INTERNATIONAL NEUROBLASTOMA RISK GROUP
TASK FORCE
PROJECT PROPOSAL

Thank you for your interest in INRG data.
Please send your completed proposal and any questions to scohn@peds.bsd.uchicago.edu

Proposal Title	Clinical and Biological Features Predictive of Survival After Relapse of Stage MS Neuroblastoma: A Report From the International Neuroblastoma Risk Group Project
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Are you including a YI?	Yes
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Statistician name	Wendy London
Statistician Affiliation	❑ COG ❑ GPOH ❑ JCCG ❑ SIOPEN ❑ Not a member of one of these Cooperative Groups ▪ Dr. London is the lead statistician for the INRG.

NOTE: Please limit your request to 5 pages

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1. Specific Aims

The central hypothesis driving this proposal is that specific clinical and biological features will differentiate overall survival rates after relapse or progression in patients initially presenting with stage MS neuroblastoma. This investigation aims to evaluate all patients in the INRG database initially diagnosed with stage MS disease, regardless of pre-treatment risk group classification, who subsequently experience disease relapse or progression to address the following three aims:

Aim 1: To describe the clinical and biological features present at initial diagnosis in patients with relapsed MS neuroblastoma.

Aim 2: To describe clinical features of and overall survival following first relapse/progression in patients with an initial diagnosis of MS neuroblastoma, including pattern of relapse/progression, time to relapse/progression, and if available, treatment for relapse and response to second-line treatment.

Aim 3: To identify factors prognostic of overall survival (OS) after relapse/progression in patients with an initial diagnosis of MS neuroblastoma.

2. Hypothesis

For patients initially diagnosed with stage MS neuroblastoma who subsequently experience disease relapse/progression, individual or combined clinical and/or biological features observed at diagnosis or at time of relapse will impart a differential risk of death after relapse.

3. Patient Cohort (Eligibility Criteria)

The overall cohort this proposal seeks to study includes all patients in the INRG database who presented with stage MS neuroblastoma and subsequently experienced disease relapse / progression. We acknowledge that the current INRG risk classification system that implemented the 'MS' stage designation was implemented in 2009. We plan to include patients with diagnosis prior to 2009 by retrospectively applying the defined criteria for the 'MS' stage to patients diagnosed before 2009 utilizing specific search criteria for age and sites of metastasis.

To capture all patients meeting inclusion criteria in our cohort using the INRG database, we first identified all patients who fit either of the following criteria for groups A, B or C:

A. 'INSS stage = 4s'
B. 'INSS stage = 4;' + 'Age at diagnosis = 12-18 months' + metastatic site exclusively involving bone marrow, liver and/or skin
C. 'INRG stage = MS'

To investigate the feasibility of this project, initial mining of the INRG cohort discovery tool was completed in October 2021, and the yield from searches A, B and C was found to be ~750, ~80 and ~120 patients, respectively, for a total of ~950 patients.

Second, we needed to isolate the patients within the cohort above who then experienced disease relapse. To gain insight into the feasibility and estimation of this population from the INRG cohort discovery tool, we next selected patients who were designated as 'yes' for an 'event.' This search yielded ~260, ~35 and ~50 for our three groups, for a total of ~345 patients.

We acknowledge that the total of 345 patients represents an overestimation, as experiencing an 'event' may not always mean experience of disease relapse/progression, rather death or a secondary malignancy. The INRG database does not allow one to distinguish which 'event' has occurred. We conservatively estimate that at least 300 patients with stage MS and initial relapse / progression will be available for this analysis.

4. Background & Significance

Neuroblastoma, the most frequent extracranial solid tumor in children, is infamous for its clinical and biological heterogeneity. While some patients are expected to have their tumors spontaneously regress, others experience fatal tumor progression despite intensive multimodal treatment. Given the heterogeneity of prognosis among patients with neuroblastoma, identification of risk factors used for differential assignment of pre-treatment risk groups is of critical importance. While ongoing work to refine risk groups at diagnosis has led to the ability to differentiate patients with great specificity, nuanced data regarding the outcomes of specific groups of patients after relapse is lacking. Insights into differential post-relapse course may aid patients and clinicians in expectations and prognosis in the relapse setting.

Neuroblastoma presenting with stage 'MS' (metastatic special) metastatic pattern further emphasizes the degree of heterogeneity within neuroblastoma and the subsequent difficulty in risk assignment. Stage MS neuroblastoma is defined by the INRG classification system as any patient presenting at <18 months of age with metastatic neuroblastoma with the metastatic sites being limited to the bone marrow, liver and/or skin. Depending upon specific tumor biologic traits (e.g., *MYCN* amplification and/or 11q aberration), patients presenting with stage 'MS' disease may have either a very-low risk of poor outcome pre-treatment or a high-risk of poor outcome. These patients are then treated differently, given their differing risk of death. However, patients from both risk groups have been documented to experience disease relapse. While prognosis and treatment course at initial diagnosis for patients with stage MS disease are defined, expectations surrounding prognosis at the time of relapse are less well defined.

5. Proposal Description

We propose investigating the post-relapse outcomes of patients initially diagnosed with stage MS disease who subsequently experience disease relapse. After identifying all patients fitting this description, we first plan to report all available clinical and biological characteristics. Second, we will report post-relapse overall survival for all patients. Last, we will analyze the cohort to assess for factors associated with significant differential post-relapse overall survival. These aims are reflected in our proposed tables and figures for our proposed manuscript.

We propose **Table 1** with descriptive statistics as shown in the Appendix to this proposal.

For **Table 2** (see Appendix), we will calculate overall survival following disease relapse/progression according to a range of potential prognostic factors. We will also construct multivariable Cox models of overall survival to understand key variables independently associated with differential risk of post-relapse survival.

For **Figure 1**, we will construct Kaplan-Meier curves comparing overall survival post-relapse for the entire cohort of patients in our study followed by >/=1 plot comparing overall survival post-relapse for specific subgroups of patients found to have differential post-relapse survival.

6. Data Requested

As discussed in Section 3, initial mining of the INRG cohort discovery tool to identify potential patients for this cohort yielded ~950 patients with stage Ms, disease, and ~345 with a subsequent event. We request that these searches be verified, and that once patients have been identified as fulfilling our baseline criteria (presenting with stage MS disease, subsequently experiencing disease relapse / progression as their first 'event'), the data needed to complete the outlined analysis be provided.

APPENDIX

Table 1. Clinical and Biological Characteristics of *** Patients with Stage MS Neuroblastoma who Subsequently Experienced Disease Relapse."

Factor	Patients	
	No.	%
Age at Diagnosis		
<12 months		
≥12 months – 18 months		
Age at first relapse / progression		
<12 months		
>12 - ≥18 months		
>18 - ≥24 months		
>24 - ≥30 months		
>30 - ≥36 months		
>36 months		
Sex		
Female		
Male		
Race		
White		
Black		
Asian		
Other		
Ethnicity		
Latino		
Non-Latino		
Primary Site		
Adrenal		
Non-adrenal abdominal		
Thoracic		
Pelvic		
Neck		
MYCN status		
Nonamplified		
Amplified		
11q		
Balanced or no aberration		
Deletion, imbalance or unbalanced		
17q		
No gain		
Gain		
1p		
No loss or aberration		
LOH, deletion, or imbalance		
Ploidy		
>1 (hyperdiploid)		
</= 1 (diploid, hypodiploid)		
Grade of differentiation		
Differentiating		
Undifferentiated		
MKI		
Low, intermediate		
High		
LDH (IU/L)		
<1400		

≥1400		
Serum ferritin (ng/mL) <90 ≥90		
Histologic Classification Favorable Unfavorable		
Site of First Relapse / Progression Primary Metastatic Primary + metastatic		
If Metastatic at Relapse, Pattern of Relapse Remains stage MS pattern Metastatic sites beyond liver, skin, marrow		
If Metastatic at Relapse / Progression, Site(s) Bone Marrow Liver Skin Bone CNS Distant Lymph Node Lung Other		
Time from Initial Diagnosis to First Relapse / Progression <6 months >6 - ≥12 months >12 - ≥18 months >18 - ≥24 months >24 - ≥30 months >30 - ≥36 months >36 months		

Table 2. Factors prognostic of overall survival following first relapse / progression in *** patients with stage MS neuroblastoma.

Factor	5yr Post-relapse OS	Post-Relapse OS	p-value
	OS +/-SE (%)	HR	95% CI
Age at Diagnosis			
<12 months			
≥12 months – 18 months			
Age at first relapse / progression			
<12 months			
>12 - ≥18 months			
>18 - ≥24 months			
>24 - ≥30 months			
>30 - ≥36 months			
>36 months			
Sex			
Female			
Male			
Race			
White			
Black			
Asian			
Other			
Ethnicity			
Latino			
Non-Latino			
Primary Site			
Adrenal			
Non-adrenal abdominal			
Thoracic			
Pelvic			
Neck			
MYCN status			
Nonamplified			
Amplified			
11q			
Balanced or no aberration			
Deletion, imbalance or unbalanced			
17q			
No gain			
Gain			
1p			
No loss or aberration			
LOH, deletion, or imbalance			
Ploidy			
>1 (hyperdiploid)			
</= 1 (diploid, hypodiploid)			
Grade of differentiation			
Differentiating			
Undifferentiated			
MKI			
Low, intermediate			
High			
LDH (IU/L)			
<1400			
≥1400			
Serum ferritin (ng/mL)			
<90			
≥90			

Histologic Classification Favorable Unfavorable			
Site of First Relapse / Progression Primary Metastatic Primary + metastatic			
If Metastatic at Relapse, Pattern of Relapse Remains stage MS pattern Metastatic sites beyond liver, skin, marrow			
If Metastatic at Relapse / Progression, Site(s) Bone Marrow Liver Skin Bone CNS Distant Lymph Node Lung Other			
Time from Initial Diagnosis to First Relapse / Progression <6 months >6 - ≥12 months >12 - ≥18 months >18 - ≥24 months >24 - ≥30 months >30 - ≥36 months >36 months			