

## Executive Summary:

Developing effective treatments for pediatric CNS tumors arguably represents the major remaining unmet need in pediatric oncology. We propose a phase I study of nivolumab and then another phase I study of the combination of ipilimumab and nivolumab in children with recurrent/refractory brain tumors. Ipilimumab and nivolumab are monoclonal antibodies that function as immune checkpoint inhibitors. Both inhibit signals that impair the immune response; ipilimumab via CTLA4 blockade and nivolumab via PD1 blockade. The result is augmentation of T-cell activation and proliferation, and enhancement of tumor-specific immune responses. Early phase clinical trials of nivolumab in adults have demonstrated evidence of efficacy in melanoma and a number of other refractory solid tumors as well as a manageable safety profile. The combination of nivolumab with ipilimumab has clinical activity in adult melanoma patients that appears to be superior to that of either single agent. The proposed work will be conducted as a sequential two-part Phase I dose-escalation study with a traditional 3+3 design for each part. Memorial Sloan Kettering Cancer Center will operate as the lead site of a 4-institutional pediatric neuro-oncology study group to include the Dana-Farber Cancer Institute, the Children's Hospital Colorado Center for Cancer and Blood Disorders, and the Johns Hopkins University/Sidney Kimmel Cancer Center. We expect that this study will allow us to determine the safety and tolerability of nivolumab alone and in combination with ipilimumab in children with recurrent/refractory brain tumors and that we will obtain preliminary data regarding the efficacy of this approach. These data should be valuable for the design of a subsequent phase II study. In addition, we plan to gather needed data on the pharmacokinetics of these drugs in pediatric patients with recurrent/refractory CNS disease. This will also aid in devising the best possible phase II study upon successful completion of the proposed study.