







Eflornithine as Postimmunotherapy Maintenance in High-Risk Neuroblastoma: Externally Controlled, Propensity Score–Matched Survival Outcome Comparisons

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ABSTRACT

PURPOSE Long-term survival in high-risk neuroblastoma (HRNB) is approximately 50%, with mortality primarily driven by relapse. Eflornithine (DFMO) to reduce risk of relapse after completion of immunotherapy was investigated previously in a single-arm, phase II study (NMTRC003B; ClinicalTrials.gov identifier: [NCT02395666](https://clinicaltrials.gov/ct2/show/study/NCT02395666)) that suggested improved event-free survival (EFS) and overall survival (OS) compared with historical rates in a phase III trial (Children Oncology Group ANBL0032; ClinicalTrials.gov identifier: [NCT00026312](https://clinicaltrials.gov/ct2/show/study/NCT00026312)). Using patient-level data from ANBL0032 as an external control, we present new analyses to further evaluate DFMO as HRNB postimmunotherapy maintenance.

PATIENTS AND METHODS NMTRC003B (2012–2016) enrolled patients with HRNB (N = 141) after standard up-front or refractory/relapse treatment who received up to 2 years of continuous treatment with oral DFMO (750 ± 250 mg/m² twice a day). ANBL0032 (2001–2015) enrolled patients with HRNB postconsolidation, 1,328 of whom were assigned to dinutuximab (ch.14.18) treatment. Selection rules identified 92 NMTRC003B patients who participated in (n = 87) or received up-front treatment consistent with (n = 5) ANBL0032 (the DFMO/treated group) and 852 patients from ANBL0032 who could have been eligible for NMTRC003B after immunotherapy, but did not enroll (the NO-DFMO/control group). The median follow-up time for DFMO/treated patients was 6.1 years (IQR, 5.2–7.2) versus 5.0 years (IQR, 3.5–7.0) for NO-DFMO/control patients. Kaplan-Meier and Cox regression compared EFS and OS for overall groups, 3:1 (NO-DFMO:DFMO) propensity score–matched cohorts balanced on 11 baseline demographic and disease characteristics with exact matching on *MYCN*, and additional sensitivity analyses.

RESULTS DFMO after completion of immunotherapy was associated with improved EFS (hazard ratio [HR], 0.50 [95% CI, 0.29 to 0.84]; *P* = .008) and OS (HR, 0.38 [95% CI, 0.19 to 0.76]; *P* = .007). The results were confirmed with propensity score–matched cohorts and sensitivity analyses.

CONCLUSION The externally controlled analyses presented show a relapse risk reduction in patients with HRNB treated with postimmunotherapy DFMO.

ACCOMPANYING CONTENT

 [Data Supplement](#)
 [Protocol](#)

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INTRODUCTION

High-risk neuroblastoma (HRNB) remains one of the most challenging forms of childhood cancer, accounting for 15% of all pediatric cancer deaths.¹ Standard treatment comprises induction, consolidation, and postconsolidation phases.² 13-cis-Retinoic acid (RA) was the primary post-consolidation therapeutic agent throughout the early 2000s.

ANBL0032 randomly assigned patients to receive RA therapy with or without dinutuximab (ch.14.18). Two-year event-free survival (EFS) was meaningfully improved in patients randomly assigned to dinutuximab + RA compared with RA alone. This supported a single-arm continuation of ANBL0032 with all patients nonrandomly assigned to dinutuximab and ultimately resulted in the addition of dinutuximab to RA post-consolidation therapy as standard of care (SoC).^{2,3} In the

CONTEXT

Key Objective

Do external control comparisons, including propensity score–matched analyses, indicate that eflornithine (DFMO) treatment after completion of postconsolidation immunotherapy in patients with high-risk neuroblastoma (HRNB) in remission is associated with improved survival outcomes?

Knowledge Generated

Analyses of similar populations of patients with HRNB who completed multiagent, multimodality up-front treatment ending with dinutuximab suggest that postimmunotherapy maintenance treatment with DFMO for 2 years significantly improved survival outcomes compared with NO-DFMO external control patients. This was further supported in propensity score–matched cohorts that reduced bias by mitigating differences in patient populations.

Relevance (S. Bhatia)

This study suggests that DFMO may potentially confer a survival benefit when used in a postimmunotherapy maintenance setting in patients with HRNB.*

*Relevance section written by JCO Associate Editor Smita Bhatia, MD, MPH, FASCO.

dinutuximab–randomly assigned group, 2-year EFS from start of immunotherapy was $66\% \pm 5\%$ ³ yet declined to $56.6\% \pm 4.7\%$ ⁴ at 5 years, and rates were similar in the group of patients nonrandomly assigned to dinutuximab.⁵ Relapse patients have a very poor prognosis⁶ with a 5-year overall survival (OS) rate $<10\%$,⁷ so additional therapeutic options are still needed to further improve outcomes despite the most recent advancements in up-front treatment.

One candidate for reducing risk of relapse is eflornithine (DFMO). DFMO has shown chemopreventative benefits on the basis of its mechanism of action^{8–11} in various cancers,^{12,13} including HRNB.¹⁴ Its effects in HRNB may be mediated via inhibition of ornithine decarboxylase^{15–17} that reverses the LIN28/Let-7 axis,^{18–20} a pathway regulating cancer stemness, and prevention of MYCN expression is important since MYCN amplification is an oncogenic driver in HRNB.^{21,22} This led to a phase II evaluation of postimmunotherapy DFMO treatment for patients with HRNB in remission (NMTRC003B).²³ The prospective, single-arm study suggested that DFMO had the potential to reduce the risk of relapse with a 2-year EFS of 85% compared with the ANBL0032 reported rate of 70%, as adjusted to estimate outcomes from end of immunotherapy.²³ Similar results were obtained in a subsequent analysis comparing the outcomes of DFMO–treated patients with patients with HRNB in a retrospective chart review across Beat Childhood Cancer (BCC) Research Consortium hospitals.²⁴

However, the single-arm design of NMTRC003B introduces potential biases that limit interpretation of the reported outcomes. Thus, we have used patient-level data from ANBL0032 as an external control database to identify a representative population that did not receive DFMO for comparison with DFMO–treated patients with more rigorous

statistical approaches, including propensity score–matched analysis. Although randomized control trials (RCTs) remain the gold standard for treatment effect, propensity score–matched analysis is a widely published statistical method for comparing two cohorts^{25–28} by effectively balancing the distribution of patient baseline characteristics and risk categories between treatment groups to reduce potential sources of confounding bias. On the basis of propensity scores (PSs), patients are placed into matched sets, and an estimation of treatment effect is obtained by comparing their outcomes.

PATIENTS AND METHODS

Study Populations

The reported analysis compares groups of patients receiving postimmunotherapy DFMO in NMTRC003B and those receiving postconsolidation immunotherapy in ANBL0032 who did not subsequently receive DFMO. Both studies followed patients for long-term EFS and OS for up to 10 (ANBL0032) and 7 (NMTRC003B) years. ANBL0032 and NMTRC003B started from different treatment time points, the beginning of immunotherapy and the end of immunotherapy, respectively. Mandatory disease evaluations at the end of immunotherapy in ANBL0032 coincided with the assessment for enrollment in NMTRC003B, thereby serving as a common starting point for the comparison (Fig 1).

Both studies required imaging assessments at the end of immunotherapy (representing therapy end in ANBL0032 and baseline for NMTRC003B) and at 3, 6, 9, 12, 18, and 24 months. Further imaging was required at 30 and 36 months in ANBL0032 and was conducted per SoC in NMTRC003B. All NMTRC003B centers were also Children Oncology Group

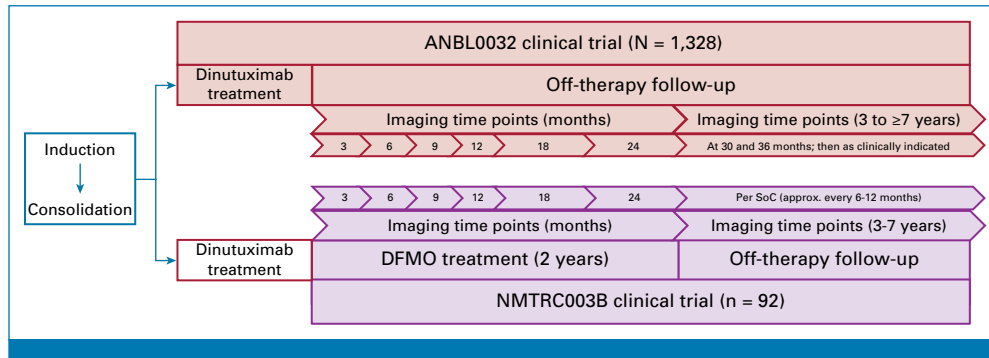


FIG 1. Study flow for the two individual clinical trials, NMTRC003B and ANBL0032. NMTRC003B is a phase II, open-label, single-dose level evaluation of 2-year maintenance treatment with DFMO in patients with HRNB in remission at the end of immunotherapy (stratum 1). Data from the independent ANBL0032 study were used as an external control for NMTRC003B to evaluate survival differences in a comparable group of eligible patients: those in remission at the end of dinutuximab immunotherapy treated with DFMO in NMTRC003B versus those who did not receive DFMO and continued follow-up without further pharmacotherapy as per current SoC in ANBL0032. Patients in ANBL0032 completed high-risk induction chemotherapy and surgery (as indicated), consolidation comprised at least one ASCT (within 12 months of high-risk induction start) and radiation (as indicated), and received dinutuximab immunotherapy on study (within 200 days from ASCT). Patients in NMTRC003B completed high-risk induction chemotherapy and surgery (as indicated), consolidation therapy (ASCT and radiation therapy, as indicated), and immunotherapy with anti-GD2 antibody (eg, dinutuximab), and achieved end of immunotherapy response of at least PR with no evidence of disease in the bone marrow on the basis of institutional assessment (Data Supplement, Table S1). Both studies followed patients for EFS and OS as end points. Protocol-required imaging was similar during follow-up/surveillance for both studies. ASCT, autologous stem-cell transplant; DFMO, eflornithine; EFS, event-free survival; HRNB, high-risk neuroblastoma; OS, overall survival; PR, partial response; SoC, standard of care.

(COG) member sites with expected similarities in long-term surveillance practices as observed with 97% of nonrelapsed DFMO patients having imaging visits beyond 24 months from the end of immunotherapy. Additionally, both studies required anatomical (computed tomography/magnetic resonance imaging) and nuclear (metaiodobenzylguanidine [MIBG] and/or positron emission tomography [PET]) imaging modalities, evaluated disease response according to modified International Neuroblastoma Response Criteria (INRC) 1993 guidelines,²⁹ and followed patients long-term with at least annual contact. EFS and OS outcomes were reported for both studies, with identical event definitions including relapse, disease progression, secondary malignancy or death due to any cause for EFS, and death due to any cause for OS (Fig 1).

The NMTRC003B intent-to-treat (ITT) population included 140 patients with HRNB treated with oral DFMO 750 ± 250 mg/m² twice a day continuously for up to 2 years, enrolled (2012–2016) into two strata. Stratum 1 included patients who completed standard up-front therapy and were in initial remission after immunotherapy. Stratum 2 included patients in remission after refractory/relapse therapy. For both cohorts, remission was defined as having achieved a partial response (PR) per modified INRC 1993 defined response categories²⁹ with no evidence of disease in the bone marrow on the basis of institutional assessment. For patients with residual MIBG-avid lesions, biopsy or PET was required to confirm

that the disease was metabolically inactive. Baseline PET was required in a small percentage of the study population; no patient was screen-failed on the basis of this criterion. The full ITT population was evaluated against four statistical analysis plan (SAP)-defined selection rules (Fig 2A) to identify the DFMO/treated group for external control comparisons. Ninety-one stratum 1 patients and a single stratum 2 patient were selected for the DFMO/treated group (n = 92). The stratum 2 patient was determined to have been originally misdiagnosed with intermediate disease, relapsed and subsequently received HRNB up-front therapy (including direct participation in ANBL0032). Although this patient had a prior HRNB relapse and later experienced a second relapse on DFMO therapy, the patient was conservatively included. Eighty-seven (95%) of the 92 DFMO/treated patients had verified prior participation in ANBL0032 (Table 1). The remaining five patients would have met ANBL0032 eligibility and received dinutuximab consistent with the protocol regimen, but accessed dinutuximab via compassionate use or represented the earliest commercial therapy patients.

ANBL0032 (enrolled 2001–2015) was conducted by COG.^{3–5} A total of 1,328 patients were randomly or nonrandomly assigned to postconsolidation therapy comprising dinutuximab, RA, sargramostim, and aldesleukin (excluding n = 112 initially randomly assigned to RA alone). Patients were required to have previously completed high-risk

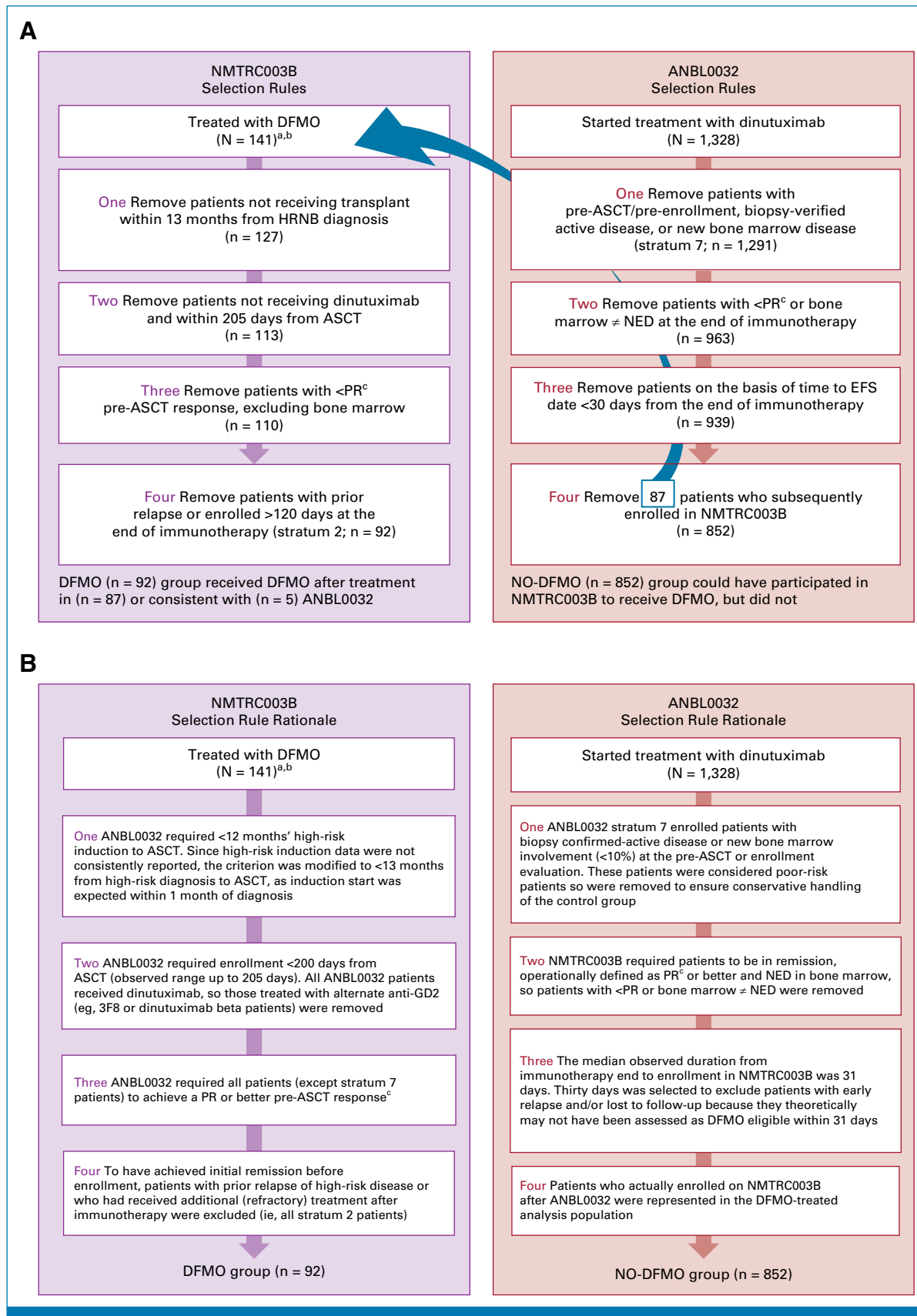


FIG 2. Selection rules specific and applied to each study group (A) and rationale for the selection criteria (B). NMTRC003B comprised N = 141 patients in remission at the end of standard up-front, refractory, or relapse therapy and receiving DFMO treatment (up to 2 years) in NMTRC003B or its identically designed predecessor trial. Eligibility criteria were intentionally aligned with patients who completed treatment in ANBL0032 (Data Supplement, Table S1; patients were enrolled during (continued on following page)

FIG 2. (Continued). 2012-2016 and long-term follow-up is ongoing with data cutoff for analyses: June 30, 2021). The ANBL0032 database comprised 1,328 dinutuximab-treated patients (excluding those initially randomly assigned to RA alone) obtained via a data transfer agreement with COG (patients were enrolled during 2001-2015, and long-term follow-up is ongoing with data cutoff for analyses: June 30, 2019). The final DFMO/test population ($n = 92$) only comprised patients who had enrolled in or received treatment consistent with ANBL0032 before DFMO treatment. The NO-DFMO/control population ($n = 852$) comprised patients eligible to enroll in NMTRC003B (stratum 1) after dinutuximab immunotherapy completion, including patients consistent with the NMTRC003B operational definition of remission (ie, overall end of immunotherapy response \geq PR and negative for bone marrow disease 30 days after immunotherapy), and excluded patients at end-of-immunotherapy PR without a bone marrow evaluation (not performed/missing in the database). ^aOne compassionate use patient was excluded from the efficacy analysis at the time of enrollment (per protocol). ^bPatient data for the predecessor trial are reported via the chart review study BCC001, which was combined with the NMTRC003B study database for analysis. ^cResponse criteria 2 and 3 for ANBL0032 and NMTRC003B, respectively, followed modified INRC 1993 international guidelines.²⁹ ASCT, autologous stem-cell transplant; COG, Children Oncology Group; DFMO, eflornithine; dinutuximab, anti-GD2 antibody therapy; EFS, event-free survival; HRNB, high-risk neuroblastoma; NED, no evidence of disease; NO-DFMO, no eflornithine (control); PR, partial response; RA, 13-cis-retinoic acid.

induction therapy and achieved at least a PR before receiving at least one autologous stem-cell transplant (ASCT) preceding enrollment^{3,4} (Figs 1 and 2). Four SAP-defined selection rules were applied to identify patients with characteristics and end of immunotherapy disease status consistent with eligibility for NMTRC003B, but did not enroll, resulting in a NO-DFMO/control analysis population of $n = 852$ (Fig 2B). In the selected group, 75% of patients completed immunotherapy in the NMTRC003B enrollment timeframe (Table 1). Patients removed from the analysis population included 87 patients who enrolled in NMTRC003B and 389 patients with an EFS event rate of 66% who were removed by other selection rules (Fig 3).

This study was conducted according to the principles of the 2004 version of the Declaration of Helsinki, the International Conference on Harmonization Guidance on Good Clinical Practice, and the requirements of all local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects. The research was approved by the Western Institutional Review Board and the local Institutional Review Boards at the 21 enrolling hospitals. Written, informed consent was obtained from all patients according to institutional guidelines.

ClinicalTrials.gov identifiers: [NCT02395666](https://clinicaltrials.gov/ct2/show/study/NCT02395666) (NMTRC003B) and [NCT00026312](https://clinicaltrials.gov/ct2/show/study/NCT00026312) (ANBL0032).

Efficacy Comparison and End Points

EFS was defined as the time from end of immunotherapy until the first occurrence of an EFS event or, if no event, until last contact. OS was defined as the time from end of immunotherapy to an OS event or, if no event, until last contact. EFS (primary) and OS (key secondary) outcomes for the selected groups of treated ($n = 92$) and control ($n = 852$) patients were analyzed by an unadjusted Cox proportional hazards model controlling only for treatment (DFMO v NO-DFMO). Statistical programming was conducted in SAS 9.4 (SAS Institute, Cary, NC).

Sensitivity Analyses

While patients with a PR, very good partial response (VGPR), or complete response (CR) were included in the eligible DFMO group, the first sensitivity analysis (ANBL0032 step 2, Fig 2B) restricted the NO-DFMO group to only those patients achieving CR postimmunotherapy. This removed any patient who may have had residual MIBG-positive lesions (ie, PR or VGPR at the end of immunotherapy), but without PET verification of inactivity as had been done to confirm baseline remission in NMTRC003B for 4 (4.4%) DFMO population patients. While the median time from the end of immunotherapy to enrollment of patients included in the eligible DFMO group was 31 days, NMTRC003B enrolled patients up to 123 days from immunotherapy end. This may have resulted in treatment of some lower-risk patients because they remained in remission for up to 4 months into the postimmunotherapy period associated with high risk of relapse. Thus, the second sensitivity analysis (ANBL0032 step 3, Fig 2B) removed all NO-DFMO patients with an EFS date (event/censored) ≤ 123 days after immunotherapy (lead-in time). The full DFMO/treated group was maintained for both sensitivity analyses, including patients both with $<$ CR responses at immunotherapy end and early EFS events (≤ 123 days from immunotherapy end). Additionally, the potential impact of evolving treatment over time was evaluated in the NO-DFMO subgroup completing immunotherapy in a timeframe consistent with NMTRC003B enrollment (2011-2015, the contemporary population). Finally, the potential difference in patients enrolled in ANBL0032 compared with those who received dinutuximab outside of the study was evaluated by restricting the treated/DFMO group to only those with verified participation ($n = 87$).

Propensity Score–Matched Analyses

PSM was implemented to balance DFMO and NO-DFMO patients according to 11 baseline covariates: age at high-risk diagnosis, sex, race, stage at HRNB diagnosis per the 1993 International Neuroblastoma Staging System²⁹ (categories of 4 or $<$ 4 including 4S), pre-ASCT response, transplant type, time from ASCT to start of immunotherapy, duration of

TABLE 1. Demographic and Disease Characteristics for the NO-DFMO/Control (ANBL0032) and DFMO/Test (NMTRC003B) Subgroups Used for the Overall Efficacy Analysis, and the Matched Populations for Both Groups Used for the Propensity Score-Matched Analyses (matched in a 3:1 NO-DFMO:DFMO ratio)

Characteristic	ANBL0032	NMTRC003B	ANBL0032	NMTRC003B
	NO-DFMO (n = 852) ^a	DFMO (n = 92) ^b	NO-DFMO Matched (n = 270) ^c	DFMO Matched (n = 90) ^c
Patient immunotherapy completion timeframe, %				
2001-2010 ^d	29.7	0	27.8	0
2011-2016	70.3	100	72.2	100
Age at high-risk diagnosis, years ^e				
N, mean (SD)	688, 3.7 (2.49)	92, 3.8 (2.86)	270, 3.6 (2.59)	90, 3.7 (2.87)
0 to <18 months, No. (%)	93 (10.9)	12 (13.0)	46 (17.0)	12 (13.3)
≥18 months, No. (%)	595 (69.8)	80 (87.0)	224 (83.0)	78 (86.7)
Unknown, No. (%)	164 (19.2)	0	0	0
Sex, No. (%) ^e				
Female	298 (35.0)	37 (40.2)	113 (41.9)	36 (40.0)
Male	390 (45.8)	55 (59.8)	157 (58.1)	54 (60.0)
Unknown	164 (19.2)	0	0	0
Race, No. (%) ^e				
Black or African American	92 (10.8)	7 (7.6)	17 (6.3)	6 (6.7)
White	493 (57.9)	81 (88.0)	236 (87.4)	80 (88.9)
Others	31 (3.6)	4 (4.3)	17 (6.3)	4 (4.4)
Unknown	236 (27.2)	0	0	0
INSS stage, No. (%) ^e				
Stage IV	565 (66.3)	80 (87.0)	233 (86.3)	78 (86.7)
Other	123 (14.4)	12 (13.0)	37 (13.7)	12 (13.3)
Unknown	164 (19.2)	0	0	0
MYCN, No. (%) ^e				
Amplified	250 (29.3)	40 (43.5)	120 (44.4)	40 (44.4)
Not amplified	345 (40.5)	51 (55.4)	150 (55.6)	50 (55.6)
Unknown	257 (30.2)	1 (1.1)	0	0
Histology, No. (%)				
Favorable	32 (3.8)	7 (7.6)	13 (4.8)	6 (6.7)
Unfavorable	550 (64.6)	76 (82.6)	229 (84.8)	75 (83.3)
Unknown	270 (31.7)	9 (9.8)	28 (10.4)	9 (10.0)
Pre-ASCT response (primary tumor, soft tissue metastases, and bone metastases), No. (%) ^e				
CR	253 (29.7)	38 (41.3)	113 (41.9)	38 (42.2)
VGPR	311 (36.5)	32 (34.8)	82 (30.4)	31 (34.4)
PR	288 (33.8)	22 (23.9)	75 (27.8)	21 (23.3)
Transplant type, No. (%) ^e				
Single	748 (87.8)	84 (91.3)	245 (90.7)	82 (91.1)
Tandem	104 (12.2)	8 (8.7)	25 (9.3)	8 (8.9)
Time from transplant (ASCT) to start of immunotherapy, days ^e				
N, mean (SD)	835, 96.9 (22.76)	92, 91.7 (21.39)	270, 92.9 (20.99)	90, 91.8 (21.62)
Overall response at the end of immunotherapy, No. (%) ^e				
CR	631 (74.1)	79 (85.9)	236 (87.4)	77 (85.6)
VGPR	166 (19.5)	9 (9.8)	21 (7.8)	9 (10.0)
PR	55 (6.5)	4 (4.3)	13 (4.8)	4 (4.4)
Time from the start of immunotherapy to the end of immunotherapy, days ^e				
No., mean (SD)	852, 185.6 (18.93)	92, 187.4 (28.98)	270, 187.0 (17.87)	90, 186.2 (25.80)

(continued on following page)

TABLE 1. Demographic and Disease Characteristics for the NO-DFMO/Control (ANBL0032) and DFMO/Test (NMTRC003B) Subgroups Used for the Overall Efficacy Analysis, and the Matched Populations for Both Groups Used for the Propensity Score-Matched Analyses (matched in a 3:1 NO-DFMO:DFMO ratio) (continued)

Characteristic	ANBL0032	NMTRC003B	ANBL0032	NMTRC003B
	NO-DFMO (n = 852) ^a	DFMO (n = 92) ^b	NO-DFMO Matched (n = 270) ^c	DFMO Matched (n = 90) ^c
Time from diagnosis to the end of immunotherapy, days ^e				
No., mean (SD)	846, 489.0 (131.36)	92, 481.3 (90.33)	270, 481.3 (130.05)	90, 480.2 (89.58)
Immunotherapy cycles, No. (%)				
≤3	7 (0.8)	1 (1.1)	1 (0.4)	1 (1.1)
4	1 (0.1)	2 (2.2)	0	2 (2.2)
5	4 (0.5)	0	0	0
6	840 (98.6)	89 (96.7)	269 (99.6)	87 (96.7)
Median OS follow-up, years				
Median (IQR)	5.0 (3.5-7.0)	6.1 (5.2-7.2)	5.0 (3.7-6.8)	6.1 (5.2-7.2)

Abbreviations: ASCT, autologous stem-cell transplant; CR, complete response; DFMO, eflornithine; INSS, International Neuroblastoma Staging System; ITT, intent-to-treat; NO-DFMO, no eflornithine (control); OS, overall survival; PR, partial response; PS, propensity score; PSM, propensity score-matching; SD, standard deviation; VGPR, very good partial response.

^aThe NO-DFMO (n = 852) analysis population comprised patients selected from ANBL0032 (N = 1,328) with disease status/characteristics consistent with eligibility requirements for enrollment to NMTRC003B. A subset of the NO-DFMO patients with complete data for the 11 covariates applied in propensity scoring, the NO-DFMO-complete case population (not shown) represented the eligible control patients for matching in the PS-based analyses.

^bThe DFMO (n = 92) analysis population comprised DFMO-treated patients selected from NMTRC003B (N = 141, including one compassionate use patient excluded from the efficacy analysis per protocol for an ITT population of n = 140) with treatment history consistent with eligibility criteria and treatment administered in ANBL0032.

^cNO-DFMO matched is a propensity score-matched selected population requiring complete covariate data and propensity scores within a common range. Two patients were dropped in the DFMO group (n = 90), and the remaining patients were matched with the three nearest neighbor matches from the NO-DFMO group (n = 270).

^dEarliest enrollment in the NO-DFMO matched group was November 2004.

^eVariables used for PSM.

immunotherapy, overall response at immunotherapy end, time from diagnosis to immunotherapy end, and MYCN (categories of amplified or nonamplified). Histology was also considered as a covariate because of its role in risk stratification; however, a large proportion of NO-DFMO patients had missing data. PSM requires complete covariates so only DFMO and NO-DFMO patients with no missing or unknown covariates were included in the population eligible for propensity score-matched analyses (treated/DFMO, n = 91 and control/NO-DFMO, n = 516). The PS is the probability that a patient would have been allocated to the DFMO group as a function of baseline characteristics using a multivariate regression model. Patients were assigned a PS based on the first 10 covariates and then matched 3:1 (NO-DFMO:DFMO) to those with the closest PS and exact matching on the MYCN category. After assigning PSs to all eligible patients, only those in the overlapping PS range for treated and control patients were matched (one DFMO patient fell outside the range, resulting in 90 DFMO patients matched to 270 NO-DFMO patients).

Matched cohorts were compared for EFS and OS using an unadjusted Cox proportional hazards model controlling only for treatment (DFMO v NO-DFMO). Sensitivity analyses described for the full NO-DFMO and DFMO populations were

repeated with PSM applied after removal of treated or control patients (ie, on the basis of modified NO-DFMO selection rules, the contemporary time period, etc). An additional propensity score-matched sensitivity analysis was performed to address missing covariate data, primarily in the control group (40% of the overall NO-DFMO population were missing at least one covariate), by multiple imputation by chained equation (MICE) analysis using a Cox regression model employing the Rubin method³⁰ from 100 multiply imputed, matched data sets.

The Data Supplement (online only) presents more information on the rationale for covariate selection, PSM (Data Supplement, Figs S1-S3), and the MICE analysis (Data Supplement, Fig S4).

RESULTS

Patient and Disease Characteristics

Table 1 presents overall demographic and disease characteristics for the DFMO and NO-DFMO groups, and data establish that selected populations were comparable and consistent with expected demography³¹ for patients with HRNB receiving standard up-front treatment.

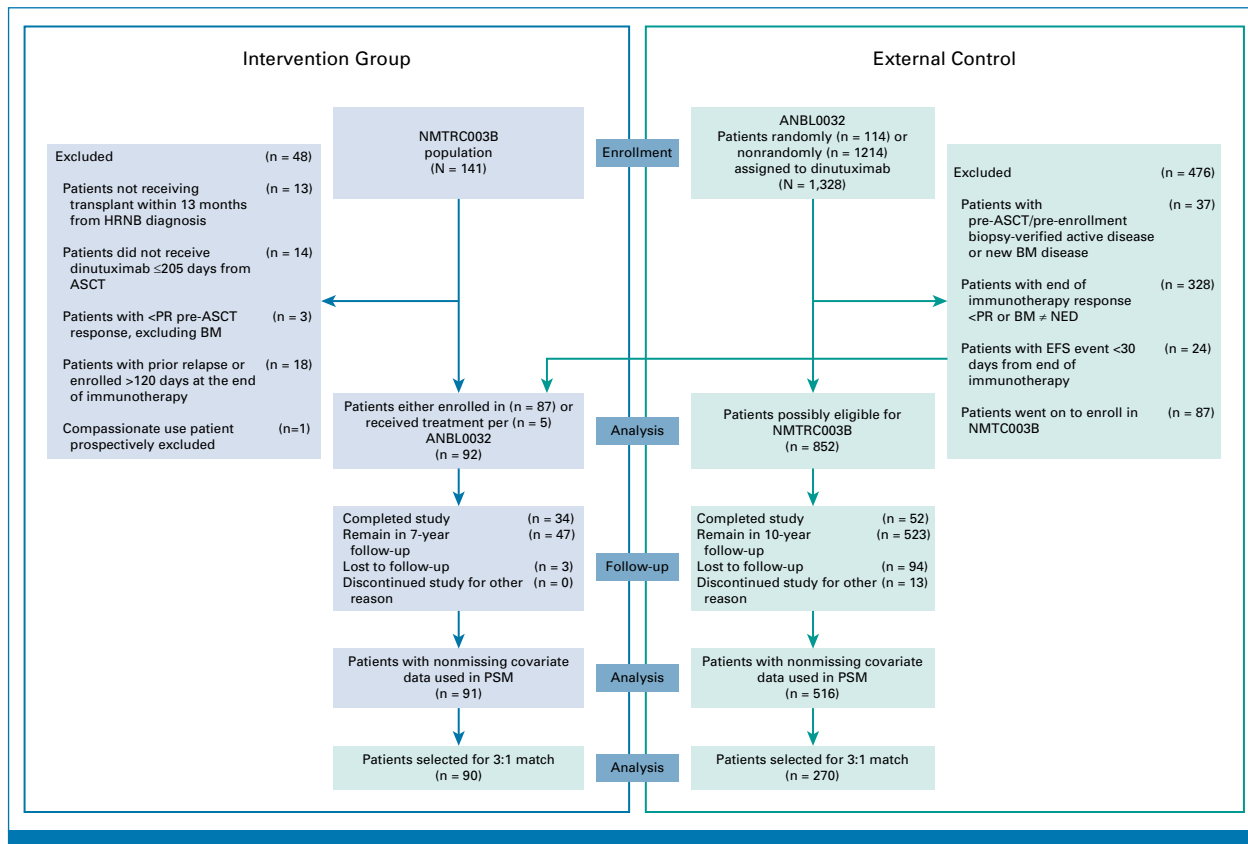


FIG 3. CONSORT diagram. Comparative cohort selection from NMTRC003B and the independent study ANBL0032. Matching ratio defined as 3 NO-DFMO/control : 1 DFMO/test. ASCT, autologous stem-cell transplant; BM, bone marrow; DFMO, eflornithine; dinutuximab, anti-GD2 antibody therapy; EFS, event-free survival; HR, hazard ratio; HRNB, high-risk neuroblastoma; NED, no evidence of disease; NO-DFMO, no eflornithine (control); OS, overall survival; PR, partial response; PSM, propensity score matching.

Although the full populations of DFMO and NO-DFMO populations had similar distributions of key demographic and disease characteristics, PSM further improved balance, simulating the effects of random assignment (Table 1).

Survival Comparisons of Overall Populations

EFS for patients with HRNB from the end of immunotherapy showed statistically significant improvement in relapse events in DFMO patients ($n = 92$) versus NO-DFMO patients ($n = 852$; hazard ratio [HR], 0.50 [95% CI, 0.29 to 0.84]; $P = .008$; Fig 4A). Four-year EFS was 84% versus 72% in the DFMO and NO-DFMO groups, respectively.

Patients receiving DFMO demonstrated a corresponding improvement in OS (HR, 0.38 [95% CI, 0.19 to 0.76]; $P = .007$) compared with NO-DFMO patients (Fig 4B). Four-year OS rates were 96% and 84% for the DFMO and NO-DFMO groups, respectively.

EFS results were consistent in sensitivity analyses that excluded NO-DFMO patients with VGPR or PR at the end of immunotherapy (HR, 0.50 [95% CI, 0.30 to 0.85]; $P = .01$; Fig 4C) and those with EFS dates ≤ 123 day from

immunotherapy end (HR, 0.57 [95% CI, 0.34 to 0.96]; $P = .03$, respectively; Data Supplement, Fig S5). OS results were also consistent across the comparisons (Fig 4D; Data Supplement, Fig S5). Additional sensitivity analyses comparing patients treated in the same period (2011–2015; Fig 4E and 4F) and those with confirmed participation in ANBL0032 ($n = 87$; Data Supplement, Fig S5) showed similar EFS and OS results.

PSM

In 3:1 matched cohorts, EFS results favoring the DFMO group were consistent with those observed in the overall population analysis (HR, 0.48 [95% CI, 0.27 to 0.85]; $P = .01$; Fig 5A). Four-year EFS was 84% versus 73% in the DFMO and NO-DFMO groups, respectively. OS comparisons also favored DFMO in the matched analysis (HR, 0.32 [95% CI, 0.15 to 0.70]; $P = .005$; Fig 5B), with 4-year OS rates of 96% and 84% for the DFMO and NO-DFMO groups, respectively. Sensitivity analyses applying more conservative control group era and selection rules showed similar HRs for both EFS (Fig 5C and 5E; Data Supplement, Fig S6) and OS (Fig 5D and 5F; Data Supplement, Fig S6) and remained statistically significant.

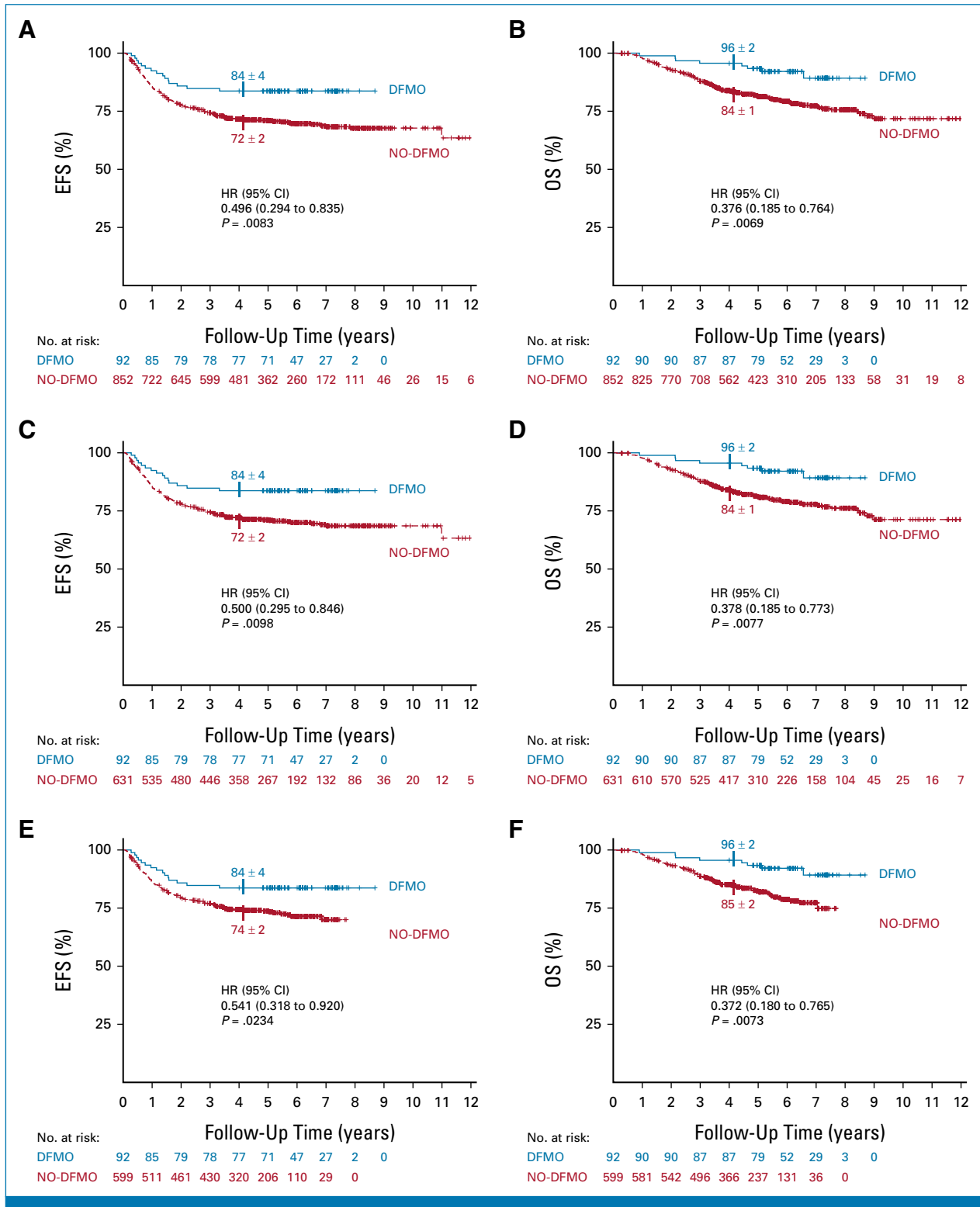


FIG 4. Survival outcomes in the overall (unmatched) study populations. KM curves with 4-year KM estimates (\pm SE) in the overall study populations (unmatched) for (A) EFS and (B) OS and corresponding sensitivity analyses to (C and D) limit NO-DFMO patients to those with CR end of immunotherapy response and the (E and F) contemporary treatment era (removing patients receiving immunotherapy before 2011). CR, complete response; DFMO, eflornithine; EFS, event-free survival; HR, hazard ratio; KM, Kaplan-Meier; NO-DFMO, no eflornithine (control); OS, overall survival.

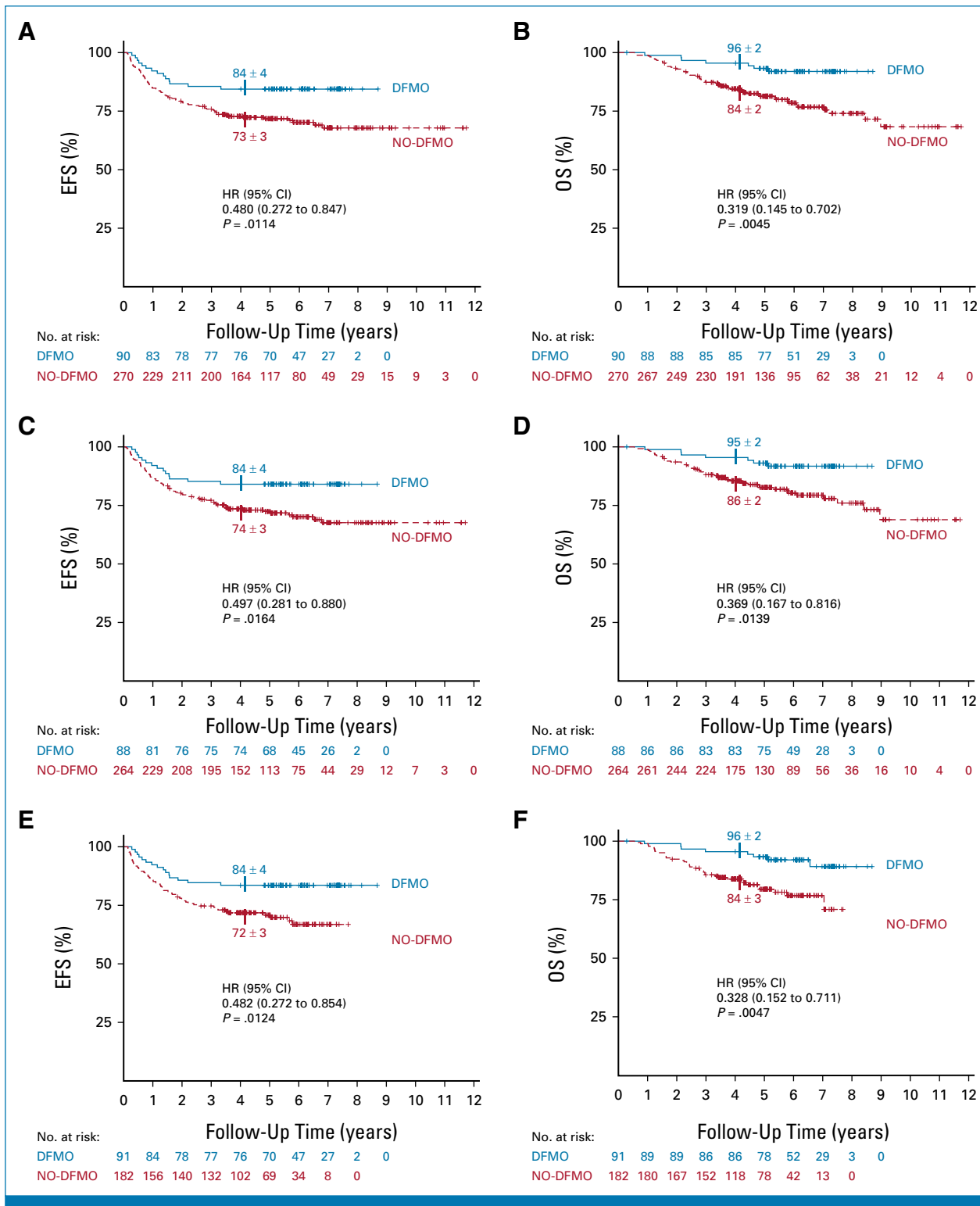


FIG 5. Survival outcomes in the matched study populations. KM curves with 4-year KM estimates (\pm SE) in the matched study populations for (A) EFS and (B) OS and corresponding sensitivity analyses to limit NO-DFMO patients to those with end of immunotherapy response (C and D) and the (E and F) contemporary treatment era (removing patients receiving immunotherapy before 2011). The contemporary sensitivity analysis is shown with a 2:1 matching ratio; contemporary patients with complete covariate data for PSM reduced the control population to $n = 370$. The 3:1 ratio forced selection of 270 patients with resulting covariate imbalances, requiring a reduction in the ratio to achieve proper balance. DFMO, eflornithine; EFS, event-free survival; HR, hazard ratio; KM, Kaplan-Meier; NO-DFMO, no eflornithine (control); OS, overall survival; PR, partial response; PSM, propensity score–matching; VGPR, very good partial response.

Missing data analyses using MICE produced a result very similar to the overall population analysis (pooled HR, 0.49 [0.27 to 0.88]; $P = .02$).

DISCUSSION

Approximately 25%–30% of patients with HRNB relapse after completion of up-front multiagent, multimodal therapy, including anti-GD2 antibody, which highlights the need for additional treatment options to improve outcomes. Here, we investigated the efficacy of post-immunotherapy DFMO treatment for patients with HRNB in remission. We report statistically and clinically significant improvements in EFS and OS rates compared with NO-DFMO/control patients selected from an external control database who received similar up-front therapy, but without DFMO maintenance.

The results demonstrate increased EFS (HR, 0.50; $P = .008$) and OS (HR, 0.38; $P = .007$) in the analysis population of treated/DFMO patients compared with external control/NO-DFMO patients. Moreover, multiple sensitivity analyses that address potential biases (eg, lead-in time, contemporary treatment period, etc) consistently favored DFMO.

Incorporation of additional propensity score–matched analyses allowed us to reduce sources of potential bias by improving covariate balance in DFMO and NO-DFMO patients before analysis of survival outcomes. RCTs most robustly increase the likelihood that comparative groups have similar characteristics so any observed differences may be attributed to the intervention. However, for rare diseases comprising small patient populations such as neuroblastoma, RCTs may not always be feasible or are associated with prohibitively long enrollment timelines to efficiently evaluate new treatments. Because PSM can address potential sources of bias, its use in evaluating a variety of diseases that includes pediatric cancers has risen, and it is being increasingly considered by regulatory agencies.^{25–28,32–34} Our analysis followed recommended PSM reporting guidelines²⁷ and achieved balance across all 11 baseline characteristics incorporated in the model.

PSM works best in a large data set, and our external control population^{3,4} without missing covariates was sufficiently large to allow a 3:1 match. Nonetheless, PSM can only be used to balance variables where information is available for both groups being compared.^{35,36} Although we included many of the known prognostic variables in neuroblastoma, potential bias from imbalance of unknown variables remains. Specifically, available data from ANBL0032 lacked granularity on certain aspects of up-front treatment, including the consolidating regimen used for single or tandem transplant. Additionally, neither data set included information on socioeconomic status or other factors³⁷ that could influence patient willingness/ability to pursue DFMO clinical trial participation, and limited information was available to evaluate potential supportive care and capability differences

on the basis of enrolling sites for the two studies. Finally, PSM reliance on covariate data limits the analyses to patients with complete information and reasons for missing data could indicate other underlying differences in patient groups. When feasible, we further explored potential differences with a variety of supportive PSM sensitivity analyses, including analyses that addressed missing data. Nonetheless, even the PSM analyses cannot fully account for all potential population differences that may exist.

Potential treatment differences after up-front therapy must also be considered when interpreting outcomes. Although we can verify that the DFMO group did not receive any other postimmunotherapy treatment because concomitant anti-cancer treatment was prohibited, such treatment information cannot be characterized for the NO-DFMO group. NO-DFMO patients may have received alternate post-immunotherapy treatment, for example, the investigational GD2/GD3 bivalent vaccine (ClinicalTrials.gov identifier: [NCT00911560](https://clinicaltrials.gov/ct2/show/study/NCT00911560)), although the potential benefits of such continued treatment would presumably favor the control group. Finally, potential differences in postrelapse therapy may exist between the groups, limiting the interpretation of OS comparisons.

The compared groups primarily comprised patients receiving single ASCT, so the incremental benefit of tandem ASCT with up-front treatment, including postconsolidation immunotherapy with and without DFMO maintenance, is not well characterized in the reported analyses. Furthermore, because the comparisons focus on patients receiving standard COG up-front therapy, these analyses do not directly evaluate whether DFMO treatment benefit applies to other groups, such as patients receiving non-COG up-front treatment, having refractory disease, achieving <PR pre-ASCT response (when considering bone marrow, because of low representation in both groups), or with a history of relapse. Further work is warranted to characterize the potential benefits of DFMO maintenance in additional HRNB populations, particularly those with the highest relapse risk.

Novel approaches to reduce relapse risk in pediatric patients with HRNB after up-front therapy would address an important unmet need. The presented externally controlled analyses of DFMO-treated patients in NMTRC003B demonstrate that DFMO maintenance is associated with improved survival outcomes in patients with HRNB in remission after post-consolidation immunotherapy. The magnitude of the effect size, with HRs consistently around 0.5 and a 4-year EFS point estimate improvement of 10%–12%, aligns with previously reported results using published historical rates²³ and a separate, control database of patients with HRNB treated at BCC sites who did not receive DFMO.²⁴ Although the limitations of a single-arm study persist, consistency in efficacy results across a range of external control analyses increases confidence in the magnitude and attributability of relapse rate improvement observed in DFMO-treated

patients. In addition, while correlated OS improvements must be interpreted with caution, reducing the rate of relapse inherently reduces the risk of death given that relapsed HRNB is associated with high mortality. Importantly, to our knowledge, the reported analyses provide the most rigorous analysis of DFMO maintenance treatment reported to date and permit characterization of potential benefit that can be weighed against potential risks.

Extensive short- and long-term toxicity and risk of serious complications associated with contemporary upfront treatment contribute to poor long-term prognosis in HRNB.^{38,39} DFMO has a favorable safety profile with <35% of patients experiencing grade 2 or higher

DFMO-related toxicities and no long-term toxicities reported to date.²³ Because oral DFMO is generally well tolerated by patients with HRNB and can be administered in the home setting, it permits chronic administration over a 2-year duration without further detriment to quality of life. Further characterization of the safety profile of DFMO is ongoing.

In the context of the well-characterized and favorable DFMO toxicity profile, the efficacy results reported here, even with consideration for possible residual biases, indicate potential benefits that outweigh the potential risks of DFMO (750 ± 250 mg/m² twice a day) as a postimmunotherapy maintenance therapy in HRNB.

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DISCLAIMER

All content is original and the sole responsibility of the authors.

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CLINICAL TRIAL INFORMATION

[NCT02395666](https://clinicaltrials.gov/ct2/show/study/NCT02395666) (aka NMTRC003B) and [NCT00026312](https://clinicaltrials.gov/ct2/show/study/NCT00026312) (ANBL0032).

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Eflornithine as Postimmunotherapy Maintenance in High-Risk Neuroblastoma: Externally Controlled, Propensity Score–Matched Survival Outcome Comparisons

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