NANT 2017-01: A Phase I Study of ^{131}I-MIBG with Dinutuximab +/- Vorinostat for Relapsed/Refractory Neuroblastoma

Blair Foundation Progress Report 2021-2022

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Background: ^{131}I-metaiodobenzylguanidine (MIBG) is one of the most effective therapies for relapsed or refractory (R/R) neuroblastoma patients. Preclinical studies showed cooperative effects when external beam radiation was combined with anti-GD2 antibody in immunocompetent mouse models of neuroblastoma, supporting radiation induced immune activation. We therefore hypothesized that MIBG would synergize with the anti-GD2 monoclonal antibody dinutuximab clinically. This is a two-part, single arm, Phase I, dose-escalation trial of ^{131}I-MIBG given in combination with dinutuximab +/- vorinostat for patients with relapsed or refractory neuroblastoma. Part A will administer escalating doses of ^{131}I-MIBG in combination with dinutuximab. Part B will add vorinostat, an agent that preclinically upregulates GD2 on neuroblastomas and clinically synergizes with MIBG therapy, to ^{131}I-MIBG plus dinutuximab at the MIBG MTD/RP2D identified in Part A.

Methods: For Part A. Patients 1-29 years of age with R/R high-risk neuroblastoma were eligible. Patients were required to have MIBG uptake in ≥ 1 site and adequate autologous peripheral blood stem cells (PBSCs) available for reinfusion. Prior anti-GD2 antibody therapy was allowed provided it was not administered with MIBG and not permanently discontinued due to toxicity. One prior MIBG therapy was allowed. Patients with active CNS disease were excluded. MIBG was administered on day 1 at one of three dose levels (DLs): 12, 15 , and 18 mCi/kg (DL1-DL3, respectively) with an expansion cohort at the Maximal tolerated dose/recommended phase 2 dose (MTD/RP2D). Doses were escalated using a rolling six design. The primary endpoint is dose-limiting toxicity (DLT) during course 1. Dinutuximab (17.5 mg/m^2/dose) is administered intravenously on days 8-11 and 29-32 and GM-CSF (250 mcg/m^2/dose) subcutaneously on days 8-17 and 29-38. PBSCs are infused to all patients on day 15 (+/- 2 days). A maximum of 2 courses per patient is allowed. Part B evaluates MIBG at Dose Level 3 from Part A (the RP2D), called Dose Level 4, in combination with dinutuximab and MIBG. See **APPENDIX I** at the end of progress report for further trial details.

The AIMS of this award have not changed:

Aim 1: Determine the safety and toxicity and antitumor efficacy of giving ^{131}I-MIBG in combination with dinutuximab +/- vorinostat for patients with relapsed or refractory neuroblastoma.

Aim 2: Determine the effect of ^{131}I-MIBG on the number and function of key immune effector cells and identify biomarkers or response.

AIM 1. RESULTS TO DATE:

Part A. Thirty-One patients were enrolled to Part A dose levels (DL) 1-3; 19 were evaluable for dose escalation (4 on DL1, 4 on DL2, and 11 on DL3 including 5 in DL3 expansion). The median age was 7.4 years (range: 3.1 – 22.0) and 20 (65%) were male. Twenty-seven (87%) patients had previously received a median of 8.5 (range: 2 – 21) cycles of chemoimmunotherapy, including 8 who had progressed while receiving anti-GD2 antibody. Only 5 (16%) patients had previously received MIBG. No patient at any dose level experienced a DLT (**Table 1**). Common grade 3/4 treatment-related toxicities were the expected hematologic toxicities attributable to MIBG and non-hematologic toxicities attributable to dinutuximab or GM-CSF. Among 26 response-evaluable patients, the institutional response rate (partial response or complete response) was 31% across all dose levels: 33% in DL1, 60% in DL2, and 20% in patients treated at DL3 (**Table 2**). *Conclusion*: The RP2D of MIBG in combination with standard doses of dinutuximab and GM-CSF is 18 mCi/kg. This regimen is well-tolerated without additive toxicity, and preliminary efficacy data shows encouraging antitumor activity. A phase 2 trial of this regimen is planned through the NANT.

Table 1. Dose limiting toxicity Summary

Dose Level	#Patients Enrolled	#Patients Eligible	#Evaluable for DLT	Course 1 DLTs	Course 2 DLTs (N=8)
1	6	6	4	0	0
2	5	5	4	0	0
3*	20	20	11	0	0
Total	**31**	**31**	**19**	**0**	**0**

*Includes patients treated in dose level 3 expansion cohort

Table 2. Best Overall response in 26 response evaluable patients

Dose Level	CR	PR	MR	SD	SD-NTL	PD	Not Evaluable	Response Rate* N (%)
1 (N=6)	0	2	0	2	0	2	0	**2/6 (33%)**
2 (N=5)	1	2	1	1	0	0	0	**3/5 (60%)**
3 (N=20)	1	2	2	6	1	3	5	**3/15 (20%)**
Total	**2**	**6**	**3**	**9**	**1**	**5**	**5**	**8/26 (31%)**

Abbreviations: CR=complete response; PR=partial response; MR=minor response; SD=stable disease; SD-NTL=stable disease-no target lesions; PD=progressive disease
***Response rate= CR + PR**

Part B of the phase 1 study, which adds the HDAC inhibitor, vorinostat, to the MIBG/dinutuximab combination, is ongoing. We have enrolled ten patients, and response and safety evaluations are underway.

AIM 2. RESULTS TO DATE:

We have successfully collected and stored serum as well as performed immunophenotyping on the peripheral blood of patients on study. Analysis of the data is ongoing and will be incorporated into the manuscript, detailing host immune system findings that may correlate with patient therapy response. Antigens that were evaluated to characterize harvested leukocytes are defined in **Figure 1A**. **Figure 1B** depicts the gating strategy used to characterize white blood cell populations harvested from patient blood. White blood cell populations include but are not limited to: neutrophils, eosinophils, monocytes, T lymphocytes, B lymphocytes, and Natural Killer (NK) lymphocytes. In the patient data analyzed to date for Part A of the trial, we observe potential differences in the immune content of patients who responded to therapy versus those that did not. For example, there may be more NK lymphocytes, specifically those with cytotoxic potential, circulating at baseline in responders compared to non-responders prior to treatment initiation (**Figure 1C**).

Meetings/Manuscripts. The data for **Part A** of NANT 2017-01trial was presented as a poster presentation at the American Society of Clinical Oncology (ASCO) National Meeting in Chicago, IL on June 2022. A manuscript of Part A results is in preparation.

Ongoing Efforts Under This Funding Mechanism: Part A plasma samples will be analyzed for circulating immune cytokines by ELISA to add to the cellular immunophenotyping data (**Figure 1**) to fully characterize the immune landscape to identify host biomarkers of responders to this therapy. **Part B** of the clinical trial is currently accruing patients and will be written up as a separate manuscript detailing patient tumor responses and host immune system changes with the addition of Vorinostat. The Blair Foundation will be acknowledged in all publications and presentations associated with this trial.

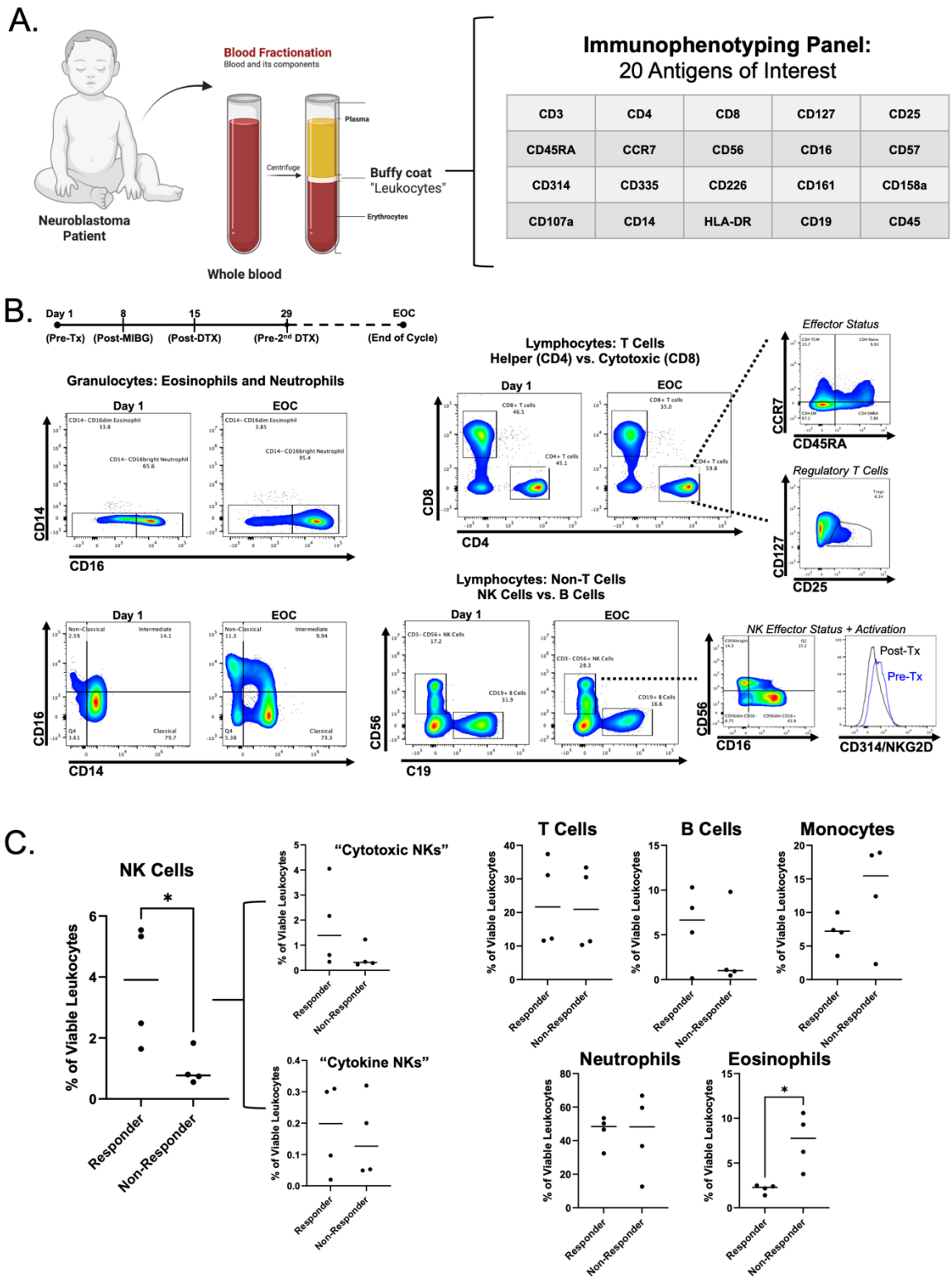

Figure 1: Immunophenotyping correlative studies. A.) Methodology for collecting and isolating plasma and leukocytes from patient whole blood and table defining the 20 antigens used to characterize immune cell subsets. B.) Sample gating strategy incorporating antigens from above, which is used to analyze patient samples following flow cytometry analysis. C.) Representative data comparing immune cell subsets in patients who responded to treatment (responders) vs. those with non-responsive/progressive disease non-responders prior to therapy initiation.

APPENDIX I. Clinical Trial Protocol Details for Reference

DOSE LEVELS

Part A:

	Dose Level	^{131}I-MIBG (mCi/kg/dose)	Dinutuximab (mg/m^2/dose)
	0	12	14
Starting Dose Level:	1	12	17.5
	2	15	17.5
	3	**18**	**17.5**

Part B:

	Dose Level	Vorinostat (mg/m^2/dose)#	^{131}I-MIBG (mCi/kg/dose)	Dinutuximab (mg/m^2/dose)
Starting Dose Level	**4**	180	18	17.5
	4a*	150	18	17.5

Experimental Design Schema

Part A:

DAY	1	2-7	8	9	10	11	12	13	14	15	16	17	18-28
^{131}I-MIBG (M) dose level assignment	M												
GM-CSF (G) 250 mcg/m^2			G	G	G	G	G	G	G	G	G	G	
DINUTUXIMAB (D) dose level assignment			D	D	D	D							
Stem Cell Infusion (HSC)										HSC +/- 2d			

DAY	29	30	31	32	33	34	35	36	37	38	43-57
GM-CSF (G) 250 mcg/m^2	G	G	G	G	G	G	G	G	G	G	
DINUTUXIMAB (D) dose level assignment	D	D	D	D							
Disease Evaluation (Eval)											Eval

Part B

DAY	0	1	2-7	8	9	10	11	12	13	14	15	16	17	18-28
Vorinostat (V) dose level assignment	V	V	V	V	V	V	V	V	V[5]					
^{131}I-MIBG (M) dose level assignment		M[1]												
GM-CSF (G) 250 mcg/m^2				G[2]	G	G	G	G	G	G	G	G	G[2]	
DINUTUXIMAB (D) 17.5 mg/m^2				D[3]	D	D	D							
Stem Cell Infusion (HSC)											HSC[5] +2d/-1d			

DAY	29	30	31	32	33	34	35	36	37	38	43-57
GM-CSF (G) 250 mcg/m^2	G[2]	G	G	G	G	G	G	G	G	G[2]	
DINUTUXIMAB (D) dose level assignment	D[3]	D	D	D							
Disease Evaluation (Eval)											Eval[4]