RESEARCH PROGRESS REPORT January 2019

PROJECT NAME: Anti PD-1 Nivolumab and Ipulumab/Ph1, CNS			
Official Protocol Title	Phase Ib /II Clinical Trial of Nivolumab Monotherapy and Nivolumab in Combination With Ipilimumab in Pediatric Subjects With High Grade Primary CNS Malignancies		
Site(s)	17 North American sites 23 European sites 5 South American sites 2 Middle East sites 5 Australian sites 2 Asian/Russian sites		
Principal Investigator(s)	Ira Dunkel, MD, Memorial Sloan Kettering Cancer Center		
Type of Study	Clinical, Phase Ib /II	**Type of Cancer**	High Grade CNS Tumors
Number of Patients Enrolled	160	**NIH Trial Listing**	**NCT03130959** https://clinicaltrials.gov/ct2/show/study/NCT03130959
Date opened	June 2017	**Date closed**	
Partners	Ty Louis Campbell Foundation, A Kids Brain Tumor Cure		

Background

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.

Although antibodies cannot cross the blood-brain barrier, immune checkpoint inhibitors such as nivolumab and ipilimumab seem to be worthy of investigation for brain tumors since activated T-cells are capable of entering the central nervous system and several studies have shown evidence of activity of ipilimumab in adult melanoma patients with CNS lesions.

The researchers will conduct a phase I (safety) study of nivolumab in children with recurrent brain tumors immediately followed by another cohort for the study of the combination of ipilimumab and nivolumab. After dose and safety are determined, then the phase II study will begin to find out how effective these medications are in children with poor prognosis brain tumors.

Trial Accrual

This study has now been open for 18 months. It is open in 54 locations worldwide, allowing for rapid accrual. The trial has so far enrolled 160 patients and is expected to hit targeted tumor-type cohorts by the end of 2018 or early 2019.

Treatment Details

There are five different strata on the study for different brain tumor types:

1. DIPG, this treatment is now available for frontline use after completion of standard radiotherapy
2. High Grade Glioma (HGG), available for recurrent or progressive
3. Medulloblastoma, available for recurrent or progressive
4. Ependymoma, available for recurrent or progressive
5. AT/RT, ETMR, other CNS high-grade tumors, available for recurrent or progressive

Four of the five strata have completed the nivo/ipi combination treatment. The DIPG strata still needs to accrue a small number of patients and full study accrual is expected to complete by the end of 2018 or early 2019.

As a result of the larger industry supported study, Dr. Dunkel has not yet received data on safety and efficacy. He and the other academic investigators, having monthly calls with the study's steering committee, have asked BMS for rapid data reporting due to the brisk accrual. Unofficially, Dr. Dunkel indicated that he sees no worrisome toxicity signals.

Impact

- First study to use these checkpoint inhibitors in pediatric brain tumors
- Low toxicity approach for typically heavily pretreated children
- Incentivized collaboration between centers of excellence
- Top tier institutions for best access for children
- Study is attractive to families and is accruing quickly
- Fastest trial for novel combination study to open
- Only clinical study providing access to this combination therapy regimen for children with brain tumors