ANBL2131: A Children's Oncology Group (COG) Phase 3 Study of Dinutuximab Added to Intensive Multimodal Therapy for Children with Newly Diagnosed High-Risk Neuroblastoma

High-risk neuroblastoma is a lethal pediatric solid tumor. Neuroblastoma's express a molecule called GD2 on every tumor cell, making GD2 a great immunotherapy target. When an antibody that targets GD2, called dinutuximab, was given at the end of standard high-risk neuroblastoma therapy it significantly improved patient survival, credentialing a role for immunotherapy in patients with neuroblastoma. Furthermore, in a Children's Oncology Group (COG) trial for patients with relapsed/refractory neuroblastoma, called ANBL1221, the combination of dinutuximab given with chemotherapy, called "chemoimmunotherapy", led to a > 50% objective response rate in patients with the most aggressive form of this disease. The success of targeting GD2 in combination with chemotherapy established a pipeline for testing chemoimmunotherapy in pilot trials of patients with newly diagnosed high-risk neuroblastoma. Initial pilot trials of dinutuximab given with Induction chemotherapy (aka, the first 4-6 courses of chemotherapy) showed that the combination was both safe and tolerable in newly diagnosed high-risk neuroblastoma patients. We now are poised to determine whether the addition of chemoimmunotherapy to upfront high-risk therapy improves overall patient survival by evaluating this regimen at scale in a larger randomized Phase 3 trial for newly diagnosed high-risk neuroblastoma patients.

The COG Phase 3 trial ANBL2131 randomly assigns newly diagnosed high-risk neuroblastoma patients to receive either standard chemotherapy and surgery or chemoimmunotherapy (chemotherapy plus dinutuximab) and surgery during Induction (the first phase of high-risk therapy; see **Figure 1**). The study also adds in a novel trial concept of offering an "Extended Induction" of chemoimmunotherapy to patients on either arm of the study should they not have a very good upfront response to 5 Induction courses (**Figure 1**). This novel approach allows all patient enrolled to have access to dinutuximab chemoimmunotherapy if they need it and is still statistically powered to answer the primary objectives (listed below). Importantly this randomized trial provides a critical opportunity to use patient specimens to identify biomarkers of response to chemoimmunotherapy in Induction as well as to identify mechanisms of therapy resistance in order to plan novel treatment approaches. **We hypothesize** that chemoimmunotherapy in Induction will improve patient event free survival (EFS) compared to standard induction chemotherapy alone, and that Extended Induction will improve EFS for those with subpar end induction responses. We further believe that differences in immune landscapes in the blood and tumor of patients can be used to identify biomarkers of response and resistance to chemoimmunotherapy. We therefore propose the following aims:

Primary Aims

- To determine if the event-free survival (EFS) of patients with newly diagnosed high-risk neuroblastoma assigned to early chemoimmunotherapy during Induction differs from that of patients who are not assigned to treatment that includes early chemoimmunotherapy

Secondary Aims

- To determine if early chemoimmunotherapy during Induction therapy improves end of Induction (EOI) response rates and overall survival (OS) for patients with newly diagnosed high-risk neuroblastoma
- To determine if Extended Induction regimen with chemoimmunotherapy in patients with progressive disease or a poor response to Induction therapy improves EFS and OS
- To compare the toxicities experienced by patients treated with chemoimmunotherapy during Induction versus those experienced by patients treated with standard Induction and to describe toxicities experienced during Extended Induction
- To determine GD2 expression on tumor tissue (Goldsmith Lab) and tumor cells in bone marrow and assess for associations with response and outcome

Exploratory Aims

- To describe the association between tumor and host Immune factors (Goldsmith Lab) and outcomes in patients receiving protocol therapy

More study information and Sample Size: ANBL2131 was activated and open to enrollment as of April 2024. Up to 478 eligible and evaluable patients are anticipated to enroll over approximately 3.2 years from trial activation. This randomized study will evaluate the efficacy of a frontline chemoimmunotherapy Induction regimen (Arm B) versus a standard chemotherapy-only Induction regimen that reserves chemoimmunotherapy only for poor responders (Arm A). Poor responders evaluated at the end of Induction (EOI), who initially receive chemotherapy only, will receive an Extended Induction regimen with chemoimmunotherapy. Poor responders who initially receive chemoimmunotherapy may also receive an Extended Induction regimen. All patients treated on both arms of the study who achieve a good end of Induction response (GEIR) and patients who achieve a subsequent GEIR following Extended Induction will receive Consolidation (tandem transplant and focal external beam radiation) and Post-Consolidation therapy (dinutuximab/GMCSF immunotherapy and Accutane, **Figure 1**). Key secondary endpoints include assessment of toxicity, end of Induction response, outcomes following Extended Induction, and overall survival. Embedded correlative studies seek to evaluate biomarkers of response and resistance to chemoimmunotherapy, changes in tumor and host factors related to therapy.

Significance. Dinutuximab chemoimmunotherapy is associated with significant toxicities. While initial trial results of relapsed patients on ANBL1221 generated great enthusiasm for this combination, there remains a group of neuroblastoma patients who do not benefit yet are still exposed to all the dinutuximab associated toxicities. Correlative studies within this clinical trial are critical to identifying biomarkers of activity that may be used in the future to select patients who are most likely to benefit from chemoimmunotherapy in Induction. Results from correlative assays tested within this trial will be transitioned to integral biomarkers (meaning to help determine eligibility for chemoimmunotherapy) in future Phase 3 trials.

Statement of Cancer Relevance. The studies proposed herein are relevant to both the pediatric and adult cancer patient populations whose tumors express the disialoganglioside GD2. Along with neuroblastoma, that includes tumors such as osteosarcoma, Ewing sarcoma, small cell lung cancer, and melanoma, where GD2 directed therapies are also being explored. Characterizing changes in GD2 expression in the blood and bone marrow of NB patients will provide insight into efficacy and timing of delivery of molecules other than dinutuximab, including GD2 targeted immunotherapies such as GD2-CAR T cells. The extensive immunologic evaluations to be performed in patients on this trial will also further our understanding of why some patients respond to immunotherapy while others do not, based upon inherent host immune environments and GD2 tumor expression that will be fully characterized by these investigations.

Innovation. This is the first trial to evaluate immune biomarkers in the largest cohort of patients with newly diagnosed HR NB to date who are receiving dinutuximab chemoimmunotherapy. Assays employed to detect GD2 in tissue and immune cell landscapes in tumors and blood are unique and were optimized in the laboratories of Dr. Kelly Goldsmith and Dr. Pat Reynolds. Biomarker data from early dinutuximab trials performed in Dr. Goldsmith's and others' labs are promising and show that certain NK cells subsets as well as circulating immune inhibitory proteins may correlate with patient survival in response to dinutuximab therapy. Therefore, these investigations deserve to be validated as well as further investigated within the context of dinutuxumab/chemotherapy regimens.

Figure 1. Treatment Schema for ANBL2131.