SYNOPSIS OF CLINICAL STUDY REPORT

Name of Sponsor/Company: Genentech, Inc.	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use Only)*
Name of Finished Product: Drozitumab	**Volume:**	
Name of Active Ingredient: Drozitumab	**Page:**	

Title of Study: **A PHASE II, SINGLE-ARM, OPEN-LABEL STUDY OF THE SAFETY, PHARMACOKINETICS, AND EFFICACY OF MULTIPLE DOSES OF APOMAB ADMINISTERED INTRAVENOUSLY IN COMBINATION WITH RITUXIMAB IN PATIENTS WITH FOLLICULAR, CD20-POSITIVE B-CELL NON-HODGKIN'S LYMPHOMA THAT HAS PROGRESSED FOLLOWING PREVIOUS RITUXIMAB THERAPY**

Phase of Development: I

Investigators: A list of investigators is provided in Appendix 16.1.4.

Study Centers: There were a total of 26 study sites in the United States, Russia, Europe, and the rest of the world.

Publications: No publications have resulted from this study.

Study Period: 10 March 2008 to 31 December 2009

Objectives

Primary:

- To evaluate the safety and tolerability of drozitumab when combined with rituximab for the treatment of patients with relapsed follicular, CD20-positive B-cell non-Hodgkin's lymphoma (NHL)
- To make a preliminary assessment of the efficacy of drozitumab when combined with rituximab for the treatment of patients with relapsed follicular, CD20-positive B-cell NHL, as measured by objective response rate

Secondary:

- To make a preliminary assessment of the efficacy of drozitumab when combined with rituximab for the treatment of patients with relapsed follicular, CD20-positive B-cell NHL, as measured by progression-free survival (PFS), duration of response, and overall survival
- To evaluate the serum pharmacokinetics of drozitumab and rituximab when combined for the treatment of patients with relapsed follicular, CD20-positive B-cell NHL

Methodology

This Phase II, single-arm, open-label, multicenter trial was designed to evaluate the safety, efficacy, and pharmacokinetics of drozitumab when combined with rituximab in patients with follicular, CD20-positive B-cell NHL that progressed following previous rituximab therapy. Patients were required to have a partial response (PR), complete response/complete response unconfirmed (CR/CRu), or stable disease lasting > 6 months after completion of their most recent rituximab-containing regimen. Approximately 50 patients (including those enrolled prior to the adoption of Amendment 2 [see Section 9.8.1 for details of the amendment]) were to be enrolled. Of these, approximately 15 patients would receive placebo + rituximab (prior to implementation of Amendment 2); the remaining patients would receive drozitumab + rituximab. Patients who were enrolled in the study prior to implementation of Amendment 2 may have been unblinded to their treatment assignment when Amendment 2 was implemented at their treatment site. Those patients randomized to receive placebo + rituximab discontinued infusions of placebo after unblinding and remained on the study treatment portion of the study until completion of rituximab treatment at the investigator's discretion.

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All patients received rituximab, 375 mg/m^2 by intravenous (IV) infusion. Following implementation of Amendment 2, all patients also received drozitumab. Treatment was not continued beyond the maximum duration specified.

Tumor assessments were performed at baseline, pre–Cycle 4, at the treatment completion/early termination visit, and at Months 8 and 12. Follow-up was to continue until 36 months after Cycle 1, Day 1, or until disease progression or initiation of other anti-lymphoma therapy (whichever occurred earlier), with tumor assessments (including computed tomography [CT] scans) performed every 6 months after Month 12 until Month 36.

Response and disease progression were assessed using modified International Working Group (IWG) criteria. All radiographic studies and pertinent clinical data required for evaluation of response and disease progression were to be submitted to the IRF for impartial and blinded assessments.

Limited blood samples for measurement of drozitumab and rituximab concentrations were collected. Whole blood samples to determine FcγRIIIa and FcγRIIa polymorphisms were obtained from all patients at baseline.

Number of Patients (Planned and Analyzed):

Planned enrollment: approximately 50 patients

Actual enrollment: 49 patients

Diagnosis and Main Criteria for Inclusion:

Patients with follicular, CD20-positive B-cell NHL, classified as WHO Grade 1, 2, or 3a, that progressed after a PR, CR/CRu, or stable disease of >6 months duration following completion of their most recent rituximab-containing regimen were eligible for participation in this trial. Patients had to be >18 years old, have an ECOG performance status of 0 or 1, and have a life expectancy of >3 months. Measurable disease was required.

Test Product, Dose and Mode of Administration, Batch Number:

Drozitumab was given as a 15 mg/kg loading dose on Day 1 of Cycle 1, followed by 10 mg/kg on Day 1 of each subsequent 21-day cycle (± 2 days). The drozitumab dose was based on the patient's body weight at screening and remained the same throughout the study.

Prior to Amendment 2, patients may have been randomized to receive placebo instead of drozitumab.

Dose modification for drozitumab was not allowed in this study.

Batch numbers are provided in Appendix 16.1.6.

Duration of Treatment:

Drozitumab dosing continued on Day 1 of each 21-day cycle (± 2 days), until disease progression or unacceptable toxicity, for a total of six cycles. Treatment was not continued beyond the maximum duration specified.

Reference Therapy, Dose and Mode of Administration, Batch Number:

All patients enrolled in this single-arm trial received rituximab by IV infusion at 375 mg/m^2 once per week (± 1 day) for up to 8 weeks. The first dose of rituximab was administered 24 to 120 hours prior to the first dose of drozitumab on Day 1 of Cycle 1. The rituximab dose was based on the patient's body surface area at screening and remained the same throughout the study.

The initial dose of rituximab was administered 24 to 120 hours prior to the first dose of drozitumab on Cycle 1, Day 1. Subsequent weekly doses of rituximab were administered on Days 8 and 15 of Cycle 1, Days 1, 8, and 15 of Cycles 2, and Days 1 and 8 of Cycle 3. On days when both drozitumab and rituximab were given, the order of study treatment administration was rituximab followed by drozitumab.

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Dose modification for rituximab was not allowed in this study.

Batch numbers are provided in Appendix 16.1.6.

Criteria for Evaluation

Efficacy:

The primary efficacy analysis included all patients who received at least one dose of drozitumab.

Safety:

Safety analyses included all patients who received any amount of study treatment (rituximab, drozitumab, or placebo).

Statistical Methods

Primary Endpoint:

The primary efficacy outcome measure for the study was objective response (defined as a PR or CR/CRu, occurring within 8 months after Cycle 1, Day 1), as determined by the IRF using modified IWG criteria.

Secondary Endpoints:

Efficacy

- PFS (defined as the time from first drozitumab exposure to the first occurrence of progression, relapse, or death from any cause), as assessed by the IRF using modified IWG criteria
- Duration of objective response (defined as the first occurrence of a documented, objective response until the time of relapse or death from any cause), as assessed by the IRF using modified IWG criteria
- Overall survival (defined as the time from first drozitumab exposure until death from any cause)
- Objective response, PFS, and duration of objective response, as determined by study site investigators' assessments using modified IWG criteria

Safety

- Incidence, nature, timing, and severity of adverse events
- Changes in vital signs, physical findings, and clinical laboratory results during and following drozitumab administration

Pharmacokinetic

- Maximal serum concentration
- Minimal serum concentration

Summary of Results and Conclusions

Efficacy and Pharmacokinetic/Pharmacodynamic Conclusions:

For the 40 patients who received drozitumab + rituximab in this single-arm, open-label study, the following point estimates were obtained:

- Objective response rate: 45.0% (95% CI: 29.3%, 61.2%)
- Median PFS: 8.6 months (95% CI: 7.8, 11.9)
- Median duration of objective response: 9.1 months (95% CI: 6.4, 10.3)

Overall survival could not be estimated as the result of the low number of deaths at the time of study termination.

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Safety Conclusions:

- Treatment with drozitumab + rituximab was generally well tolerated, and the safety profile of this novel combination was overall favorable.
- The vast majority of adverse events (90.0%) reported for drozitumab + rituximab patients had a maximum severity of Grade 1 or 2.
- The most frequent adverse events in the drozitumab + rituximab patients were fatigue (25.0%), pyrexia (20.0%), diarrhea (17.5%), chills, nasopharyngitis, ALT increased, oropharyngeal pain, and rash (12.5% each).
- Hypersensitivity reactions, including anaphylaxis, were reported. These events were subsequently identified as adverse drug reactions and added to the Drozitumab Investigator Brochure.
- One case of PML occurred during the study follow-up period and resulted in the patient's death. Of note, this patient had received multiple cycles of cytotoxic therapy and rituximab-containing regimens prior to beginning the study.

Overall Conclusions:

Treatment with drozitumab + rituximab was generally well tolerated among patients with relapsed follicular, CD20-positive B-cell NHL that had progressed following previous rituximab therapy. Most reported adverse events were NCI CTCAE Grade 1 or 2. The most frequent adverse events were fatigue (25.0%), pyrexia (20.0%), diarrhea (17.5%), chills, nasopharyngitis, ALT increased, oropharyngeal pain, and rash (12.5% each). Events of anaphylactic reaction and hypersensitivity were reported and were subsequently added as adverse drug reactions to the Drozitumab Investigator Brochure. A case of PML occurred during the study follow-up period and resulted in the patient's death. These adverse events have been reported in studies of rituximab treatment alone. Overall, the safety profile of this combination was favorable.

The observed objective response rate in this study was 45.0% (95% CI: 29.3%, 61.2%), which was comparable to that seen in the rituximab alone arm in a randomized, controlled Phase II trial of rituximab + dulanermin (Belada et al. 2010). Rituximab did not alter the pharmacokinetics of drozitumab. Although this combination treatment was well tolerated, it did not show significant efficacy in this patient population.

Date of the Report

9 December 2010