Sponsor

Novartis

Generic Drug Name

Lucatumumab

Therapeutic Area of Trial

CD40 positive relapsed follicular lymphoma

Approved Indication

Investigational

Protocol Number

CHCD122A2104

Title

A phase Ib, multicenter, open-label study of HCD122 administered intravenously in combination with bendamustine in patients with CD40+ relapsed follicular lymphoma

Study Phase

Phase Ib

Study Start/End Dates

Study dates: 07-Feb-2011 (last patient last visit) to 11-May-2012 (last patient last visit).

The CHCD122A2104 study was terminated on 04-Jun-2012 due to challenges in patient enrollment (due to low incidence of CD40-positivity in screened patients), as well as an unclear regulatory path forward. Early termination of the study was not due to any safety concerns.

Study Design/Methodology

A phase Ib, multicenter, open-label study of HCD122 administered intravenously in combination with bendamustine in patients with CD40+ relapsed follicular lymphoma. A dose escalation phase using a 3-parameter Bayesian logistic regression model to determine maximum tolerated dose (MTD) of HCD122 when administered in combination with bendamustine; followed by a dose expansion phase to better characterize the safety, tolerability, and make a preliminary assessment of anti-tumor activity of the combination.

Centers

17 centers initiated in 8 countries: Australia (1), Belgium (2), Canada (1), France (2), Italy (4), Netherlands (1), Spain (2), and USA (4).

Publication

No publications were created from this study

OutcomeMeasures

Efficacy was not powered for analysis because of the low recruitment.

Test Product (s), Dose(s), and Mode(s) of Administration

Treatment cycles consisted of 28 days. During the combination treatment period, both HCD122 and bendamustine were administered during each cycle for 6 cycles. HCD122 infusion was administered once every 14 days at the assigned dose (during dose escalation) or at the MTD (during dose expansion). Bendamustine infusion was administered on the first two days of each 28-day combination treatment cycle at a starting dose of 90 mg/m2.

Statistical Methods

The primary objectives of the study were to determine the maximum tolerated dose (MTD) of HCD122 when administered in combination with bendamustine to adult patients with CD40+ follicular lymphoma (FL) who are relapsed to rituximab and have received at least one prior chemotherapeutic regimen (dose escalation) and to further assess the safety and tolerability of this combination (dose expansion).

The corresponding primary analysis method was an adaptive Bayesian logistic regression model guided by the escalation with overdose control (EWOC) principle based on Babb et al (1998).

The corresponding primary analysis method was chi-square test with continuity correction.

The proposed dose escalation methodology has been designed to provide an ethical dose escalation strategy that optimizes the proportion of patients treated at doses sufficiently close to the MTD while assigning fewer patients to overly toxic dose levels compared to traditional up-and-down methods. Also, the choice of dose at any stage of the trial was based on the entire history of all available information from previous cohorts as opposed to only the number of DLTs observed in the last group of patients. Rogatko et al (2007) has noted that “in simulation studies, up-and-down methods treated, on average, 35% of the patients [were treated] at the optimal levels, whereas EWOC treated 55% of the patients at optimal levels. Furthermore, EWOC assigned fewer patients to either sub-therapeutic or severely toxic dose levels and estimated the MTD with smaller average bias and mean squared error than the up-and-down methods.”

The dose-limiting toxicity (DLT) relationship in the dose escalation part of the study was described by a 3-parameter Bayesian logistic regression model:

psd = Ps + (1-Ps)□(d),

Where psd was the probability (chance) of DLT under the combination of dose level d of HCD122 and the fixed dose level (90 mg/m2) of the standard agent bendamustine. PS was the chance of occurrence of DLT only due to the standard agent (bendamustine) and it is assumed to be following a beta distribution.

logit(π(d)) = ln (□(d)/(1-□(d))), where π(d) was the conditional probability that a patient who did not experience a DLT clearly attributed to only the standard of care will experience a DLT due to HCD122 at dose level d. Doses (of HCD122) were rescaled as d/d* with reference dose d*=6mg/kg of HCD122. As a consequence α was equal to the conditional odds of toxicity at d*. Note that for a dose of HCD122 equal to zero, the conditional probability of toxicity was zero. However, at zero dose of HCD122, total chance of DLT of the combination therapy, given by psd (=Ps) was not zero.

If an alternative schedule was explored during the course of the trial, the statistical model was be adjusted by the addition of a covariate term to account for the schedule effect and sharing of information across the schedules.

The key secondary efficacy objective was to assess the anti-tumor activity of HCD122 in combination with bendamustine.

Corresponding secondary efficacy endpoints are overall response rate (CR or PR), duration of response, time to progression and progression free survival.

Overall response rate and time to progression was planned to be reported by descriptive statistics by dose cohort and treatment groups. Standard survival analysis using the Kaplan-Meier approach was planned to be performed for progression free survival. Duration of response was only to be analyzed for responders and was defined as the time from first documented response (CR or PR) to disease progression.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Patients must had a confirmed diagnosis of follicular lymphoma, according to the Revised European American Lymphoma/World Health Organization [REAL/WHO] classification
- Patients must had a restaging tissue specimen available for CD40 expression confirmation that was collected within 1 year or since completion of the most recent previous therapy, or were willing to undergo a tissue biopsy.

- Patients must have documented CD40+ follicular lymphoma
- Patients must had progressive disease
- Patients must had received at least 1 prior rituximab-containing regimen
- Patients must had received at least 1 prior chemotherapeutic regimen
- Patients must had discontinued any previous anti-cancer and investigational therapy including radiation, radioimmunotherapy, and monoclonal antibody therapy for at least 28 days before study treatment administration, and must had recovered fully from the adverse effects of such treatment before beginning study treatment
- Patients must had at least one lesion of measurable disease (accurately measurable in at least 2 perpendicular dimensions):
  - At least 1 measurable nodal lesion > 20 mm in the long axis; OR
  - At least 1 measurable extranodal lesion with long and short axes ≥ 10 mm
- Patients were ≥ 18 years
- Patients must had WHO Performance Status grade 0, 1, or 2
- Patients must had a life expectancy > 3 months
- Patients must have met the following laboratory criteria (must have been obtained within 14 days of enrollment):
  - Absolute neutrophil count (ANC) ≥ 1,250/µL
  - Platelet count ≥ 100,000/µL (must not have been transfused within previous 10 days)
  - Hemoglobin ≥ 9.0 g/dL (may have been transfused)
  - Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or 24 hour clearance ≥ 50
- mL/min.
  - AST/SGOT ≤ ULN; ALT/SGPT ≤ ULN
  - Serum bilirubin ≤ 1.5 x ULN
  - Serum amylase ≤ ULN
  - Serum lipase ≤ ULN
  - Fasting serum triglyceride level ≤ 500 mg/dL
- Written informed consent had to be obtained before any screening procedures

Exclusion criteria:

- Grade 3b follicular lymphoma or evidence that the indolent lymphoma has transformed to
- aggressive lymphoma (i.e. DLBCL)
- Patients who have received prior treatment with any anti-CD40 antibody, including HCD122
- Patients who have undergone major surgery within 28 days before study treatment or have not recovered fully from the adverse effects of any major or minor surgical procedures before study treatment
- Patients who have a history of another primary malignancy that is currently clinically significant or currently requires active intervention
- Patients who have received prior allogeneic stem cell transplantation
- Patients who have had a prior anaphylactic or other severe infusion reaction such that the patient is unable to tolerate human immunoglobulin or monoclonal antibody administration
- Patients who have a history or clinical evidence of central nervous system, meningeal, or epidural disease, including brain metastasis
- Impaired cardiac function or clinically significant cardiac disease, including any one of the following:
  - New York Heart Association Class III or IV cardiac disease, including pre-existing clinically significant arrhythmia, congestive heart failure, or cardiomyopathy

- Angina pectoris ≤ 3 months before starting study treatment
- Acute myocardial infarction ≤ 3 months before starting study treatment
- Other clinically significant heart disease (e.g. uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
- Patients who had a history of acute or chronic pancreatitis, surgery of the pancreas, or any risk factors that could increase the risk of pancreatitis
- Patients who had cystic fibrosis
- Patients who had a history of an active infection (viral, bacterial, or fungal) requiring systemic therapy within 28 days before study treatment. Prophylactic antibiotics and antiviral therapies were permitted.
- Patients who had an active autoimmune disease requiring immunosuppressive therapy
- Known diagnosis of human immunodeficiency virus (HIV) infection (testing for HIV was not mandatory)
- Evidence of previous hepatitis viral infection such as hepatitis B or hepatitis C (testing for viral hepatitis was not mandatory)
- Ongoing corticosteroid use (>10 mg/day prednisone or equivalent)
- Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (> 5 mIU/mL)
- Fertile women of child bearing potential not willing to use double barrier methods of contraception (abstinence, oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly, or surgically sterile). Male patients whose partners were not willing to use double-barrier methods of contraception.

Participant Flow

The study was open for patient enrollment from 7-Feb-2011 to 20-Mar-2012 across 17 study sites in Australia, Belgium, Canada, France, Italy, The Netherlands, Spain and USA. A total of 11 patients provided written consent to enter the screening period. Of these patients, only one (0201/10101; Belgium) met all inclusion and exclusion criteria and received treatment. Ten patients did not meet the eligibility requirements due to the following reasons: CD40 negative disease (5 patients), elevated bilirubin (1 patient), withdrew consent (1 patient), no prior chemotherapy (1 patient), no follicular lymphoma (1 patient) and administrative issues (1 patient).

Baseline Characteristics

One patient received HDC122 combination therapy (0201/10101; Belgium) in the CHCD122A2104 study.

Patient 0201/10101 was a 64 year old, Caucasian male, initially diagnosed with FL on 18-May-2009. Just prior to study initiation, on 26-Jan-2012, the patient was diagnosed with stage IIIa, grade 1 FL and presented with bulky disease. The patient's baseline disease was positive for CD40 expression, a required inclusion criteria for entry into the study.

The patient's received two antineoplastic therapy regimens prior to the start of the study. The first regimen was rituximab combined with CHOP (R-CHOP), administered from 8-Jun-2009 to 30-Nov-2009, resulting in a CR lasting for 12 months. Approximately one year later, the patient received rituximab monotherapy from 17-Nov-2010 to 8-Dec-2010. Within 21 days of the last dose of rituximab (29-Dec-2010), the patient presented with disease progression. Therefore, the patient's disease was determined to be rituximab-refractory. At the time of study entry, the patient presented with active medical conditions including hypertension and lymphopenia. Past medical history, not active at the time of study entry, included transurethral prostatectomy, inguinal hernia, and umbilical hernia.

Safety Results

No serious adverse events or deaths were reported in this study.

Adverse events, regardless of study drug relationship, included chills, cough, diarrhea, dyspepsia, hypokalemia, hypophosphatemia, leukopenia, lymphopenia, nausea, neutropenia, productive cough, upper respiratory tract infection, and vitamin D deficiency. Grade 3/4 adverse events included hypokalemia, hypophosphatemia, neutropenia, lymphopenia and leukopenia.

The patient received her last dose of study treatment on 26-Sep-2011. The patient discontinued treatment in the HCD122 maintenance period due to grade 4 neutropenia that started on 10-Oct-2011. This adverse event caused a delay in treatment that lasted greater than 28 days, which, per protocol, required the patient to be discontinued from further treatment. For treatment of neutropenia, the patient received filgrastim starting on 17-Oct- 2011 and ending on 21-Oct-2011. The grade 4 neutropenia resolved by 23-Oct-2011.

Serious Adverse Events and Deaths No serious adverse events or deaths were reported in this study.
Other Relevant Findings Not applicable
Date of Clinical Trial Report 19-December-2012
Date Inclusion on Novartis Clinical Trial Results Database 6-March-2013
Date of Latest Update