DFMO (Eflornithine) as Maintenance Therapy for High-Risk Neuroblastoma

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Oncologic Drugs Advisory Committee

US WorldMeds

Introduction

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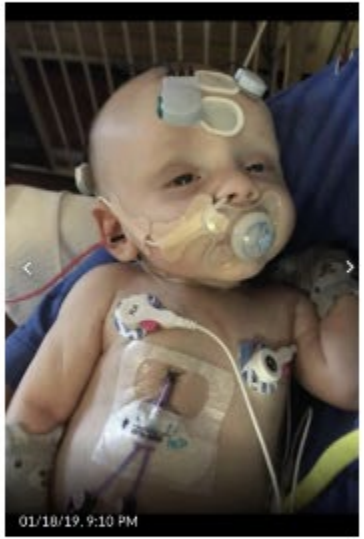
Goal to Improve Treatment Outcomes for Patients with High-Risk Neuroblastoma (HRNB)

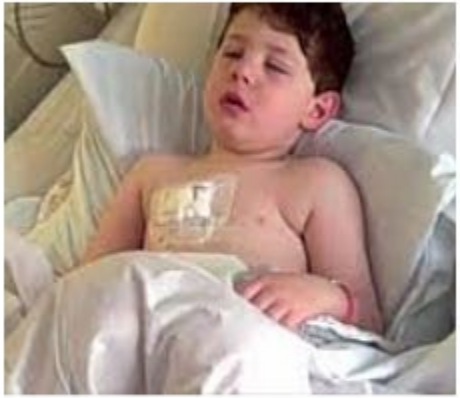
CO-3



Finn
3 months

BEAT CHILDHOOD CANCER

Network of universities and children's hospitals working to discover new therapies and cures for children with cancer



Will
4 years

Meeting the Needs of Young Children Diagnosed with High-Risk Neuroblastoma

Standard of Care	• Intense, toxic SoC leaves children vulnerable to relapse and death • Relapse risk highest in first few years
Unmet Medical Need	• About half of children diagnosed with HRNB die within five years of diagnosis • High mortality driven by relapse • No treatments to follow SoC to sustain remission
DFMO Efficacy	• Extends remission, improves EFS and OS beyond published historical rates or propensity matched populations • Few events occur after patients reach 2-year milestone
DFMO Safety	• Safety data consistent with expected risks • Generally well tolerated and outweighed by benefits

SoC = Standard of Care; EFS = Event Free Survival; OS = Overall Survival

DFMO Clinical Program Demonstrates Substantial Evidence of Effectiveness

- Program influenced by disease rarity, high mortality
- Study 3b design added DFMO maintenance to improve EFS and OS
- Used rigorous, propensity-matched control from landmark registration study ANBL0032
  - Comparison to highly similar population with common characteristics and backbone therapy
  - Approach consistent with emphasis on need for regulatory flexibility in rare diseases
- Supported by confirmatory evidence

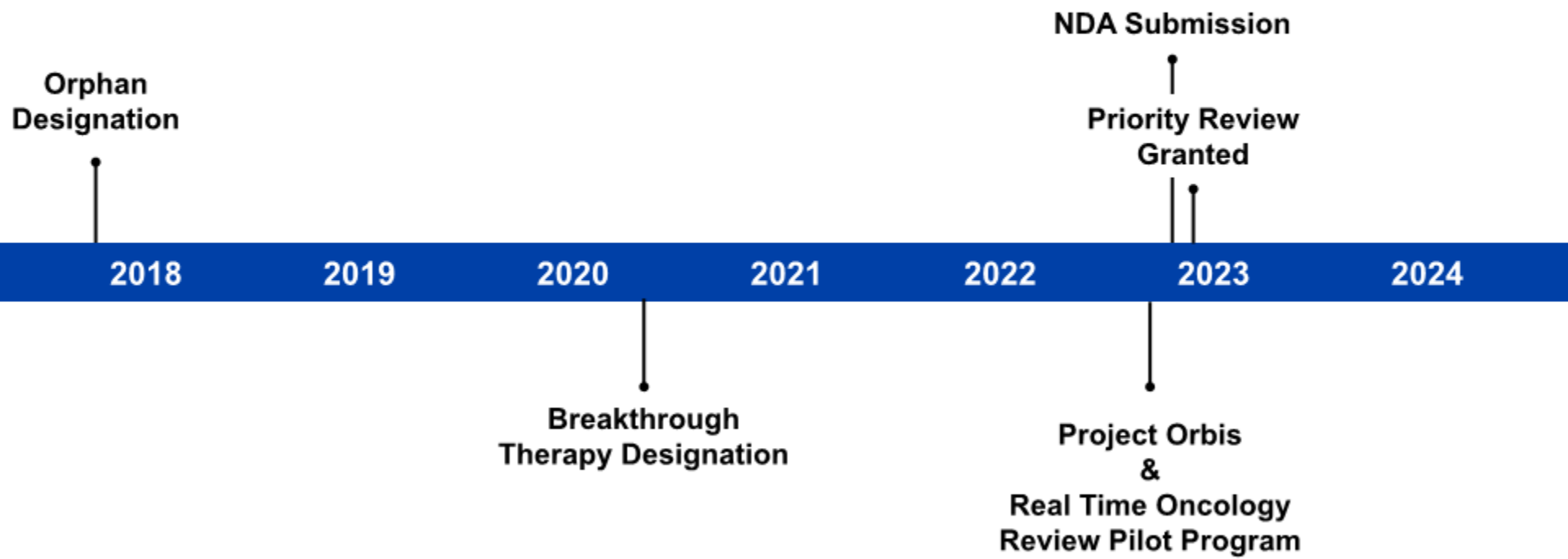
EFS = Event Free Survival; OS = Overall Survival

DFMO Clinical Program Demonstrates Positive Safety Profile (Pooled Safety Population, n = 311)

- Grade ≥ 3* AEs generally consistent with known risks
  - Hearing loss (12%), Grade 3+ indicates need for intervention
  - Hepatotoxicity (12% ALT increased, 7% AST increased)
  - Myelosuppression (4% anemia, 4% neutrophils decreased)
- SAEs occurred in 17%, mostly related to infections
- No deaths due to AEs
- Generally well tolerated with dose management when needed
  - AEs leading to dose modification (12%) or discontinuation (5%)
- Hearing loss thoroughly characterized to inform labeling recommendations
  - Only 2% discontinued due to hearing loss
  - > 60% patients improved/resolved with dose management

AE = adverse event; SAE = serious adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase
*Grading according to Common Terminology Criteria for Adverse Events (CTCAE)

DFMO Regulatory History Included Frequent Interactions, Collaboration with FDA



Proposed Indication for DFMO Oral Tablets

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

Agenda

HRNB Unmet Need and DFMO Development History	**Giselle Sholler, MD** Division Chief, Pediatric Hematology, Oncology and Bone Marrow Transplant at Penn State Health Children's Hospital Professor of Pediatrics at Penn State College of Medicine
DFMO Efficacy **Pivotal Externally Controlled Study 3b Confirmatory Data Package**	**Thomas Clinch** Senior Director, Biometrics and Clinical Development US WorldMeds
Clinical Perspective	**Susan L. Cohn, MD** Professor and Director of Clinical Sciences Department of Pediatrics University of Chicago Medicine
Conclusion / Q&A Moderator	**Kristen Gullo** Vice President of Development and Regulatory Affairs US WorldMeds

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HRNB Unmet Need and DFMO Development History

Giselle Sholler, MD

Chair, Beat Childhood Cancer Research Consortium

Division Chief, Pediatric Hematology, Oncology and Bone Marrow Transplant at Penn State Health Children's Hospital

Professor of Pediatrics at Penn State College of Medicine

Neuroblastoma is a Rare Pediatric Cancer

~800 children diagnosed per year in North America

- Most common cancer in infants
- 90% diagnosed by age 5

Solid tumor cancer

- Tumors most often begin in adrenal glands
- Can start in nerve tissue near spine in neck, chest, abdomen, or pelvis

Patients classified by their risk for relapse

- Treatment tailored based on risk group classification including low-, intermediate- and high-risk disease
- High-risk patients face poorest outlook in terms of survival

Survival Rates for High-Risk Neuroblastoma Much Poorer than for Low-, Intermediate-Risk Disease

- Low-, intermediate-risk neuroblastoma successfully managed with monitoring, limited therapy
  - Long-term survival > 90%
- High-risk neuroblastoma accounts for half of diagnoses
  - Most aggressive form of disease
  - Long-term survival ~50-60%, despite intensive multimodality treatment

High-Risk Neuroblastoma Patients Face Three Phases of Difficult, Toxic Treatment

~18-month Standard of Care in HRNB

1 Induction

- Chemotherapy
- Surgical resection

2 Consolidation

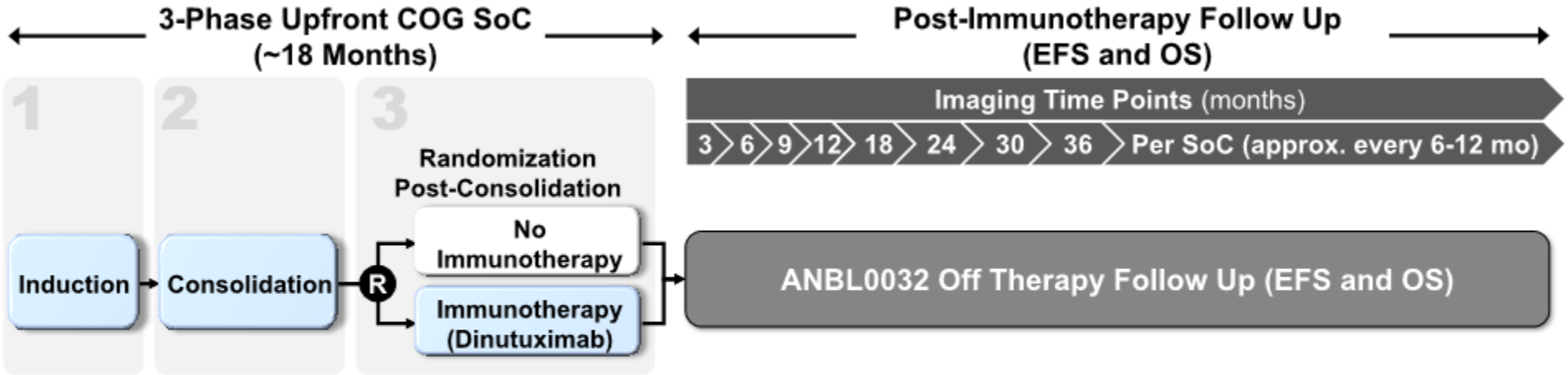
- High-dose chemotherapy
- Autologous stem cell transplantation (ASCT)
- Radiation

3 Immunotherapy

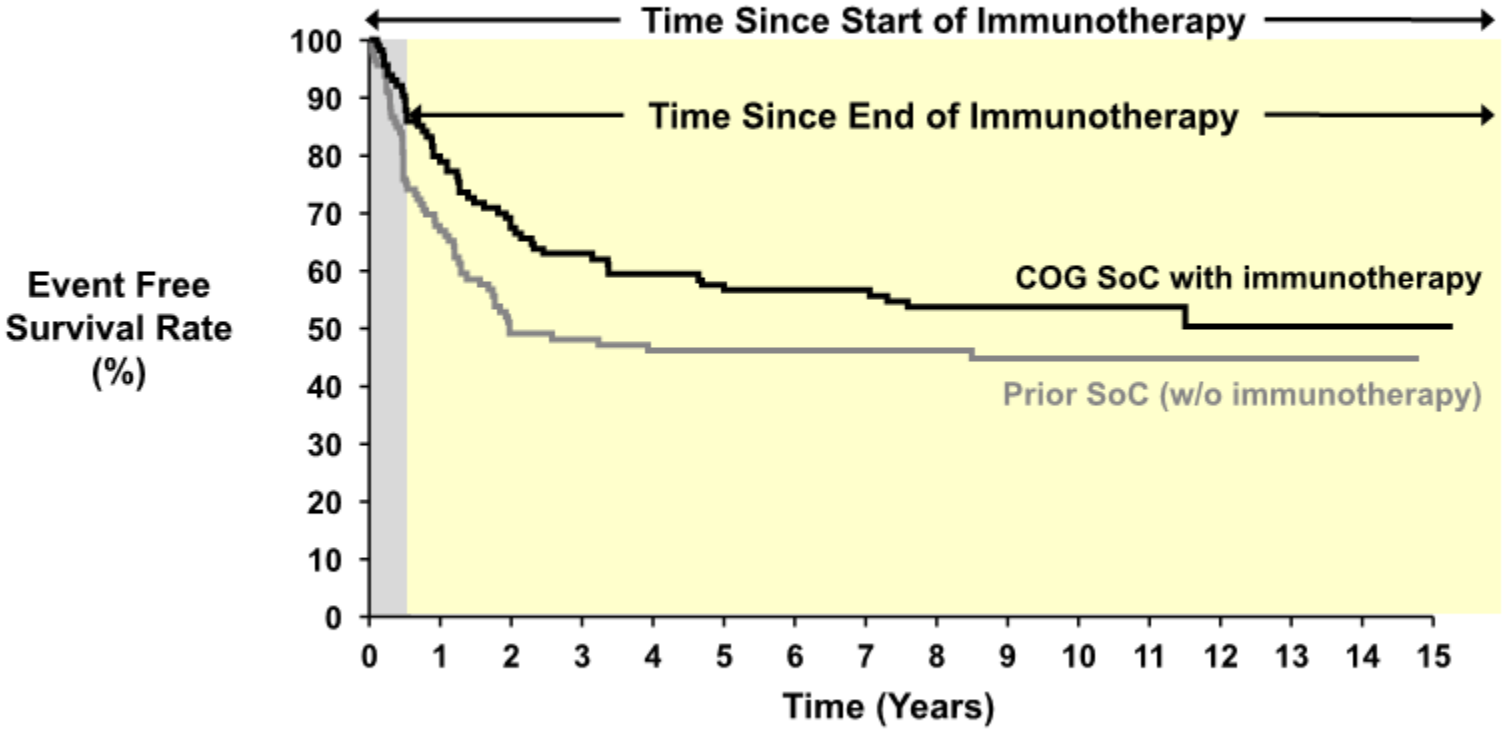
- anti-GD2 (Dinutuximab)
- cis-RA

Children's Oncology Group (COG) landmark study ANBL0032 resulted in addition of immunotherapy to Standard of Care

Randomized Phase of ANBL0032 Evaluated Adding Immunotherapy After Induction and Consolidation Therapy



ANBL0032 Randomized Controlled Phase Showed Adding Immunotherapy Improves EFS



COG therapy with immunotherapy	114	89	76	70	66	63	59	58	48	38	29	22	10	5	2	1
Prior SoC (w/o immunotherapy)	112	73	52	49	46	44	44	44	41	35	27	16	7	5	2	0

Adapted from Yu, 2021

Need to Avoid Relapse to Give Patients Best Chance at Survival

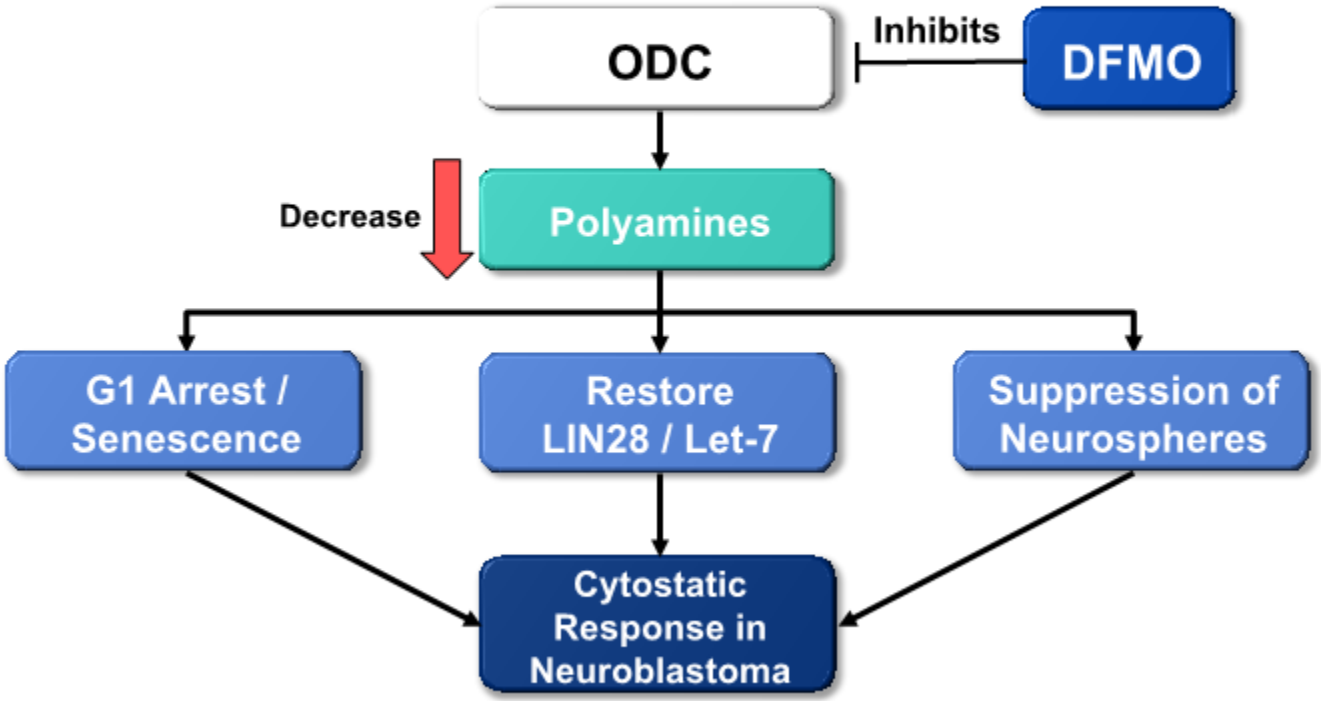
- ~30% remain at risk for relapse within 2 years after completing immunotherapy
- Most relapsed HRNB patients die within 5 years[1,2,3]
- DFMO investigated as maintenance therapy to enable more patients to sustain remission

1. Santana, 2008; 2. London, 2017; 3. Dubois, 2022

DFMO Development History

Giselle Sholler, MD

DFMO Exerts Anti-Cancer Activity by Driving Cytostatic Effects in Neuroblastoma Cells



ODC = ornithine decarboxylase
In vitro studies performed at clinically relevant concentrations
Wallick, 2005; Koomoa, 2013; Lozier, 2014

Preclinical and Published Clinical DFMO Data Led to Phase 1 Dosing

- In vitro data identified DFMO concentrations effective for ODC inhibition and neurosphere formation
- DFMO in published adult chemoprevention studies supported pharmacodynamic effects, positive outcomes[1,2,3]
  - Skin cancer prevention – 500 mg/m^2/day
  - Colon cancer prevention – 500 mg/m^2/day
  - Prevention of recurrent colorectal adenomas – 500 mg/day (+sulindac)

ODC = ornithine decarboxylase

1. Bailey, 2010; 2. Meyskens, 2008; 3. Love, 1998

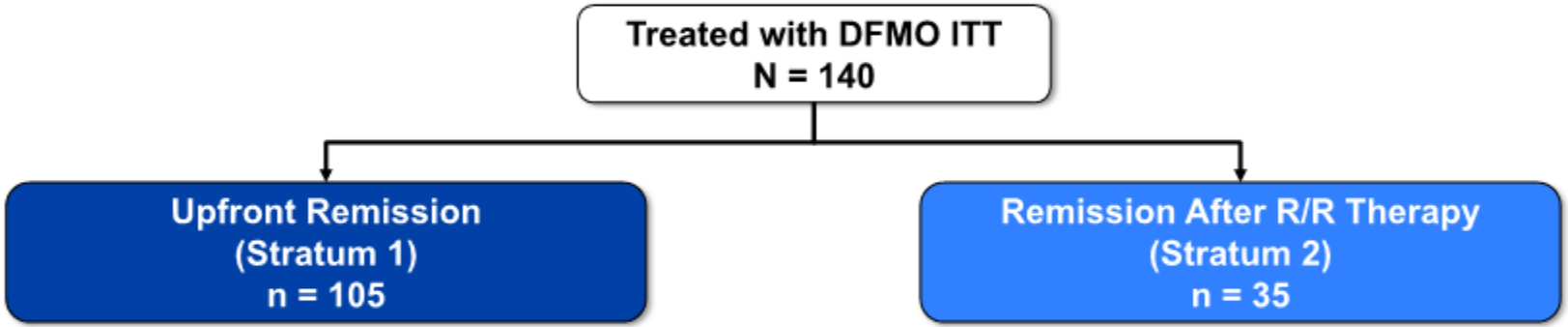
Phase 1 Safety Study Results Supported Selection of Study 3b Dose

- Evaluated 500-1500 mg/m^2 BID in patients with R/R active disease (n = 18)[1]
  - DFMO alone Cycle 1, DFMO + oral etoposide chemotherapy Cycles 2-5
  - No maximum tolerated dose identified
  - Across dose range, showed trends for polyamine reduction, disease stabilization or response
  - 7 of 18 continued DFMO after Cycle 5, 3 long-term survivors
- PK confirmed concentrations consistent with in vitro drug effects
- 750 ± 250 mg/m^2 BID selected for Study 3b

1. Sholler, 2015

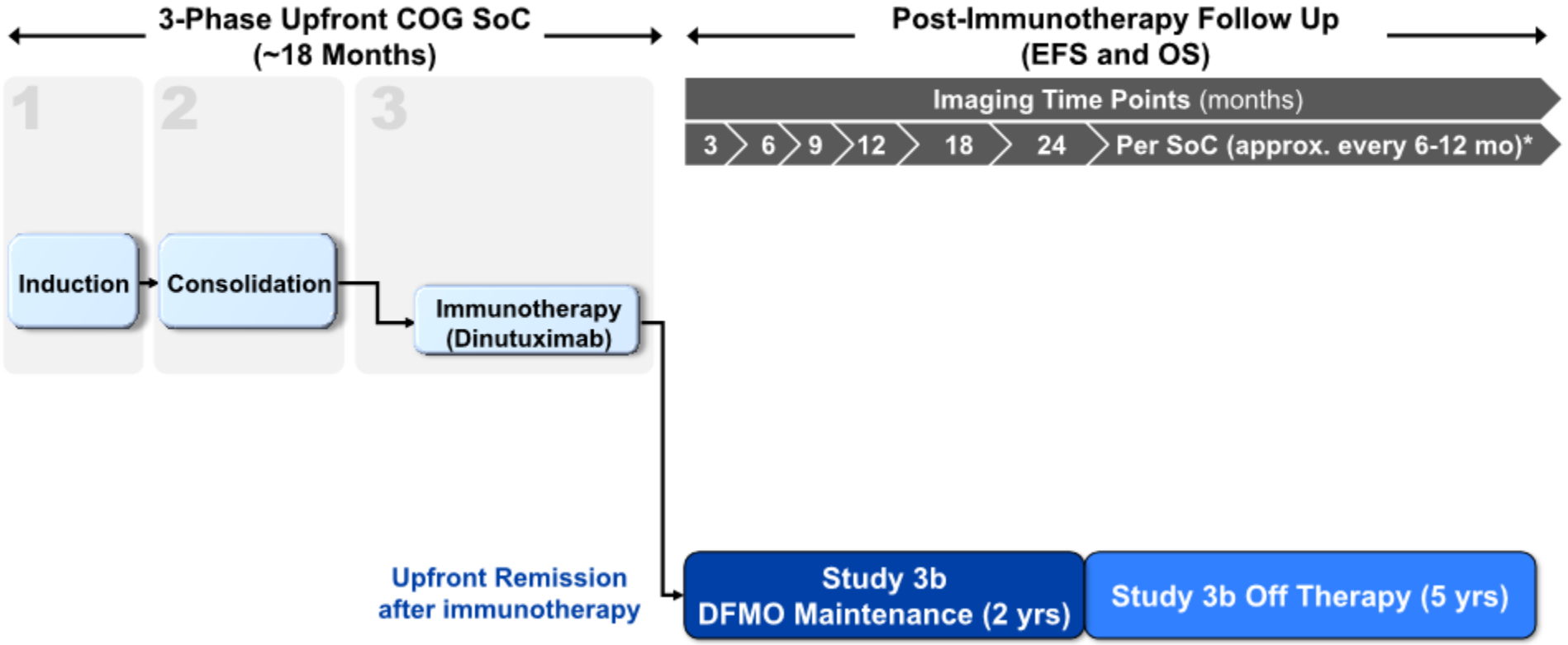
R/R = Relapse/Refractory

Study 3b: 140 ITT Patients Treated with DFMO



R/R = Relapsed/Refractory

Study 3b: Single-Arm Study Adding DFMO Maintenance Following Remission with COG SoC



*Study ANBL0032 mandated imaging at 30 and 36 months

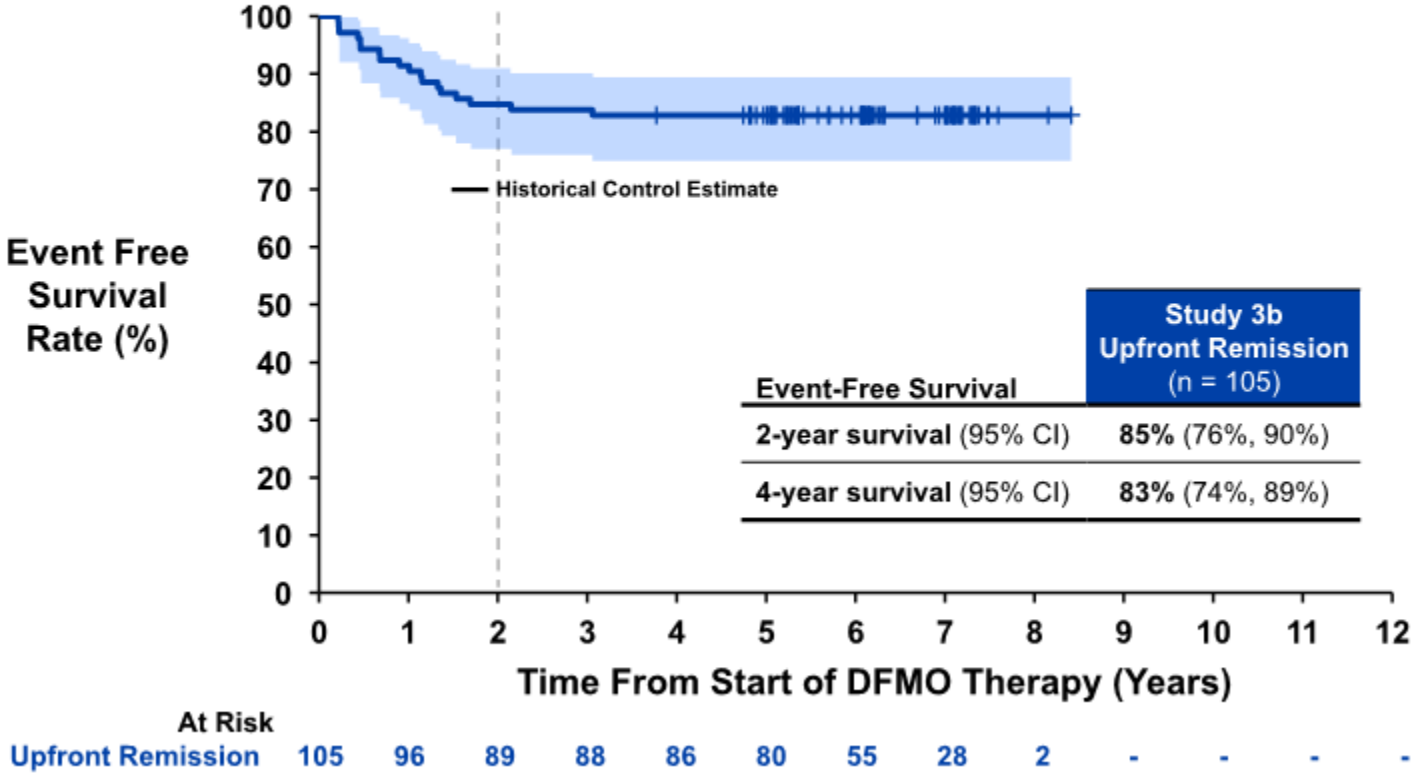
Study 3b Upfront Remission Patient Characteristics As Expected for HRNB Population

% of population with non-missing data	Study 3b Upfront Remission (n = 105)
Age at Diagnosis ≥ 18 months	**86%**
INSS Stage 4	**89%**
MYCN Amplified	**45%**
Pre-ASCT Response	
CR/VGPR	**76%**
PR	**21%**
Unfavorable Histology	**78%**

Upfront Remission = Stratum 1

CR = Complete Response; VGPR = Very Good Partial Response; PR = Partial Response; INSS = International Neuroblastoma Staging System; ASCT = Autologous stem cell transplant

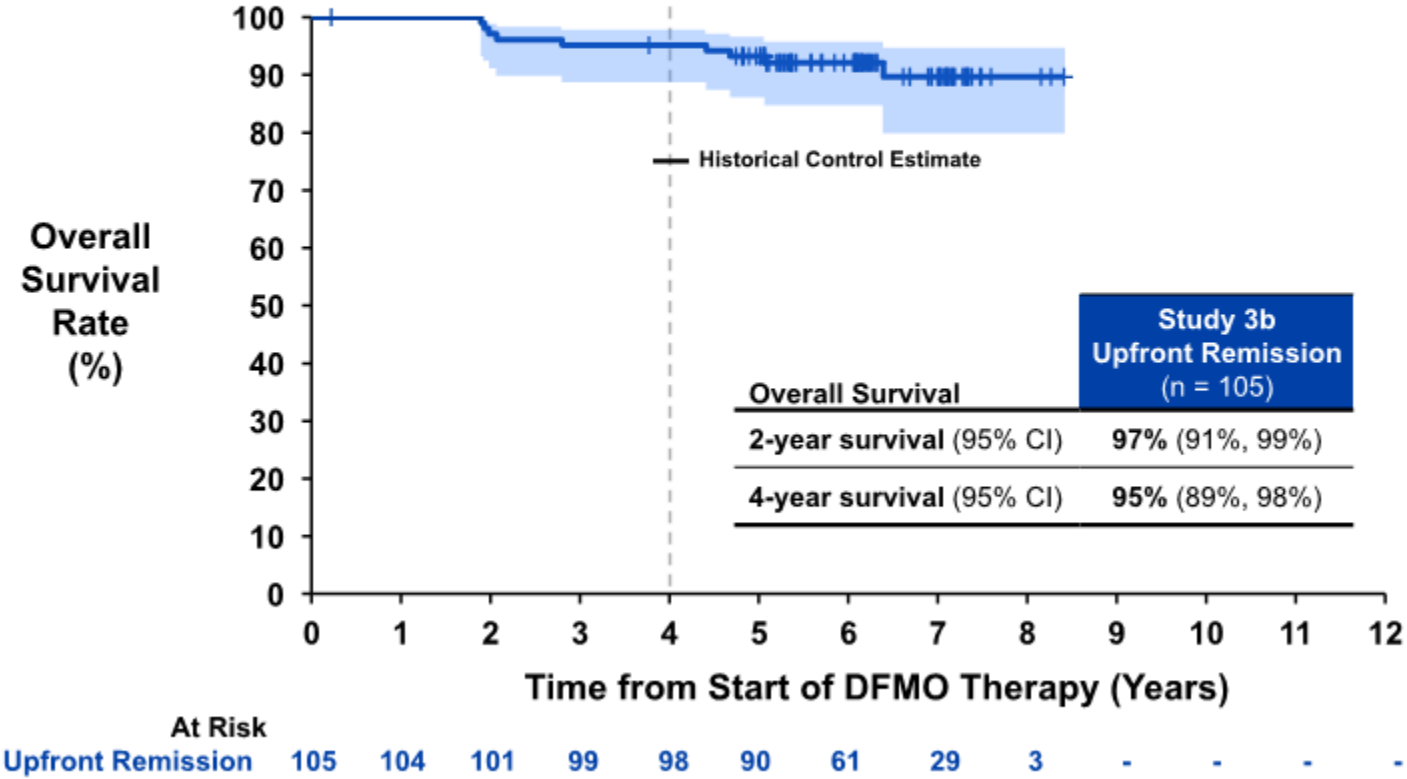
Study 3b Upfront Remission: 85% EFS 2-Year Estimate, with Lower 95% CI Above Historical 70% Rate



Event-Free Survival	Study 3b Upfront Remission (n = 105)
2-year survival (95% CI)	**85%** (76%, 90%)
4-year survival (95% CI)	**83%** (74%, 89%)

Upfront Remission = Stratum 1

Study 3b Upfront Remission: 95% OS Estimate at 4 Years



Overall Survival	Study 3b Upfront Remission (n = 105)
2-year survival (95% CI)	**97%** (91%, 99%)
4-year survival (95% CI)	**95%** (89%, 98%)

Upfront Remission = Stratum 1

3b Positive Results Prompted Discussions with FDA About Registration Pathways for DFMO Maintenance

- 2015-2016: Discussion of interim results with FDA
  - FDA recommended follow-on RCT
  - BCC proposed external control for Study 3b as viable alternative, aligned with regulatory requirements
- 2018: Full 2-year outcome data for all enrolled patients
  - Reinforced earlier EFS, OS results
  - Aligned with timing of FDA RWE initiatives
  - ANBL0032 patient data provided optimal external control
  - Confirmed registration plan with externally controlled Study 3b

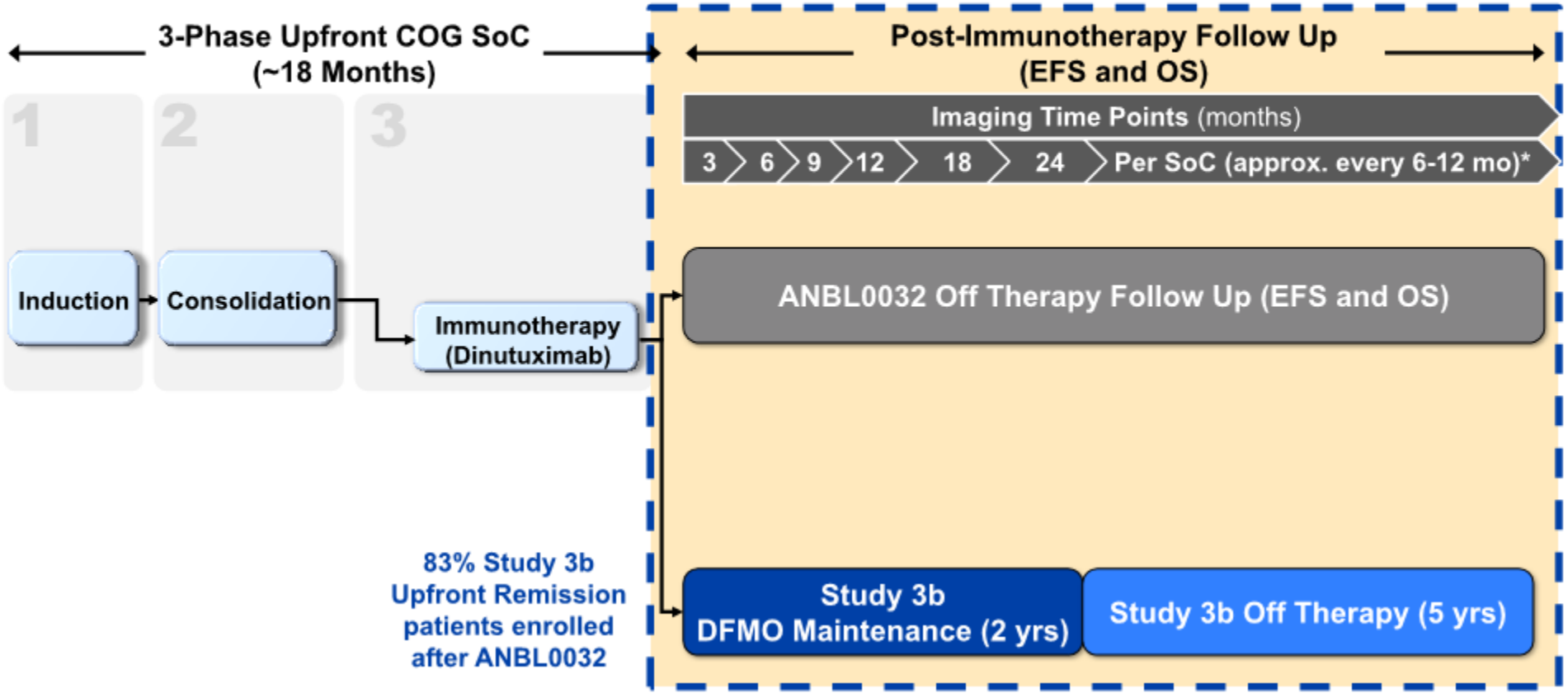
DFMO Efficacy
Pivotal Study 3b Externally Controlled by ANBL0032

Thomas Clinch

Senior Director, Biometrics & Clinical Development

US WorldMeds

ANBL0032 Post-Immunotherapy Follow Up Aligns with Study 3b



* Study ANBL0032 mandated imaging at 30 and 36 months

ANBL0032 Provided Optimal External Control for Study 3b, Aligns with Expert Guidance

- ✓ Similar demographics and disease characteristics
- ✓ Consistent upfront therapy
- ✓ Consistent long-term follow up, including outcome measures and frequency
- ✓ Identical event definitions for clinically meaningful survival endpoints

USWM Followed FDA Advice on Using Study 3b as Registration Study

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

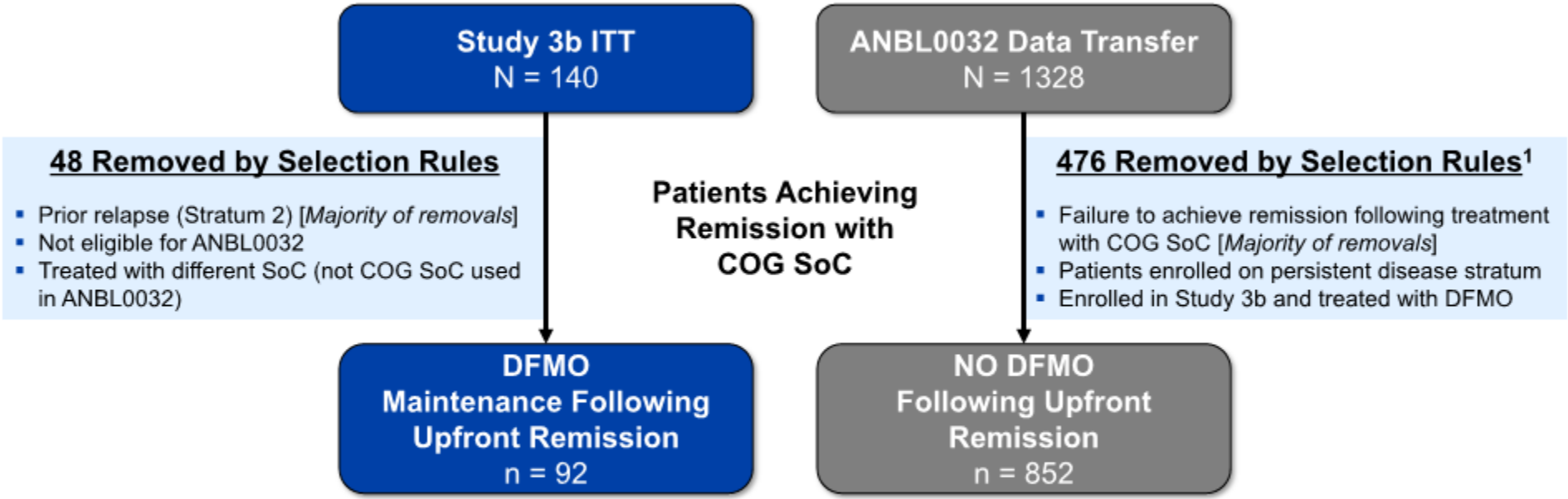
BICR = Blinded Independent Central Review

External Control Selection Criteria Identified Comparable Patients

- **DFMO**: Study 3b patients in remission following COG SoC
  - Received DFMO

- **NO DFMO**: ANBL0032 patients completing COG SoC with disease status consistent with Study 3b eligibility
  - Did not receive DFMO

Selection of Comparable Upfront Remission Patients



1. 65% event rate observed in removed ANBL0032 population

Selection Rules Resulted in Similar Populations

% of population with non-missing data	Study 3b DFMO (n = 92)	Study ANBL0032 NO DFMO (n = 852)
Male	60%	57%
Race: White	88%	80%
Age at HRNB Diagnosis ≥ 18 months	87%	86%
INSS Stage 4	87%	82%
MYCN Amplified	44%	42%
Pre-ASCT Response		
CR/VGPR	76%	66%
PR	24%	34%
End of Immunotherapy Response		
CR/VGPR	96%	94%
PR	4%	6%
Single Transplant Type	91%	88%

CR = Complete Response; VGPR = Very Good Partial Response; PR = Partial Response; INSS = International Neuroblastoma Staging System; ASCT = Autologous stem cell transplant

Study 3b Primary Efficacy Analysis Based on Propensity Score Matching (PSM)

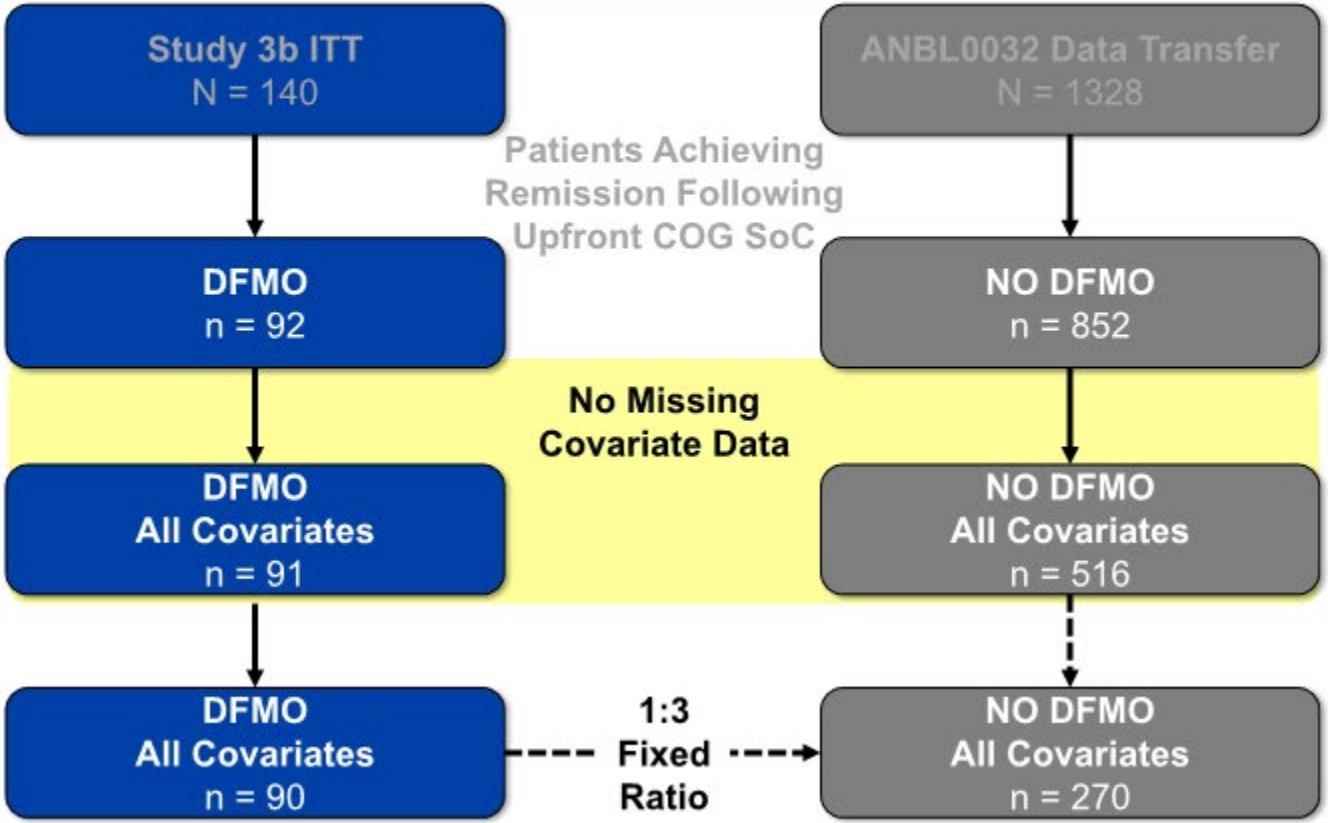
Propensity Score Matching – Effective statistical tool

- Reduces biases when comparing patient data from different sources
- Balances baseline covariates between treated and control patients
- Matches individual patients based on propensity scores to optimize similarity of compared groups
- Reduces confounding differences to better isolate treatment effect for evaluated outcomes

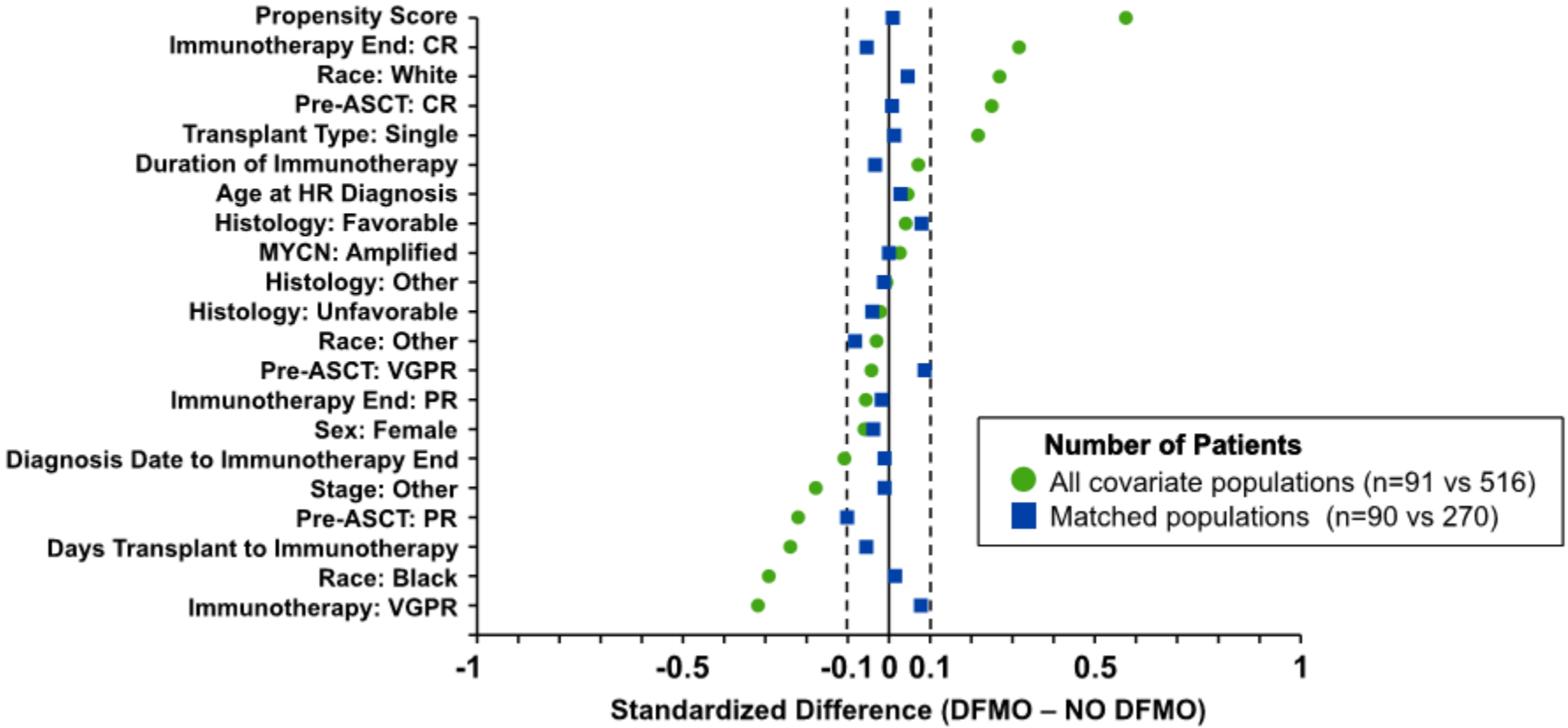
11 Key Covariates Used in Propensity Score Matching of ANBL0032 and Study 3b

- MYCN (*exact match*)
- Race
- Sex
- Age at high-risk diagnosis
- Stage at diagnosis
- Pre-ASCT response without bone marrow
- Transplant type (single/tandem)
- Overall response at end of immunotherapy
- Time from ASCT to start of immunotherapy
- Time from start to end of immunotherapy
- Time from diagnosis to end of immunotherapy

Available Upfront Remission Population for Propensity Score Matching



Standardized Differences Pre- and Post-Matching for Upfront Remission Populations

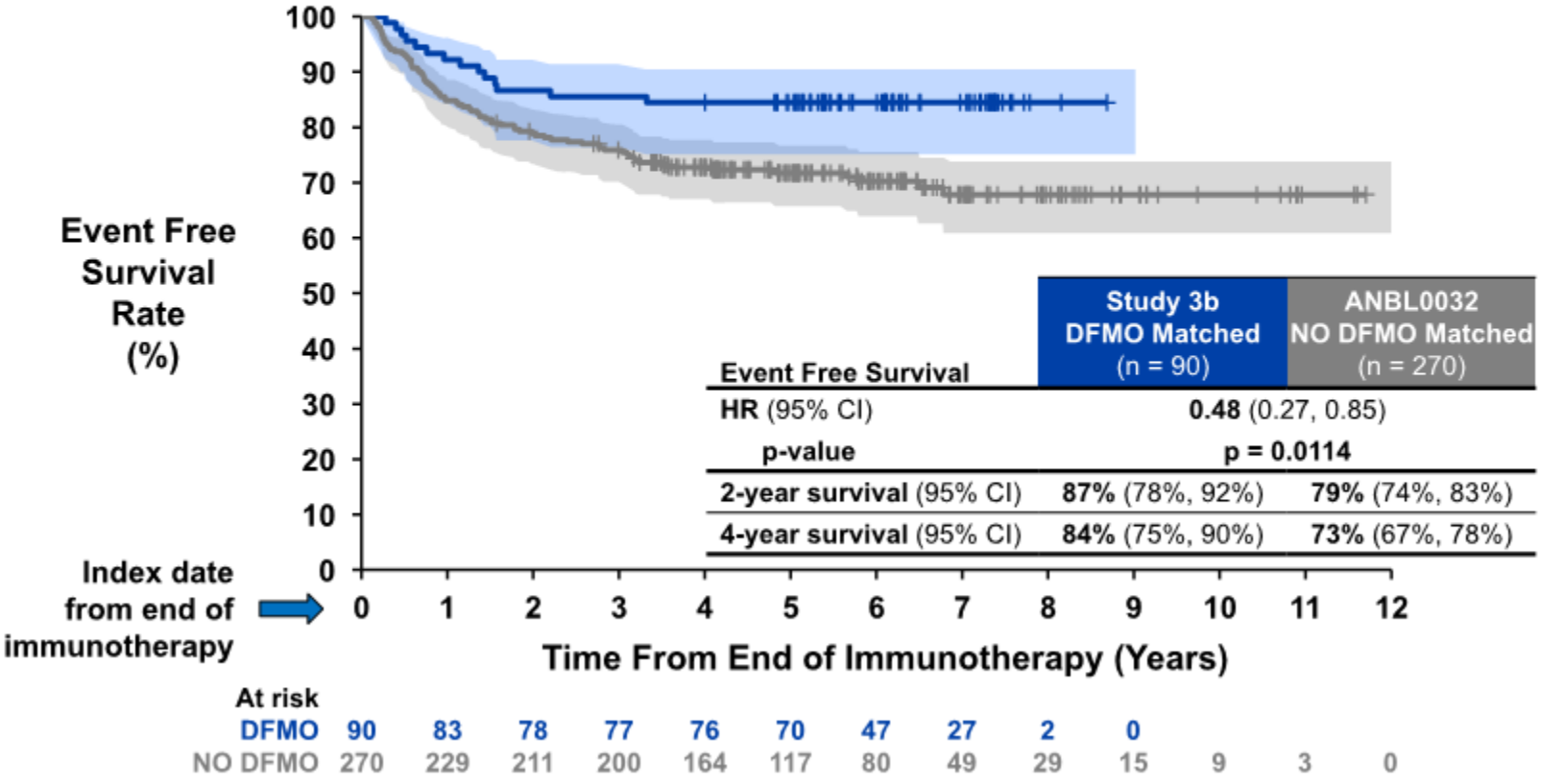


Highly Similar Upfront Remission Populations Using Propensity Score Matching

	Study 3b DFMO Matched (n = 90)	Study ANBL0032 NO DFMO Matched (n = 270)
Male	60%	58%
Race: White	89%	87%
Age at HRNB Diagnosis ≥ 18 months	87%	83%
INSS Stage 4	87%	86%
MYCN Amplified	44%	44%
Pre-ASCT Response		
CR/VGPR	77%	72%
PR	23%	28%
End of Immunotherapy Response		
CR/VGPR	96%	95%
PR	4%	5%
Single Transplant Type	91%	91%

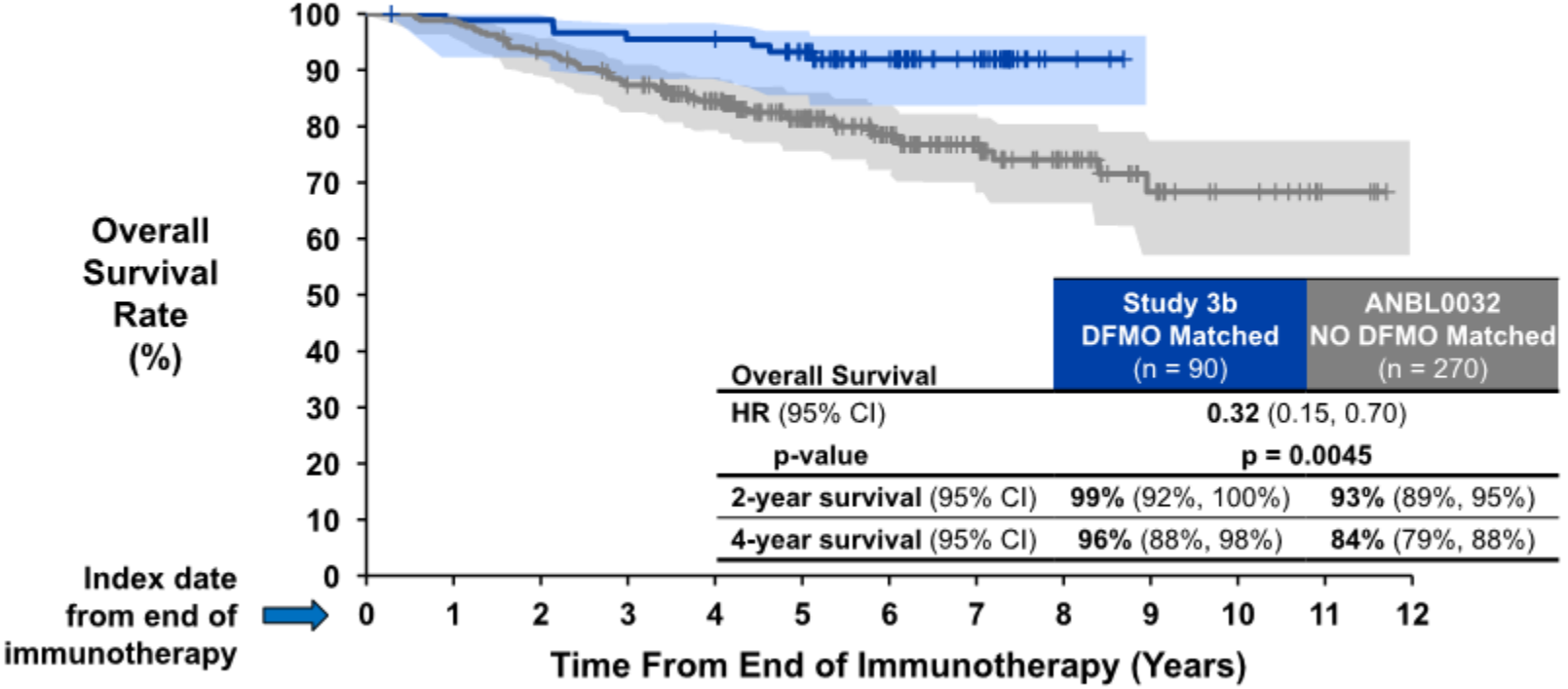
CR = Complete Response; VGPR = Very Good Partial Response; PR = Partial Response; INSS = International Neuroblastoma Staging System; ASCT = Autologous stem cell transplant

DFMO Treatment Improves EFS in Primary Matched Upfront Remission Comparison



Event Free Survival	Study 3b DFMO Matched (n = 90)	ANBL0032 NO DFMO Matched (n = 270)
HR (95% CI)	**0.48** (0.27, 0.85)	
p-value	**p = 0.0114**	
2-year survival (95% CI)	**87%** (78%, 92%)	**79%** (74%, 83%)
4-year survival (95% CI)	**84%** (75%, 90%)	**73%** (67%, 78%)

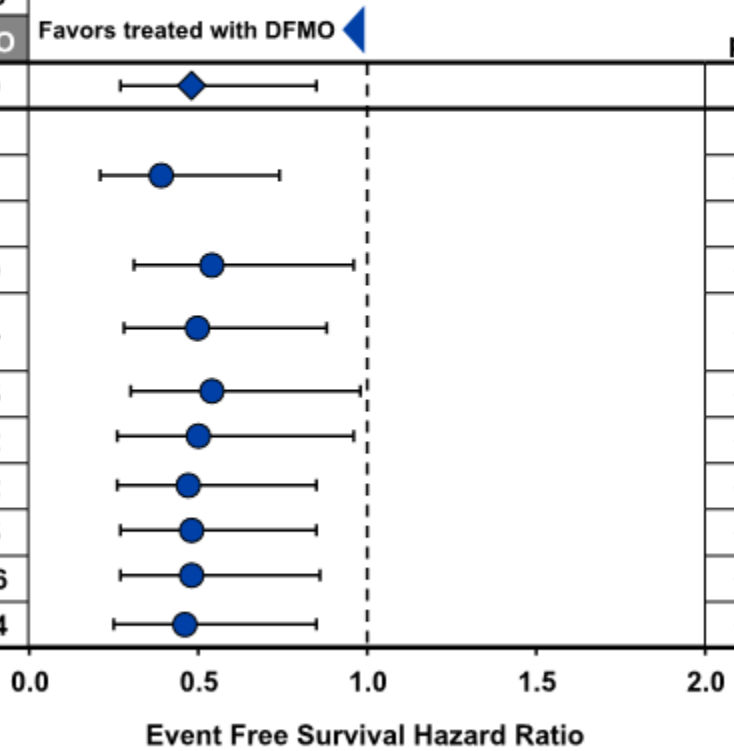
Primary Matched Upfront Remission Comparison of Overall Survival Favors DFMO



Overall Survival	Study 3b DFMO Matched (n = 90)	ANBL0032 NO DFMO Matched (n = 270)
HR (95% CI)	**0.32** (0.15, 0.70)	
p-value	**p = 0.0045**	
2-year survival (95% CI)	**99%** (92%, 100%)	**93%** (89%, 95%)
4-year survival (95% CI)	**96%** (88%, 98%)	**84%** (79%, 88%)

Event Free Survival Sensitivity Analyses Favor DFMO

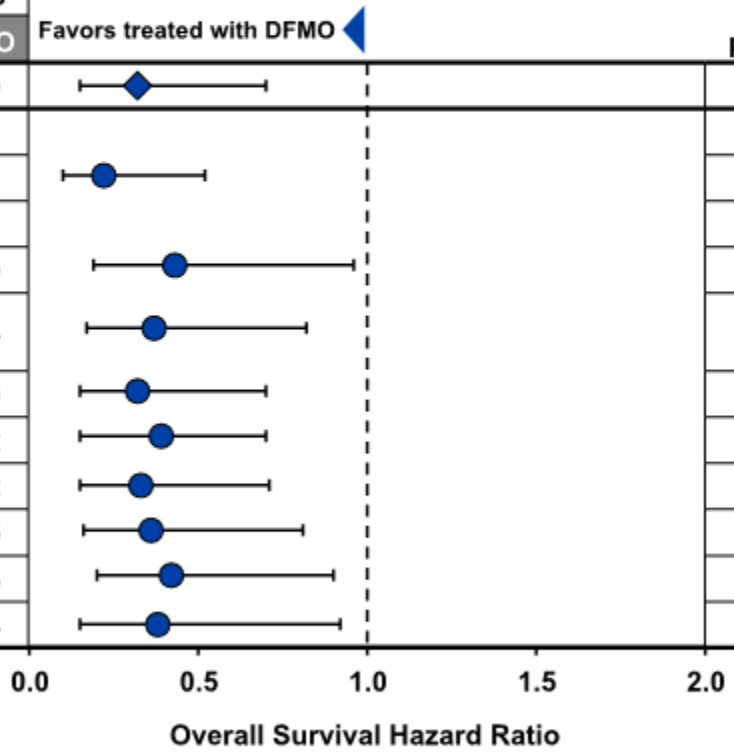
	# Events / # Patients		p-value
	DFMO	NO DFMO	
Primary Analysis (DFMO vs NO DFMO 1:3)	14 / 90	79 / 270	0.0114
Change PSM Model			
Ratio 1:1	14 / 90	31 / 90	0.0038
Change Patient Selection			
Remove NO DFMO patients with EFS ≤ 123 days	14 / 90	72 / 270	0.0363
Remove NO DFMO patients with a VGPR or PR at 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	0.0125
Keep only NO DFMO Contemporary patients (1:2)	15 / 91	55 / 182	0.0124
MICE imputation of missing covariate data	15 / 92	82 / 275	0.0140
Stratification of the propensity score	15 / 91	150 / 516	0.0125
Inverse probability weighting	14 / 90	141 / 494	0.0377



MICE = Multiple Imputation by Chained Equations

Overall Survival Sensitivity Analyses Favor DFMO

	# Events / # Patients		p-value
	DFMO	NO DFMO	
Primary Analysis (DFMO vs NO DFMO 1:3)	7 / 90	57 / 270	0.0045
Change PSM Model			
Ratio 1:1	7 / 90	24 / 90	0.0005
Change Patient Selection			
Remove NO DFMO patients with EFS ≤ 123 days	7 / 90	45 / 270	0.0395
Remove NO DFMO patients with a VGPR or PR at end of Immunotherapy	7 / 88	50 / 264	0.0139
Landmark < 120 days with matched patients	7 / 89	57 / 270	0.0045
Remove 5 DFMO patients not treated on 0032	7 / 84	48 / 252	0.0206
Keep only NO DFMO Contemporary patients (1:2)	8 / 91	37 / 182	0.0047
MICE imputation of missing covariate data	8 / 92	55 / 275	0.0128
Stratification of the propensity score	8 / 91	97 / 516	0.0247
Inverse probability weighting	7 / 90	93 / 494	0.0319



MICE = Multiple Imputation by Chained Equations

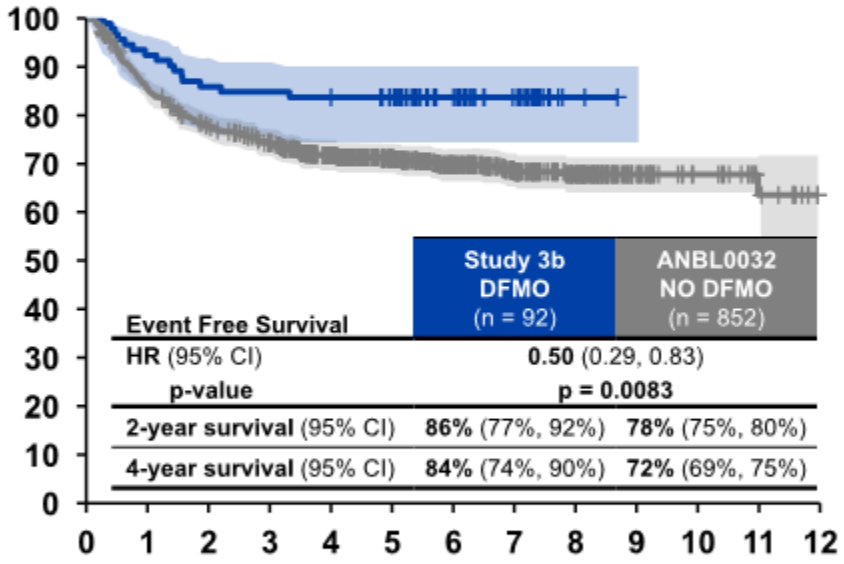
No Population Differences Identified Through Additional Characterization Efforts

- Little opportunity for DFMO selection bias and related sensitivity analysis consistent with primary
- Consistent results when other baseline covariates (histology, number immunotherapy cycles) included in PSM
- Similar US distribution in DFMO and NO DFMO groups
- Improved outcomes at high volume ANBL0032 sites do not benefit DFMO group
- 30% of primary DFMO group with household poverty exposure, similar to published rate of 35%[1]

1. Bona 2021: Household poverty exposure defined as sole coverage by Medicaid or CHIP, N=371 patients in COG immunotherapy studies

EFS and OS Consistently Favor DFMO in the Full Population Selected for Analysis

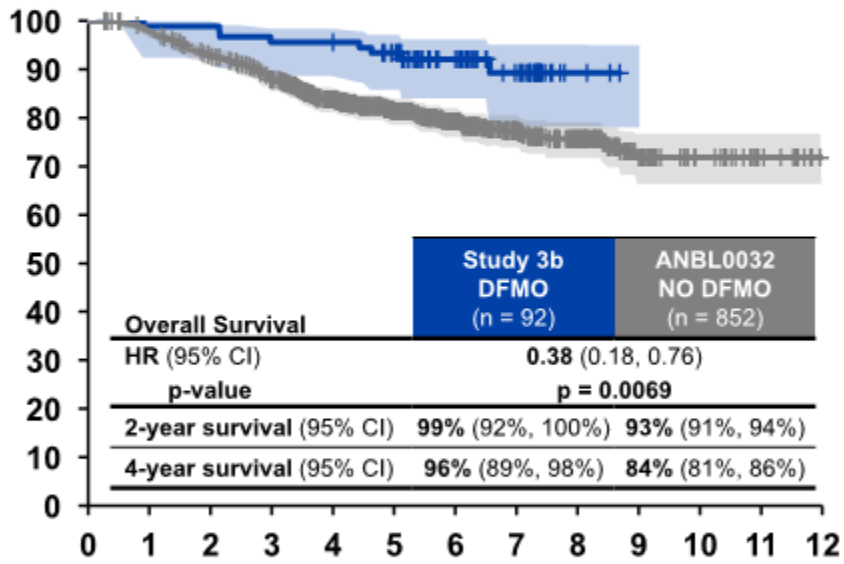
Event Free Survival Rate (%)



Event Free Survival	Study 3b DFMO (n = 92)	ANBL0032 NO DFMO (n = 852)
HR (95% CI)	0.50 (0.29, 0.83)	
p-value	p = 0.0083	
2-year survival (95% CI)	86% (77%, 92%)	78% (75%, 80%)
4-year survival (95% CI)	84% (74%, 90%)	72% (69%, 75%)

At risk													
DFMO	92	85	79	78	77	71	47	27	2	0			
NO DFMO	852	722	645	599	481	362	260	172	111	46	26	15	6

Overall Survival Rate (%)



Overall Survival	Study 3b DFMO (n = 92)	ANBL0032 NO DFMO (n = 852)
HR (95% CI)	0.38 (0.18, 0.76)	
p-value	p = 0.0069	
2-year survival (95% CI)	99% (92%, 100%)	93% (91%, 94%)
4-year survival (95% CI)	96% (89%, 98%)	84% (81%, 86%)

At risk													
DFMO	92	90	90	87	87	79	52	29	3	0			
NO DFMO	852	825	770	708	562	423	310	205	133	58	31	19	8

Blinded Independent Central Review (BICR) of DFMO Upfront Remission Patients Confirmed No Bias

- DFMO group for externally controlled analysis (n = 92)
- Reviewed all imaging through long term follow up
  - Most patients had > 2 years of images
- Evaluation based on dual read with ad hoc adjudication
- Near perfect agreement between local and central review[1]
- EFS using BICR outcomes confirms primary analysis

ANBL0032 external control imaging not available for BICR

1. Concordance assessed by Kappa coefficient= 0.92; category >0.8 to <1.0 = near perfect agreement (McHugh, 2012)

DFMO Efficacy
Confirmatory Data Package

Totality of Confirmatory Evidence Supports Pivotal Study

Nonclinical	In Vitro Effects	▪ In vitro inhibition of ODC and neurosphere formation at physiological concentrations
	In Vivo Effects	▪ Animal models establish cytostatic and anti-tumorigenic effects[1]
Supporting Clinical Data	Pharmacodynamic Response	▪ Decreased urinary polyamines in patients treated with DFMO[2] ▪ Increased Let-7 expression in patients treated with DFMO
	Maintenance Efficacy	▪ Patients in remission after European upfront therapy ▪ Study 3b Stratum 2 patients in remission after R/R therapy ▪ Expanded Access patients in upfront remission ▪ Expanded Access patients in remission after R/R therapy
	Improvement of Active Disease	▪ Phase 1 data in patients with active disease[2] ▪ Expanded Access Study evaluation of patients with active disease

1. BCC data and Hogarty, 2008; 2. Sholler, 2015

Nonclinical In Vivo Data Support DFMO as an Effective Anti-Tumorigenic Agent

Nonclinical

- In Vitro Effects
- **In Vivo Effects**

Supporting Clinical Data

- Pharmacodynamic Response
- Maintenance Efficacy
- **Improvement of Active Disease**

- Extreme Limiting Dilution Analysis (ELDA)
  - Mouse xenograft with human NB cells
  - DFMO decreased frequency of tumor formation by over 60% ($p=0.02$) compared to control mice
  - Additional analyses showed that DFMO:
    - Reduced expression of MYCN and LIN28B
    - 6-fold increase expression of pro-senescence markers ($p<0.0001$)

Anti-Tumorigenic Activity Verified by Independent Research

Nonclinical

- In Vitro Effects
- **In Vivo Effects**

Supporting Clinical Data

- Pharmacodynamic Response
- Maintenance Efficacy
- **Improvement of Active Disease**

- Independent published research[1]
  - Transgenic mice over-expressing human MYCN (*TH-MYCN)*
    - Spontaneously develop neuroblastoma tumors
  - DFMO treatment led to an ~65% reduction in tumor formation (p=0.035) compared to control
  - Reduced polyamine levels demonstrated on-target activity

1. Hogarty, 2008

Pharmacodynamic Effects in Patients Support On-Target DFMO Activity

Nonclinical
- In Vitro Effects
- In Vivo Effects

Supporting Clinical Data
- **Pharmacodynamic Response**
- Maintenance Efficacy
- **Improvement of Active Disease**

- Reduced trends in urinary polyamines
  - In Phase 1 patients with active disease[1]
  - In preliminary analysis of Study 3b remission patients (n = 21)
- Increased trends in Let-7 miRNA tumor suppressor expression
  - Preliminary analysis of ongoing study (n = 33)
  - Median 3-fold increase in pre- vs post-DFMO plasma samples

1. Sholler, 2015

DFMO Maintenance in Patients Achieving Remission After European Upfront or After Relapsed/Refractory Treatment

Nonclinical
- In Vitro Effects
- In Vivo Effects

Supporting Clinical Data
- Pharmacodynamic Response
- **Maintenance Efficacy**
- Improvement of Active Disease

- DFMO maintenance following European SoC (n = 47)[1]
  - 3-phase treatment approach similar to COG
  - 5-year EFS outcomes similar to COG[2]

- Study 3b Stratum 2 patients in remission after R/R treatment
  - Patients (n = 35) received same DFMO treatment and follow up as Stratum 1 (Upfront Remission)
  - Prospectively planned for separate analysis due to worse prognosis (historical 2-year control rate of 10%[3])

1. Patients treated on or consistent with immunotherapy arm of HRNBL-1 (Ladenstein, 2020); 2. Desai, 2022; 3. Santana, 2008

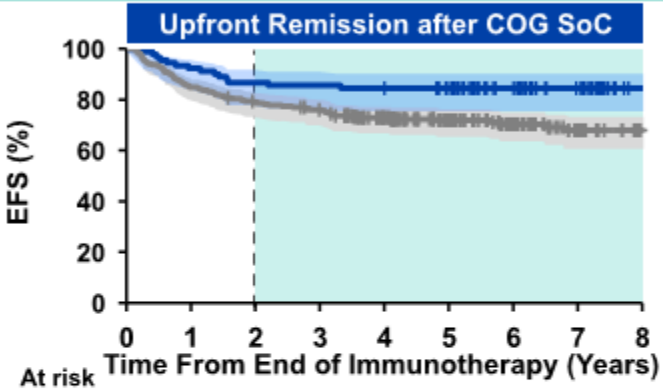
Consistent Durability of Effect After Completing 2 Years of DFMO Treatment

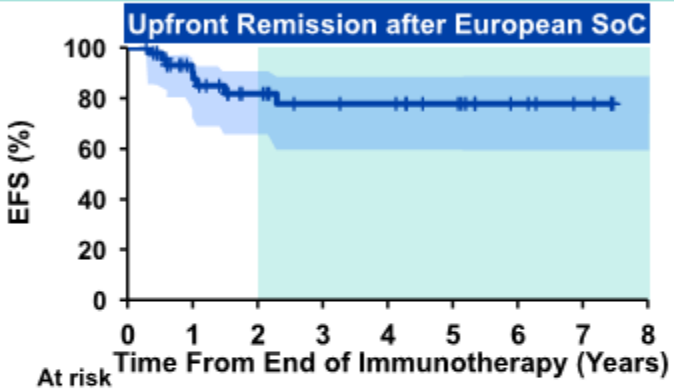
Nonclinical

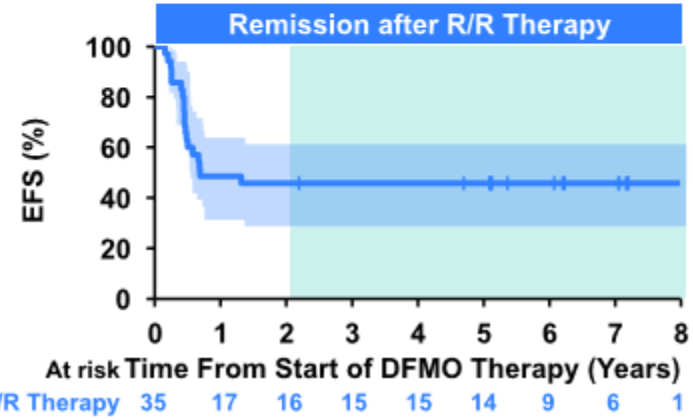
- In Vitro Effects
- In Vivo Effects

Supporting Clinical Data

- Pharmacodynamic Response
- **Maintenance Efficacy**
- Improvement of Active Disease

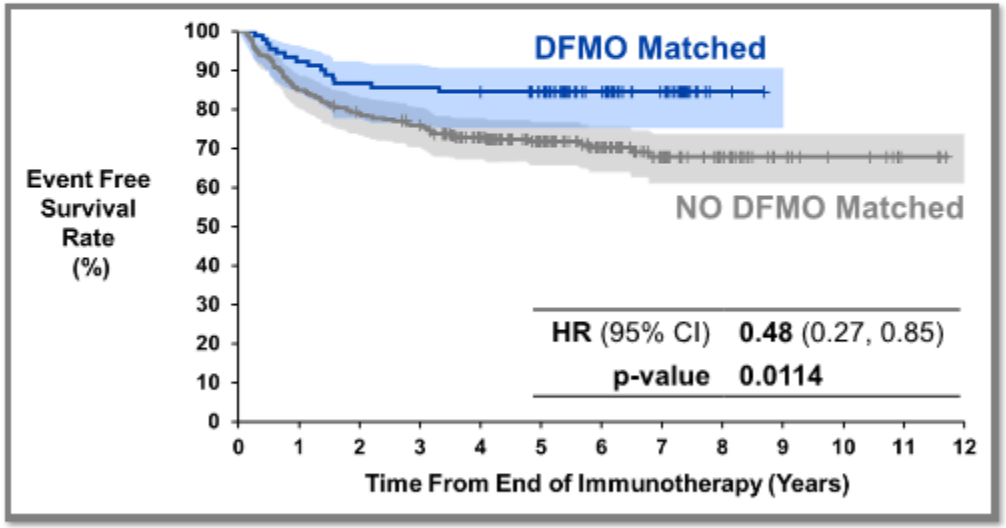






DFMO Program Meets FDA Requirements for Substantial Evidence of Effectiveness

- Study 3b vs ANBL0032 meets FDA requirements for adequate and well-controlled study, supports meaningful benefit



- Confirmatory evidence supports conclusions from pivotal comparison

Clinical Perspective

Susan L. Cohn, MD

Professor and Director of Clinical Sciences
Department of Pediatrics
University of Chicago Medicine

Current Treatment Paradigm for HRNB

Current Treatment Paradigm

- Survival has improved with increasingly intensive, multimodality treatment and post-consolidation immunotherapy

Treatment Outcomes

- Significant risk of relapse remains
- ~30% of patients will relapse from end of immunotherapy

Unmet Need Remains

- New therapies and approaches needed to improve outcomes of high-risk patients

Initial Investigations into DFMO for HRNB

- Single arm trial design prevented ability to draw conclusions regarding efficacy
- Needed a comparator arm to allow objective evaluation

Comparison with External Arm of Matched Population Shows Consistent, Compelling Benefit in Favor of DFMO

Benefit for HRNB Patients	▪ Data demonstrate activity of DFMO in patients with HRNB ▪ Addition of post-immunotherapy DFMO improves EFS and OS ▪ DFMO can offer a benefit to HRNB patients
Risks Adequately Characterized	▪ Risks outweighed by potential benefits ▪ Data enable treating physicians to include option of post-immunotherapy DFMO as we counsel families once their children achieve remission
Strength of Evidence	▪ Study design, strength of evidence demonstrate importance of regulatory flexibility ▪ Ability to meet an unmet medical need with consistent data providing compelling evidence

Conclusion

Kristen Gullo

Vice President of Development and Regulatory Affairs

US WorldMeds

Needs of Children with High-Risk Neuroblastoma Inspire Efforts Toward New Evidence-Based Treatment Options

Will
11 years

iwilfin™
(eflornithine) tablets

FDA tentatively approved tradename

Finn
3 years

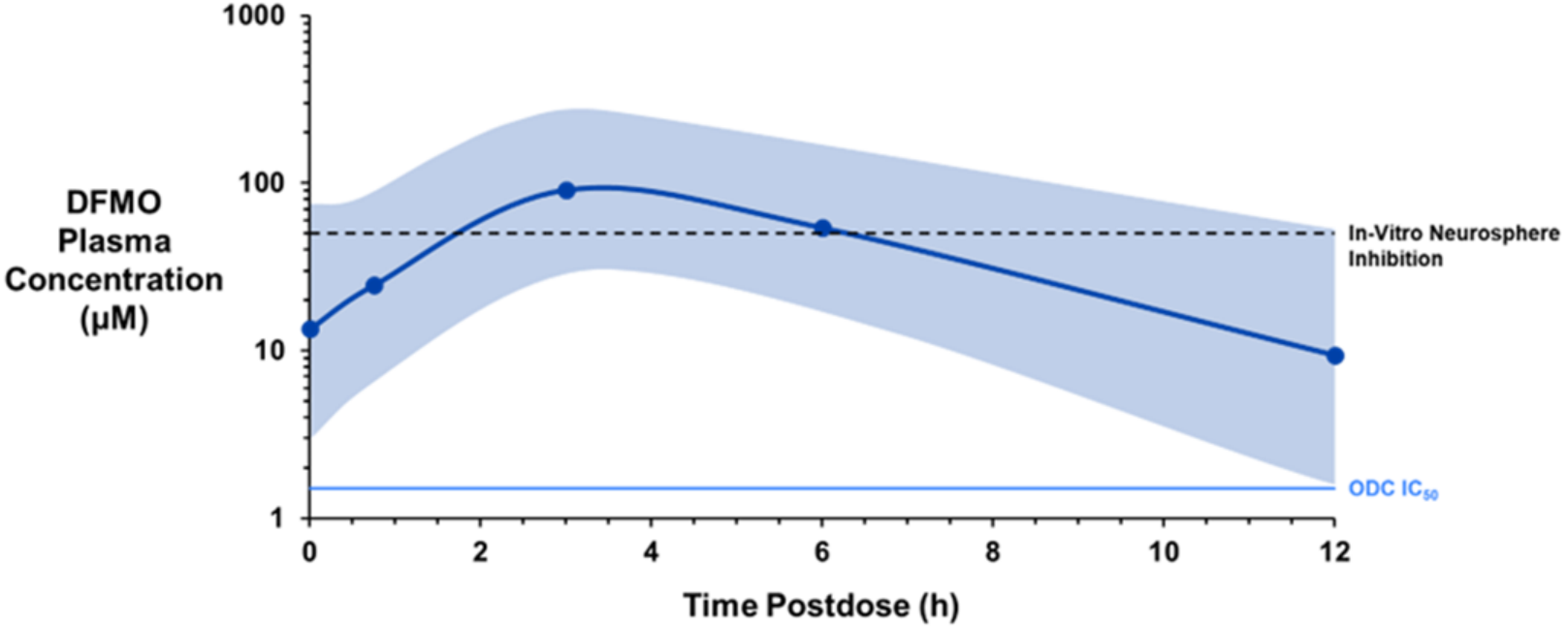
DFMO (Eflornithine) as Maintenance Therapy for High-Risk Neuroblastoma

October 4, 2023

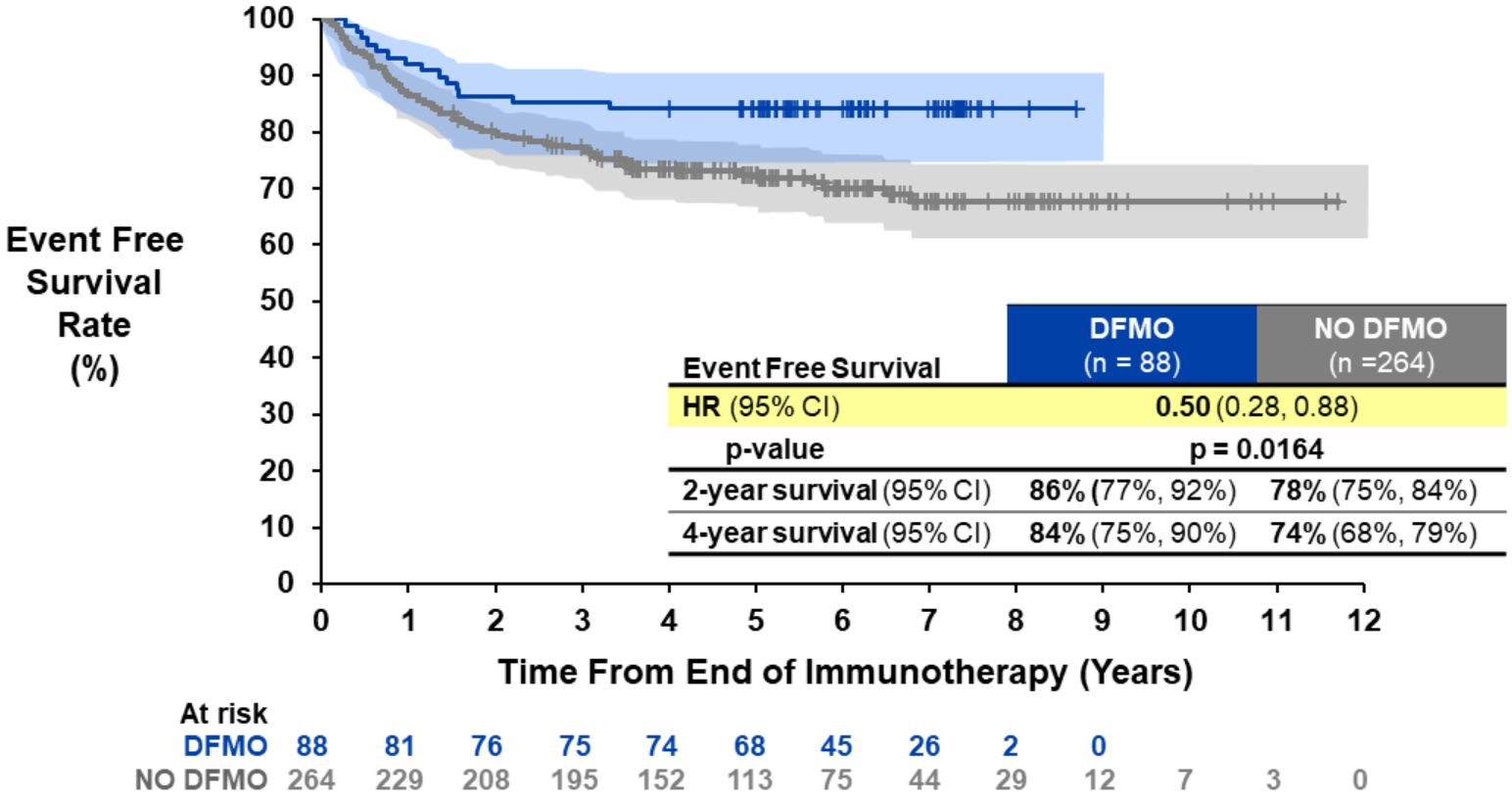
Oncologic Drugs Advisory Committee

US WorldMeds

DFMO Steady-State Exposures in Patients Treated at Recommended Dose (Study 14, n=177) are above DFMO's *in vitro* Concentration Thresholds for ODC and Neurosphere Inhibition



Consistent Results In Sensitivity Analysis Removing NO DFMO Patients with a VGPR or PR at End of Immunotherapy

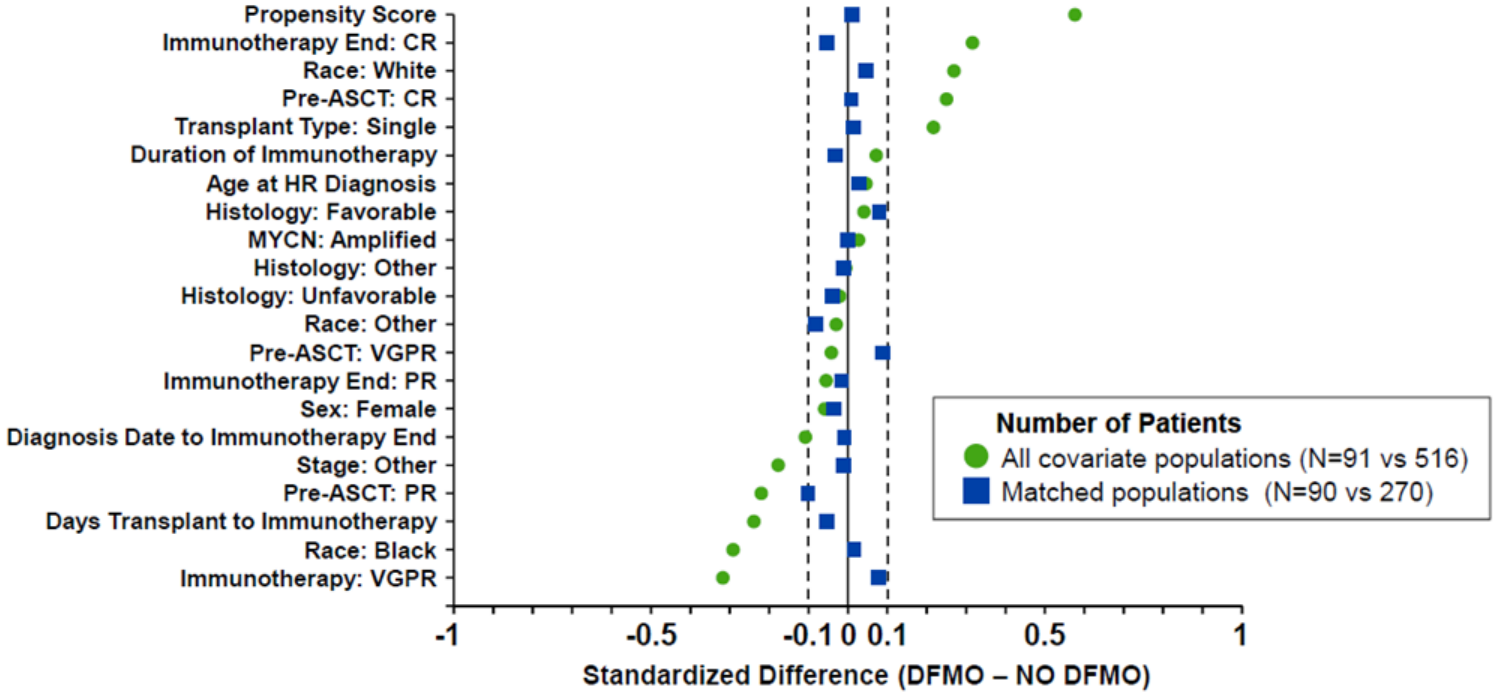


Event Free Survival	DFMO (n = 88)	NO DFMO (n =264)
HR (95% CI)	**0.50** (0.28, 0.88)	
p-value	**p = 0.0164**	
2-year survival (95% CI)	**86%** (77%, 92%)	**78%** (75%, 84%)
4-year survival (95% CI)	**84%** (75%, 90%)	**74%** (68%, 79%)

DFMO in Chemo-preventative Studies

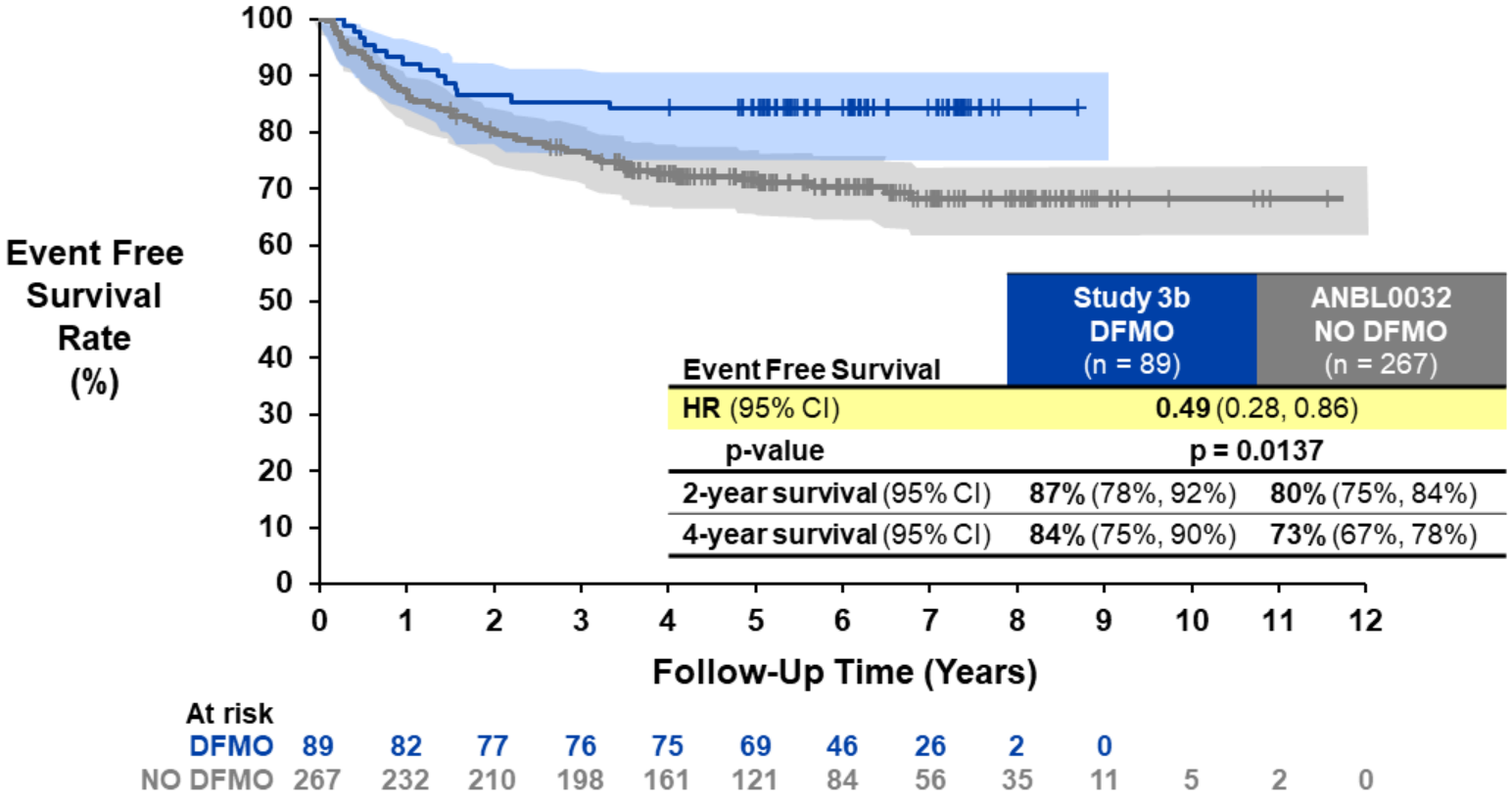
Study	Meyskens, 2008	Bailey, 2010	Love, 1998
Indication	Prevention of sporadic colorectal adenomas	Prevention of skin cancer in patients with previous history of skin cancer	ODC and polyamine levels in rectal, rectosigmoidal, and cecal colonic mucosae.
Dose	500 mg/day (+sulindac)	500 mg/m^2/day	500 mg/m^2/day
Clinical outcome	Adenoma recurrence 41.1% DFMO+sulindac vs 12.3% placebo HR: 0.30 (0.18-0.49; P < 0.001)	Reduction in basal cell carcinoma occurrence in rates/patient-yrs: Control = 0.40 DFMO = 0.28 p=0.03	Evidence of global ODC suppression and decreased polyamine levels.
Pharmacodynamic effects	Reduction of polyamines in colorectal mucosa at studied dose	Decrease in skin putrescine and spermidine concentrations.	ODC levels globally suppressed (p=0.035). Significantly decreased putrecine and spermidine in colonic mucosae (p=0.03 and p=0.04) at 3 months.

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.

Consistent Results in Comparison Using Exact Match on Pre-ASCT Response



Event Free Survival	Study 3b DFMO (n = 89)	ANBL0032 NO DFMO (n = 267)
HR (95% CI)	**0.49** (0.28, 0.86)	
p-value	**p = 0.0137**	
2-year survival (95% CI)	**87%** (78%, 92%)	**80%** (75%, 84%)
4-year survival (95% CI)	**84%** (75%, 90%)	**73%** (67%, 78%)

Evaluation of Overall Survival in Primary Matched Relapsed Patients

- Lower proportion of DFMO patients die after relapse
  - 7 / 14 (50%) in DFMO vs. 57 / 79 (72%) in NO DFMO
- Median time from relapse to death was 1 year longer in DFMO
- Median follow-up time in patients that remained alive was > 1.5 years longer in DFMO
- No clear differences in post-release therapy based on data available for review
- Same findings in contemporary population