Name of Sponsor/Company: Genentech, Inc.	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use Only)*
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Title of Study: **A Phase II, Multicenter, Randomized, Controlled, Open-Label Study of the Safety, Efficacy and Pharmacokinetics of ABT-263 in Combination with Dose-Intensive Rituximab, or Dose-Intensive Rituximab Alone, in Previously Untreated Patients with B-Cell, Chronic Lymphocytic Leukemia (CLL)**

Phase of Development: **II**

Study Period: **31 March 2010 to 16 August 2012**

Objectives

Primary:

- To evaluate the efficacy of ABT-263 when given according to two different regimens in combination with dose-intensive rituximab in previously untreated patients with B-cell CLL, as measured by PFS based on investigator assessments

Secondary:

- To evaluate the efficacy of dose-intense, rituximab monotherapy in previously untreated patients with B-cell CLL, as measured by progression-free survival (PFS), overall response rate (ORR), response duration, complete response (CR) rate, and overall survival (OS)
- To evaluate the efficacy of ABT-263 when given according to two different regimens in combination with dose-intensive rituximab in previously untreated patients with B-cell CLL, as measured by ORR, response duration, CR rate, and OS
- To evaluate the efficacy of rituximab either alone or when administered with ABT-263 according to two different regimens in previously untreated patients with B-cell CLL, as measured by PFS, ORR, CR rate, and duration of response, based on assessments by a blinded, independent review facility
- To evaluate the safety and tolerability of ABT-263 when given according to two different regimens in combination with dose-intensive rituximab in previously untreated patients with B-cell CLL
- To compare the pharmacokinetics of ABT-263 and rituximab when administered alone with that when the two therapies are administered in combination
- To investigate the effects of rituximab on the pharmacokinetics of ABT-263 and the effects of ABT-263 on rituximab pharmacokinetics through use of a population and covariate analysis approach
- To evaluate the efficacy, safety, and tolerability of rituximab in combination with ABT-263 in those patients who have been crossed over to Arm B treatment (rituximab weekly for 8 weeks plus daily ABT-263 for a maximum of 12 weeks beyond the lead-in dose period) from Arm A (rituximab monotherapy weekly for 8 weeks)

Methodology

Details of the study can be found in the protocol (see [redacted]).

Redacted information – 02Sep2015

Efficacy Evaluations

Because of the limited follow-up, efficacy results are preliminary and are provided in the appendix tables.

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Safety Conclusions

- The percentage of patients who experienced any adverse events (AEs) was higher for Arms B (37; 97.4%) and C (40; 100.0%) than for Arm A (33; 86.8%).
- Treatment-emergent AEs (all grades) with an absolute increase in frequency ≥10% in either Arm B or Arm C above the frequency in Arm A included the following: thrombocytopenia, neutropenia, diarrhea, nausea and vomiting, pyrexia, infusion-related reactions, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin, decreased platelet count, and decreased neutrophil count. In general, the highest frequency of events occurred in treatment Arm C.
- The percentage of patients who experience Grade 3–5 AEs was greater in Arms B (25; 65.8%) and C (36; 90.0%) than in Arm A (12; 31.6%). The percentages of patients who experienced Grades 4 and 5 AEs were similar between Arms B and C. Two patients experienced Grade 5 AEs, 1 each (2.6%) in Arms A and B, neither of which was related to treatment with ABT-263. More patients experienced Grade 3 AEs in Arm C (34; 85.0%) than in Arm B (23; 60.5%), both of which were greater than in Arm A (11; 28.9%).
- AEs of Grade 3–4 that were more common (>5% greater) in Arms B and C compared with Arm A included thrombocytopenia, neutropenia, leukopenia, anemia, gastrointestinal symptoms (diarrhea, abdominal pain), chills, fatigue, ALT/AST/bilirubin elevations, and infusion-related reactions (to rituximab).
- The percentages of patients who experienced serious AEs (SAEs) were similar among the treatment arms (Arm A, 5 [13.2%]; Arm B, 5 [13.2%]; Arm C, 4 [10.0%]). No unusual SAEs were reported.
- A total of 12 patients discontinued ABT-263 because of an AE, 4 (10.5%) in Arm B and 8 (20.0%) in Arm C. AEs that led to ABT-263 discontinuation included ALT/AST elevations (6 patients), ALT elevation and pain (1), hyperbilirubinemia (1), neutropenia (1), thrombocytopenia (1), serum sickness (1), and infusion-related reaction to rituximab (1).

  Of the 12 patients who discontinued ABT-263 because of an AE, 10 patients (12.8% of 78 patients, overall) discontinued ABT-263 because of laboratory abnormalities (6 because of ALT elevations [1 also with pain, 1 also with AST elevation, and 1 also with neutropenia and decreased WBC count], 1 because of increased liver enzymes activity, 1 because of thrombocytopenia, 1 because of increased bilirubin, and 1 because of neutropenia). Increased ALT was a cause for discontinuation of ABT-263 treatment in 6 of 78 patients (7.7%) in Arms B and C, including 1 of 38 (2.6%) patients in Arm B and 5 of 40 patients (12.5%) in Arm C. One additional patient (Arm C) discontinued ABT-263 treatment because of increased liver enzyme activity.
- Platelet counts decreased rapidly with initiation of treatment with ABT-263, with substantial decreases from baseline observed as early as lead-in Day 3. However, after the initial decreases noted at Week 1 Day 1, mean and median platelet counts remained relatively stable over the course of the study, albeit at substantially lower mean and median counts than at baseline. Only one SAE related to thrombocytopenia, epistaxis in 1 patient in Arm C, was reported, and only 1 patient, also in treatment Arm C, had to discontinue treatment because of thrombocytopenia, which was categorized as non-serious but related to treatment.

Overall Summary and Conclusions

Overall, the safety of combination treatment of ABT-263 with rituximab was acceptable. No increase in SAEs was reported with ABT-263 treatment compared with rituximab alone (low number in all treatment arms). The on-target AEs of cytopenias (especially thrombocytopenia) and liver function abnormalities were monitored and were manageable in most instances with

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dose adjustments, growth factor, or temporary discontinuation to avoid Grade 3 or Grade 4 toxicities. Nonetheless, cytopenias (1 each of thrombocytopenia and neutropenia) and transaminase elevations (6 patients) led to ABT-263 discontinuation in a minority of patients (2.6% and 7.7% of patients, respectively). Two additional patients discontinued ABT-263 because of hyperbilirubinemia and increased hepatic enzymes (1 each).

Pharmacokinetic data showed no indication of drug interaction between ABT-263 and rituximab.

In summary, toxicity was manageable with the dosing regimen employed. The regimen of ABT-263 and rituximab was generally well tolerated; the principal toxicities were mechanism-based thrombocytopenia (presumably due to inhibition of Bcl-xL) and transaminase elevations. The trial was stopped prematurely, not because of safety concerns of the tested regimens but because of a decision by Abbott and Genentech to focus development resources on a different Bcl-2 inhibitor.

Date of the Report

17 June 2013