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Developing More Effective, Less Toxic Treatments for High-Risk Neuroblastoma

Prepared for the Juliana Greenfield Family Foundation

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Pediatric hematologist-oncologist **Brian H. Kushner, MD,** an Attending Member of MSK Kids, has dedicated his career to developing novel ways to treat high-risk neuroblastoma more effectively and with fewer late effects. The goal is to prepare for a future where the number of cycles of chemotherapy will be reduced, and long-term toxicity is minimal. Less chemotherapy without compromising survival is realistic because of all the recent advances using an anti-GD2 monoclonal antibody, which combined with an immune-stimulant, GM-CSF, is highly effective against chemo-resistant neuroblastoma persisting in patients' bones and bone marrow.

Dr. Kushner's N9 clinical trial demonstrated that the use of a new protocol with fewer chemotherapy cycles and less toxic drugs may prove to be a better strategy for treating high-risk neuroblastoma, even without the use of stem cell transplants. With the N9 enrollment complete and follow-up ongoing, his team has launched a new N10 phase 2 trial to test whether adding an anti-GD2 monoclonal antibody, such as naxitamab (or Danyelza®), to the N9 regimen can further enhance patient outcomes. Naxitamab works by getting a child's own white blood cells to kill neuroblastoma.

The Children's Oncology Group (COG), a worldwide collaborative research organization focused on conducting clinical trials of childhood and adolescent cancers, continues to conduct multiple studies on neuroblastoma to address treatment safety and efficacy, as well as factors such as health equity and survivorship and late effects. A comparison of COG's current approach to treating neuroblastoma with that of MSK Kids is included below.

Although Dr. Kushner's team is not the only one that is determined to revolutionize treatment for advanced neuroblastoma, MSK stands out due to its long tradition of omitting transplants—a practice that is now gaining greater attention in the pediatric oncology field—along with its offering outpatient immunotherapy, using lower dose hyper fractionated radiation, and incorporating an anti-neuroblastoma vaccine as standard. MSK's constant emphasis upon

preserving quality of life and its “less is more” philosophy is upheld by decreasing the number of chemotherapy cycles to minimize any long-term consequences in neuroblastoma patients, including hearing loss and effects on the heart.

Our N10 study, which has been approved by the center’s Institutional Review Board (IRB) and is actively enrolling participants, possesses the potential to transform future treatment regimens for children and families affected by high-risk neuroblastoma at MSK and globally.

Backed by strong research and generous philanthropic support, Dr. Kushner and his team are devoted to advancing ever more promising therapies for high-risk neuroblastoma, accelerating progress toward superior therapies with reduced toxicity. This steadfast commitment to delivering the most effective treatment for high-risk neuroblastoma with as few side effects as possible, while also preventing any relapse, will ultimately result in improved pediatric cancer care everywhere.

Treatment Phase	***COG***	***MSK N10***	***Rationale***
Adjuvant therapy	Same for all	Based on response to induction chemotherapy	Chemosensitivity to guide post-induction therapy to maximize chances for CR
Induction	5 cycles	4 cycles	Waning effect of chemotherapy with additional initial cycles
Cisplatin	Yes	No	Avoid ototoxicity
Topotecan dosage	Standard	High	Crosses blood-brain barrier, could reduce risk of CNS relapse
Cyclophosphamide dosage	Lower	Higher	Exploit dose-response effect of alkylating agents
Stem Cell Collection	After cycle 2	After cycle 3	Less risk of occult contamination by NB cells

Timing of Antibody	After radiotherapy	First cycle precedes radiotherapy	Treat systemic disease as soon as possible
Antibody	Dinutuximab	Naxitamab	>2.5x higher dosage, outpatient
GM-CSF	Standard dosing	Stepped-up dosing	Induces stronger immune effect
Timing of radiotherapy	Prior to antibody	After first cycle with antibody	Local control in conjunction with systemic therapy
Radiotherapy schedule	Once daily	Twice daily (hyper fractionated)	To reduce toxicity to normal tissues and completed in half the time
Auto Transplant	Yes	No	Avoid potential toxicity that can be lethal or result in delay of immunotherapy and radiotherapy