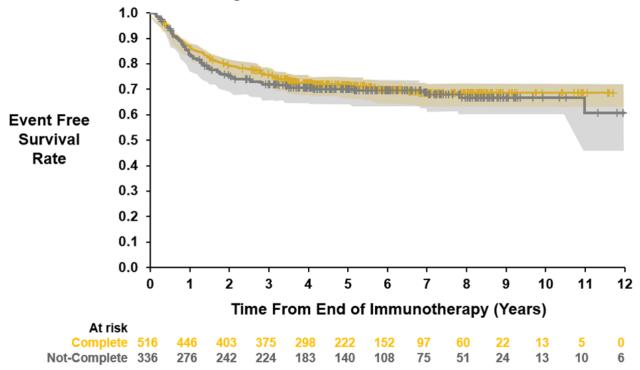
CI=confidence interval; HR=hazard ratio; PSM=propensity score matched.

The curves between these newly matched groups of DFMO and NO DFMO patients are highly similar to the primary analysis, supporting the removal of patients that theoretically had an opportunity to consider DFMO but did not pursue it were not impactful to the comparison outcomes.

### 10.2.5 Potential Differences in NO DFMO Patients with and without Missing Covariates

Propensity score matching analyses require complete covariate data; however, the requirement to have all covariate data ultimately limits the PSM eligible NO DFMO group to 516 out of 852 patients, with 336 patients (approximately 35%) of the overall analysis population not able to be considered in matched analyses. This exclusion has the potential to introduce biases as missing covariate data could theoretically indicate other underlying differences between those groups of patients. Available demographic and disease characteristic data were reviewed and groups NO DFMO-All Covariate population and NO DFMO patients with 1 or more missing covariates (N=336) were generally similar.

Additionally, outcomes in these two groups of patients were evaluated to understand if missing data could indicate an underlying difference associated with better or poorer EFS. EFS for the NO DFMO-All Covariate (N=516) and NO DFMO missing 1 or more covariates (N=336) were compared (Figure 36).



# Figure 36: Event Free Survival Comparison in NO DFMO-All Covariate patients vs. NO DFMO Patients Missing ≥ 1 Covariate

The curves between these groups of NO DFMO patients are highly similar, supporting that missing covariate data does not appear to be associated with differences in outcomes, lending further confidence to the reported PSM analyses which are restricted to those patients with complete covariates.

### 10.2.6 Conclusions from Additional Population Characterizations

Given the externally controlled design of Study 3b, it is important to understand potential differences, beyond those covariates that can be balanced through PSM, in the populations of DFMO and NO DFMO patients being compared. The additional characterizations presented herein do not identify differences in the populations that contribute to differences in outcomes. The additional sensitivity analyses performed did not identify underlying biases in the comparison and provide consistent support for interpretation of the primary PSM analysis of the DFMO and NO DFMO groups.

### **10.3 Reasons for Censoring**

Reasons for censoring are presented in Table 29 for the DFMO PER COG and NO DFMO populations. The majority of patients in both groups are censored because they are ongoing in the long-term follow-up phase of their respective studies. This is expected in accordance with the enrollment timelines for both studies. Although ANBL0032 started years earlier than Study 3b, enrollment to the randomized portion of the study was very slow, whereas following the cessation of randomization in 2009, and in particular following the published findings in 2010, enrollment picked up significantly, with the majority of control patients enrolling post 2010.

DFMO patient status was defined based on Study 3b off study reporting categories. Patients without the Off Study CRF are considered ongoing.

ANBL0032 did provide a specific data field option to report completion of the study. Per the ANBL0032, a completer for the NO DFMO group is defined as a patient with at least 10 years of follow-up from the beginning of immunotherapy. The final data transfer (June 2019 cutoff) did not include data for 141 patients, being described by COG as those patients that had no additional data beyond the preliminary data transfer provided. All patients in this group are considered either completed or lost to follow-up (no patient is considered ongoing given they originally enrolled 10 or more years ago) based on date of last contact from the preliminary data transfer compared to their start of immunotherapy date.

NO DFMO patients (other than the 141 described above) were considered ongoing if the data cutoff date (June 2019) was within 15 months (to allow a 3-month window around the expected yearly follow-up) of their last reported contact date and the prior contact confirmed the patient was still being followed and was not lost to follow-up.

Patients without an event who had not completed the study or did not meet the criteria to be considered ongoing represent discontinued patients. Discontinued patients either withdrew consent, were lost to follow-up, or specifically for NO DFMO group, enrolled on another COG protocol with therapeutic intent.

|   | Overall P      | opulation All Covari |                | ate Population     |  |
|---|----------------|----------------------|----------------|--------------------|--|
| Event Type:   | DFMO<br>(N=92) | NO DFMO<br>(N=852)   | DFMO<br>(N=91) | NO DFMO<br>(N=516) |  |
| EFS Event   | 15 (16.3)      | 252 (29.6)           | 15 (16.5)      | 150 (29.1)         |  |
| Relapse   | 15 (16.3)      | 234 (27.5)           | 15 (16.5)      | 138 (26.7)         |  |
| Death   | 0              | 10 (1.2)             | 0              | 7 (1.4)            |  |
| Second malignancy   | 0              | 8 (0.9)              | 0              | 5 (1.0)            |  |
| Alive with no event   | 77 (83.7)      | 600 (70.4)           | 76 (83.5)      | 366 (70.9)         |  |
| Completed study   | 30 (32.6)      | 44 (5.2)             | 30 (33.0)      | 23 (4.5)           |  |
| Ongoing   | 45 (48.9)      | 467 (54.8)           | 44 (48.4)      | 290 (56.2)         |  |
| Withdrawal of consent for further data submission   | 0              | 2 (0.2)              | 0              | 2 (0.4)            |  |
| Lost to follow-up   | 2 (2.2)        | 84 (9.9)             | 2 (2.2)        | 48 (9.3)           |  |
| Enrollment onto another COG therapeutic study with tumor therapeutic intent (e.g., at recurrence) | 0              | 3 (0.4)              | 0              | 3 (0.6)            |  |
| OS Event -Death   | 8 (8.7)        | 170 (20.0)           | 8 (8.8)        | 97 (18.8)          |  |
| Alive   | 84 (91.3)      | 682 (80.0)           | 83 (91.2)      | 419 (81.2)         |  |
| Completed study   | 34 (37.0)      | 52 (6.1)             | 34 (37.4)      | 27 (5.2)           |  |
| Ongoing   | 47 (51.1)      | 523 (61.4)           | 46 (50.5)      | 332 (64.3)         |  |

# Table 29:Event and Censoring Reasons for Event Free Survival and OverallSurvival in Study 3b DFMO and ANBL0032 NO DFMO Populations

|   | Overall Population |                    | All Covariate Population |                    |
|---|--------------------|--------------------|--------------------------|--------------------|
| Event Type:   | DFMO<br>(N=92)     | NO DFMO<br>(N=852) | DFMO<br>(N=91)           | NO DFMO<br>(N=516) |
| Withdrawal of consent for further data submission   | 0                  | 3 (0.4)            | 0                        | 2 (0.4)            |
| Lost to follow-up   | 3 (3.3)            | 94 (11.0)          | 3 (3.3)                  | 49 (9.5)           |
| Enrollment onto another COG therapeutic study with tumor therapeutic intent (e.g., at recurrence) | 0                  | 10 (1.2)           | 0                        | 9 (1.7)            |

COG=Children's Oncology Group; EFS=event free survival; OS=overall survival. Additional Characterization of SIOPEN-DFMO Cohort (N=47)

Source records were thoroughly reviewed in order to more fully characterize the DFMO Per SIOPEN cohort described in Section 6.4.1.2.

Key demographic and disease characteristics of DFMO Per SIOPEN population are presented in Table 18, along with the published data for the patients assigned to dinutuximab-beta post-consolidation therapy in HRNBL-1 (SIOPEN, N=378) (Ladenstein 2020).

| Table 30:  | Key Demographic and Disease Characteristics for DFMO Per SIOPEN |
|------------|---|
| Cohort and | as Published for HRNBL-1 Patients Receiving Dinutuximab-beta    |
| Immunothe  | гару  |

| Parameter:                         | DFMO<br>Per SIOPEN<br>(N=47) | SIOPEN*<br>(N=378) |
|------------------------------------|------------------------------|--------------------|
| Sex, n (%)                         |                              |                    |
| Female                             | 46.8%                        | 37.0%              |
| Male                               | 53.2%                        | 63.0%              |
| Age at high-risk diagnosis (years) |                              |                    |
| < 1.5                              | 14.9%                        | 14.6%              |
| ≥ 1.5 to < 5                       | 68.1%                        | 67.2%              |
| ≥ 5                                | 17.0%                        | 18.3%              |
| Stage                              |                              |                    |
| Localized                          | 12.8%                        | 8.5%               |
| 4                                  | 85.1%                        | 89.7%              |
| 4s                                 | 2.1%                         | 1.9%               |
| MYCN amplified                     |                              |                    |
| NR                                 | 2.1%                         | 4.2%               |
| No                                 | 51.1%                        | 52.1%              |
| Yes                                | 46.8%                        | 33.3%              |
| TVD                                |                              |                    |
| NR                                 | 12.8%                        | 2.6%               |
| Ν                                  | 61.7%                        | 66.1%              |
| Y                                  | 25.5%                        | 31.2%              |
| MC                                 |                              |                    |
| NR                                 | 2.1%                         | 6.1%               |
| 0                                  | 17.0%                        | 8.5%               |

| Parameter:        | DFMO<br>Per SIOPEN<br>(N=47) | SIOPEN*<br>(N=378) |
|-------------------|------------------------------|--------------------|
| 1                 | 12.8%                        | 9.3%               |
| 2                 | 17.0%                        | 29.6%              |
| 3                 | 10.6%                        | 29.6%              |
| >3                | 40.4%                        | 16.9%              |
| Surgery           |                              |                    |
| NR                | 2.1%                         | -                  |
| No                | 2.1%                         | -                  |
| Yes               | 95.7%                        | 100.0%             |
| Surgery resection |                              |                    |
| CME               | 35.6%                        | 69.0%              |
| IME               | 13.3%                        | 23.0%              |
| UNK               | 51.1%                        | 0.0%               |
| Status prior HDT  |                              |                    |
| NR                | 4.3%                         | 8.7%               |
| CR                | 36.2%                        | 30.7%              |
| VGPR              | 25.5%                        | 39.4%              |
| PR                | 34.0%                        | 21.2%              |
| HDT regimen       |                              |                    |
| BuMel             | 93.6%                        | 92.1%              |
| Other             | 6.4%                         | 7.9%               |
| Pre-immunotherapy |                              |                    |
| NR                | 8.5%                         | 4.5%               |
| CR                | 70.2%                        | 55.6%              |
| VGPR              | 10.6%                        | 26.2%              |
| PR                | 10.6%                        | 13.8%              |

BuMel=busulfan and melphalan; CME=complete macroscopic excision; CR=complete response; HDT=high dose chemotherapy; IME=incomplete macroscopic excision; MC=metastatic compartments; NR=not reported; PR=partial response; SIOPEN=European Association Involved in the Research and Care of Children with Neuroblastoma; TVD=topotecan, vincristine and doxorubicin; UNK=unknown; VGPR=very good partial response.

\* Source: (Ladenstein 2020).

The published results identify key risk factors associated with lower EFS including older age; stage 4; involvement of more than one metastatic compartment; disease status prior to maintenance therapy; addition of topotecan, vincristine and doxorubicin (TVD) for patients with inadequate response following induction (Ladenstein 2020).

Key demographic and disease characteristics of the DFMO group are generally consistent with the attributes of the patients evaluated in HRNBL-1, including those associated with lower EFS.

### **10.5** Characterization of Refractory and Relapsed Cohorts in Study 3b (Stratum 2)

Study 3b patients who achieved remission after R/R therapy (Stratum 2) were prospectively defined to include patients in remission after either refractory therapy or in remission after one or more relapses. However, EFS rates were also assessed for two subgroups of these patients to

separately investigate the effects of prior relapse and refractory disease before remission to the overall EFS rate. (Table 31).

# Table 31:Study 3b Stratum 2 Relapsed and Refractory Subgroup Event FreeSurvival Rates

| Remission After R/R Therapy Patients (Stratum 2): | N  | 4-year Event Free Rate |
|---|----|------------------------|
| All R/R Patients                                  | 35 | 45.7%                  |
| Remission after refractory therapy                | 7  | 85.7%                  |
| Remission after 1 or more relapses*               | 28 | 35.7%                  |
| Remission after single prior relapse*             | 23 | 39.1%                  |
| Remission after multiple prior relapse*           | 5  | 20.0%                  |

R/R=relapsed and refractory.

\*Includes one patient in Stratum 2 patient who was included in the DFMO group for the pivotal externally controlled comparisons. This patient contributes a relapse event to both the pivotal study comparisons and the supporting Stratum 2 comparisons.

### Discussion of Remission After Refractory Treatment Cohort

The Refractory group is defined as those in initial remission following treatment that violated the ANBL0032 preceding treatment duration eligibility criteria [e.g., greater than 12 months between induction and first transplant (or >13 months between diagnosis and first transplant if induction date was not reported), greater than 200 days between last transplant and immunotherapy] or who received additional treatment beyond the standard upfront phases (induction, consolidation, post-consolidation immunotherapy) to achieve remission, and are considered a poorer risk group of patients than those Upfront Remission patients evaluated in Stratum 1 and in the externally controlled analysis. The refractory subgroup of Stratum 2 is very small, including just 7 patients. However, only one patient experienced relapse during DFMO therapy, producing a subgroup EFS rate of 85.7%, which was similar to the results of the larger Study 3b Upfront Remission (Stratum 1) cohort, an unexpected finding considering the generally poorer prognosis for refractory patients.

### Discussion of the Remission After Relapse Therapy Cohort:

As discussed in Section 2.3, ANBL1221-based chemoimmunotherapy is the current standard relapse therapy due to preliminary reporting of promising OR rate and 1 year survival rates (Mody 2017; Mody 2020). ANBL1221 enrolled only 17 patients (of whom 9 were relapse patients and 8 were refractory patients) receiving chemoimmunotherapy in the randomized phase which concluded in March 2015, and the expanded chemoimmunotherapy cohort study did not initiate until August 2016. Study 3b Stratum 2 enrolled from 2012 to early 2016, so there were very few patients and a very limited time window for ANBL1221 patients to consider DFMO maintenance in Study 3b. As such, only one Stratum 2 patient (a relapsed patient) received DFMO after having received ANBL1221 chemoimmunotherapy (Table 31). Therefore, expected outcomes for patients with relapsed HRNB in the era of Study 3b enrollment are based on relapse studies prior to the introduction of ANBL1221 chemoimmunotherapy.

Long-term outcomes for relapsed patients were consistent across several investigational trials conducted over two decades, as reported by Santana, 2008 and London, 2017. While the London, 2017 study does not report on disease intervals between recurrences in order to inform EFS rates following second remission, PFS and OS rates for patients with HRNB from start of

relapse/refractory treatment across these two publications were highly similar. The historical 2year EFS control rate of 10% estimated from Santana's published findings in 2008 is not well characterized which limits interpretability of the prespecified analysis. The literature and other sources were reviewed to support characterization of the natural history for Remission After R/R Therapy patients; however, particularly in the pre-ANBL1221 treatment era, patients achieving remission after R/R disease were rare and remain poorly understood. Given long-term, postrelapse survival outcomes were similar in Santana's report and in London's report (covering the era of Study 3b Stratum 2 relapses), the historical rate estimated from Santana's work provides some context for expected outcomes without DFMO during the era of Study 3b Stratum 2 enrollment, but should be interpreted with caution.

Expectedly, outcomes in multiply relapsed patients were poorer than in patients achieving remission after a single prior relapse. In the group of 23 patients with a single relapse, 4-year EFS was 39%. While a similarly robust comparison to an external control was not possible, these results are considered encouraging especially given the general recognition that relapsed patients are at a high risk of subsequent multiple relapses and death, particularly in the era preceding chemoimmunotherapy for treatment of relapse.