Phase III, Randomized, Open-Label Study of Daily Imatinib Mesylate 400 mg Versus 800 mg in Patients With Newly Diagnosed, Previously Untreated Chronic Myeloid Leukemia in Chronic Phase Using Molecular End Points: Tyrosine Kinase Inhibitor Optimization and Selectivity Study

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Data Supplement

Sample size

Planned enrollment was 420 patients. Sample size was based on detecting a 20% difference in the rate of MMR at 12 months, from 40% to 60% with 90% power for the analysis of imatinib 400 mg versus 800 mg.

Primary inclusion criteria

Patients with newly diagnosed Ph+ CML-CP (within 6 months of diagnosis) were eligible. Chronic phase was defined by the presence of all of the following: <15% blasts in peripheral blood and bone marrow, <30% blasts plus promyelocytes in

peripheral blood and bone marrow, <20% basophils in the peripheral blood, and ≥ 100 x 10^9/L platelets. The protocol was amended in March 2008 to include patients whose platelets were less than 100 x 10^9/L if related to therapy, provided all other criteria for CML-CP were fulfilled. Other eligibility criteria included: no evidence of extramedullary leukemic involvement except hepatosplenomegaly, adequate hepatic and renal function (liver aminotransferases < 2.5 x upper limit of normal [ULN], total serum bilirubin < 1.5 x ULN, serum creatinine < 1.5 x ULN), and ECOG performance status 0-2.

Primary exclusion criteria

Primary exclusion criteria included: prior treatment with tyrosine kinase inhibitor(s) with the exception of any dose of imatinib for up to 2 weeks prior to study entry, women who were breast-feeding, pregnant, or of childbearing potential without a negative pregnancy test within 7 days before initiation of study drug, other uncontrolled serious medical conditions, major surgery within the preceding four weeks, known seropositivity for HIV (screening not required), or existence of another primary malignancy (except if neither currently clinically significant nor requiring active intervention).

Response Definitions not included in Methods section

Cytogenetic responses were defined as follows: complete (CCyR; Ph+ cells 0%), partial (PCyR; Ph+ > 0% - ≤ 35%), major (MCyR; Ph+ ≤ 35%), minor (Ph+ > 35% – ≤ 65%), and minimal (Ph+ > 65% – ≤ 95%).

Loss of complete hematologic response was defined by any of the following, confirmed ≥1 month later: white blood cells >20 x 10^9/L, platelets ≥600 x 10^9/L, splenomegaly ≥5 cm below left intercostal margin, ≥ 5% myelocytes and metamyelocytes in peripheral blood, blasts or promyelocytes in peripheral blood).

The time for PFS was censored at the last assessment date (hematology, extramedullary disease or cytogenetic evaluation) for patients without an event on treatment.

Overall survival was the time between randomization and death due to any cause. Overall survival analyses were censored at date of last examination for patients still on treatment and at date of last contact for patients who discontinued study treatment.

Assessment of Molecular Response

In order to monitor molecular response under study treatment, 20 ml of peripheral blood was collected at each sampling time point in all patients randomized to each treatment arm. The first PCR sampling was performed at screening and baseline. Subsequent samples were to be obtained from all patients monthly for the first 3 months, then every 3 months up to 5 years after the patient's start of study. The blood was analyzed for the presence of BCR-ABL transcripts by RQ-PCR in each respectively assigned regional PCR laboratory.

Samples obtained at the 12 month time point were also forwarded to the Institute of Medical and Veterinary Science, Adelaide, Australia (IMVS) for central evaluation. Results obtained from IMVS (central evaluation) formed the basis of the analysis of the primary endpoint.

RNA stabilization was performed within 24 hours of collection. The PCR laboratories in this study calculated the values of BCR-ABL/control gene. Ratios were scaled to the standardized baseline as defined in the IRIS trial. The baseline value was established in each of the PCR laboratories for this study by exchange of reference samples between laboratories. Individual PCR laboratory results were then calculated and adjusted to the scale used in the IRIS trial.