Study Protocol Title:	A Phase 1 Study of Lenalidomide in Combination with Vorinostat in Pediatric Patients with High Grade or Progressive Central Nervous System Tumors
NCT Number:	03050450
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STATISTICAL CONSIDERATIONS

1.1 Study Design/Endpoints

This is a single arm phase I dose escalation study, designed to determine the safety of lenalidomide and vorinostat when administered to children with relapsed or progressive central nervous system tumors. The starting dose and schedule are indicated in the treatment plan section. The study will follow a standard 3+3 patient cohort escalation design with escalation through five dose levels. Thus, a minimum of 6 patients and a maximum of 20 patients will be required to establish a recommended phase II dose. At Johns Hopkins All Children's Hospital, approximately 50-60 patients with brain and spinal cord tumors come for evaluation and treatments. Many of these patients relapse or have progressive disease. We anticipate the enrollment of approximately 20 patients during the study period at an enrollment rate of approximately 10 subjects per year. With this sample size, the 80% confidence interval if two, four , six, eight and ten patients show responses will be (1.8%-16.8%), (5.9%-24.9%), (10.9%-32.5%), (16.2%-39.7%) and (21.8%-46.6%) respectively.

Statistical analysis will be conducted at the completion of the study after accrual goals have been met. We will describe the baseline demographic and clinical characteristics, adverse events and response in all patients. Continuous variables will be summarized using mean, standard deviations, median, maximum and minimum values. Discrete variables will be summarized using counts and percentages with the corresponding 95% confidence intervals where appropriate. Time to event variables will be analyzed using Kaplan Meier methods. Progression free survival (PFS) and overall survival rates and the corresponding confidence intervals at fixed time points will be derived from the Kaplan Meier estimate. PFS will be defined as the time between date of first dose of the study therapy and date of progression or death, whichever occurs first. Patients will be censored on the date of last tumor assessment if they remain alive and do not have tumor progression. Surviving patients who did not receive any on-treatment tumor assessment will be censored on the date of first dose of study medication. A window of 1 week prior to the PFS rate time points will be applied to account for different tumor assessments dates, since not all patients adhere to scheduled dates. Descriptive statistics will be used to summarize time to event endpoints, if Kaplan Meier methods fail to provide estimates. All statistical analysis will be performed using SAS software version v 9.3 (SAS Institute, Inc., Cary, NC)

All toxicities will be graded on all patients that receive any amount of study drug. Only patients who receive 12 week of therapy will be used for final analysis. The dose escalation schema, definition of DLT, and endpoints are in section 5.

1.2 Sample Size/Accrual Rate

We anticipate the enrollment of approximately 20 patients during the study period at an enrollment rate of approximately 10 subjects per year.

1.3 Stratification Factors

The MTD determination and dose escalation are uniform per stratum.

1.4 Analysis of Secondary Endpoints

Responses will be reported as a secondary endpoint. Every report should contain all patients included in the study. For the response calculation, the report should contain at least a section with all eligible patients. Another section of the report may detail the response rate for evaluable patients only. However, a response rate analysis based on a subset of patients must explain which patients were excluded and for which reasons. It is preferred that 95% confidence limits are given.

1.5 Reporting and Exclusions

1.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment.

1.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub analyses may not serve as the basis for drawing conclusions

concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.