J1403 - Pilot Study of a Surgery and Chemotherapy-Only Approach in the Upfront Therapy of Children with Wnt Positive Standard Risk Medulloblastoma

NCT02212574

September 12, 2016

18. STATISTICAL CONSIDERATIONS

Overview: This is a single arm, prospective pilot study to explore the strategy of omitting radiation therapy in pediatric patients with standard risk, WNT positive standard risk medulloblastoma. This is not an intent-to-treat design; some eligible patients will be excluded from the assessment of the primary objective due to receiving radiation or starting chemotherapy too late.

Accrual and study duration: 10% of all medulloblastoma belong to the Wnt-positive subgroup. We would therefore anticipate there to be approximately 45 children diagnosed with Wnt-positive medulloblastoma in the USA each year. Ten 'evaluable' children will be required to provide adequate operating characteristics for the stopping rule below. We estimate at most 3 children will be inevaluable. Therefore a total of up to 13 children will be enrolled (fewer, if there are less than 3 inevaluable patients). At an accrual rate of 5-6 children per year, these 13 children can be enrolled within 2-3 years. Study duration will be at least 4-5 years (2-3 years for accrual, plus a minimum of 2 years follow up on the last patient enrolled).

Endpoints: The primary endpoint will be the occurrence of relapse, progression, or death due to disease within the first two years after study enrollment. Secondary endpoints are the patterns of failure in those children that do have progressive disease, progression-free survival (PFS) (calculated from the time of enrollment until the first occurrence of relapse, progressive disease or death due to disease, or until last contact if no event occurs), and overall survival (OS).

Evaluability: To be evaluable for inclusion in the stopping rule for assessment of the primary objectives, children:

a) must be eligible;

b) must commence treatment with chemotherapy by day 31 after resection;

c) must not receive radiation therapy within two years after study enrollment. However, any child who has a relapse or progression prior to receiving radiation therapy is evaluable.

Safety Monitoring and Stopping Rule

To address the primary objective of the utility of eliminating radiation therapy, the following one-stage monitoring rule will be used: Of the first 10 evaluable patients enrolled, if at any time 3 or more patients have an event (relapse, progression, or death due to disease), then the study will be stopped and we will conclude that removal of radiation therapy is unsafe in children with standard risk, Wnt-positive medulloblastoma. If there are 2 or fewer children who have an event out of 10, then we will conclude that removal of radiation therapy in children with standard risk, Wnt-positive medulloblastoma is feasible. This rule tests the null hypothesis that the proportion of patients with relapse/progression/disease-death by 2-years is ≤0.1versus the alternative that it is ≥0.45, with 90% power and alpha=0.07. The choices of the null and alternative were based on the results of Packer et al (10).

Methods to address study objectives: To address the primary objective, the stopping rule above will be applied. To address the secondary objectives, the data will be descriptively summarized. Kaplan-Meier curves of PFS and OS will be generated. Toxicities will be tabulated.

19. PUBLICATION PLAN

The study team will aim to publish the study results within 24 months of the end of data collection in a peer reviewed journal.