Statistical Analysis Plan

A. Analytic Approach

The first analysis will determine if VA is noninferior (EFS, OS) to VAC for patients with T- I PPB using progression free-survival (PFS). The primary endpoints for statistical analysis will be time from date of diagnosis to an event, defined as progression to T-II and T-III PPB, or death from any cause. The second objective of this study is to estimate EFS and OS of patients with T-II and T-III PPB treated with a prescribed regimen of single-arm chemotherapy (IVADo) for comparison to historical controls. The primary endpoints for statistical analysis will be time from date of diagnosis to an event, defined as progression, recurrence, occurrence of a second malignant neoplasm or death from any cause. Secondary endpoints will include best overall response to chemotherapy among patients with radiographically measurable tumor following initial surgery. This uniformly treated group, the first of its kind, will also serve as the comparison cohort for future therapeutic studies. For analysis of cardiac function outcomes, ejection fraction and shortening fraction will be compared to standard reference ranges and to published outcomes in other childhood cancer survivors. Similarly, for pulmonary function outcomes, FEV1/ and FEV1/FVC will be compared to reference ranges. Incidence rates of specific neoplasms will be compared to SEER data.

B. Power or Effect Size

The accrual goal for this study will be based on expected number of patients with this uncommon disorder with concomitant goal of achieving sufficient precision for estimating 5-year DFS.. At the end of the initial2 year period, progression-free analysis using product limit (Kaplan Meier) estimate with Greenwood standard errors.[34,35] will be done to determine whether 16 weeks of VA results in progression-free survival that is equivalent to historical controls. Since the risk of T-I/Ir is only for progression to T-II/III, progression free event will include only death and progression to Type II/III whichever comes first. For Aim 2, assuming a minimum of 2 years follow-up on the last patient enrolled on this study at the time of final analysis and a 5% loss to follow-up rate overall, enrollment of 60 T-II or T-III patients over 2 years will provide a standard error for the 5-year EFS estimate of approximately ±5.2%. Similar precision will be achieved for the 5-year OS estimate. Precision of EFS and OS estimates and estimates of response in T-II and T-III patients will depend on the number of patients enrolled and on the number of T-II and T-III patients with radiographically measurable tumors. Estimates of EFS percent and OS percent will be based on the product-limit (Kaplan Meier) estimate with Greenwood standard errors.