Online Material

Study procedures and endpoints

The primary endpoint of this phase I study was to determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLTs) of escalating doses of lenalidomide given in combination with fixed doses of R-CHOP in elderly patients with untreated DLBCL. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (Bethesda, MD: National Cancer Institute; 2003). Secondary endpoints included complete remission CR and overall response rate. Safety evaluations included adverse events, vital signs, laboratory safety assessments (hematology, clinical chemistry). DLT was defined as the maximum dose inducing any grade ≥3 non-hematologic toxicity or a delay >15 days of a planned cycle date observed during the first two cycles. Due to the occurrence of a grade 3 motor neurotoxicity in the third LR-CHOP21 course of the fourth enrolled patient [ID patient 0301], a protocol amendment in March 2008 stated to assess DLTs evaluation during the first three cycles.

The intermediate response to treatment was assessed after three courses of treatment by computed tomography. The final response was assessed after six courses of treatment by 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET/CT) and by contrast-enhancement computed tomography (CT scan) using standard outcome measures for clinical trials (CR, PR, stable disease [SD], and PD) according to the recommendations of an International Workshop to standardize response criteria in non-Hodgkin lymphoma.[Cheson et al, 2007]

Statistical analysis

Adverse events were used to identify the MTD, defined as the dose at which a DLT occurred in 33% of patients. The continual reassessment method [O'Quigley & Zohar, 2006] was used to allocate doses. Before trial onset, prior opinions about DLT probability at each dose level (5, 10, 15, 20 mg) were elicited from expert clinicians ((i.e. principal investigator, co-principal investigators, and statisticians), and were fixed at 0.15, 0.20, 0.25, and 0.30, respectively. The uncertainty in this

dose–DLT relationship was incorporated into a prior model. A design with grouped inclusions of three patients per dose level was chosen, with a 10 mg starting dose to be administered to the first patient cohort. Based on the observed responses (DLT or not), DLT probabilities of all dose levels were updated using Bayes theorem, and the process repeated until a fixed sample size (N=24) was reached, or a stopping criterion fulfilled [Zohar & Chevret. 2001], using the Bayesian Phase I Dose-Ranging (BPCT) software.[Zohar et al, 2003] These criteria measuring futility of trial continuation are based on the computation of predictive gains from further inclusions of patients, both on the estimated DLT probability of the MTD and on precision of DLT probability of the MTD as measured on the width of its 95% credibility interval. Trial is recommended to stop when expected gains appear too tiny (usually <5%). [Zohar et al, 2003] On final analysis of the entire seven patient cohorts, a stopping trial decision was made by the expert committee, which considered three out of four stopping criteria to have been satisfied.

As compared to standard phase I designs, the continual reassessment method is expected to require fewer patients overall, and fewer patients to attain the MTD.[O'Quigley et al, 2006] In addition, the continual reassessment method concentrates a higher percentage of patients at and near to the MTD.

At the completion of phase I study, a phase II Simon's two stage design was conducted.