THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Phase II Study of Ofatumumab as Front-line Treatment in Elderly, Unfit Patients with Chronic Lymphocytic Leukemia (CLL)
2011-0520

Core Protocol Information

Short Title	Phase II Study of Ofatumumab in Elderly Patients with CLL
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

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Phase II Study of Ofatumumab as Front-line Treatment in Elderly, Unfit Patients with Chronic Lymphocytic Leukemia

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1.0 Background

Ofatumumab

Ofatumumab, a novel anti-CD20 antibody, has been tested in various hematologic malignancies, and is currently FDA approved for treatment of patients with CLL that is relapsed/refractory to prior treatments with fludarabine and alemtuzumab.

Ofatumumab is a human immunoglobulin (Ig) G1k antibody which binds to a different epitope of CD20 than rituximab, a site which includes the small extracellular loop (residues 74 to 80) and the N-terminal region of the second large extracellular loop, that includes amino acids 163 and 166 (Cheson, J Clin Oncol, July 20, 2010) (Teeling JL, et al. J Immunol, 177:362-371, 2006).

Ofatumumab has been demonstrated to have greater binding avidity than rituximab and can bind closer to the cell membrane than rituximab, which may lead to be more effective complement-dependent cytotoxicity (CDC) and therefore has a potential advantage over other anti-CD20 antibodies in the setting of CLL (Teeling, 2006 and Teeling JL, et al. Blood 104:1793-1800, 2004).

Chronic lymphocytic leukemia (CLL)

CLL is the most common form of adult leukemia in the United States. It affects males more frequently than females and affects elderly individuals with more than 50% of the patients being 70 years of age or older at the time of diagnosis. It has been estimated that there are approximately 150,000 individuals living with CLL in the United States (SEER database). The course of the disease is diverse with patients that may not require therapy for many years and eventually die of unrelated causes and patients with high risk features that survive only a few months despite treatment.

Treatment options for patients with newly diagnosed CLL in the United States consist of treatment with fludarabine as single-agent or in association with chemoimmunotherapy. In our center, frontline treatment consists of the combination of fludarabine, cyclophosphamide and rituximab (FCR) (Keating MJ, et al., J Clin Oncol, 2005, 23: 4079-4088). This combination chemoimmunotherapy has resulted in a high percentage of responses. When we reviewed our experience in elderly patients (defined as age 70 or older) treated with this combination, response rate observed in 54 patients showed an overall response rate of 80% indicating that this treatment is active. We also noted that 75% of the patients treated with this approach developed myelosuppression and were able to receive only a median of 4 out of the 6 cycles of planned chemotherapy, indicating that the FCR is poorly tolerated by older patients (Ferrajoli A, et al. Leuk and Lymph, 46 (Suppl.1):S86, 2005). Furthermore, the positive results with FCR have been reported in patients that are fit, have a low

number of co-morbidities and, most importantly, have a normal renal function (Hallek M, et al. Lancet 2010;376(9747):1164-1174).

Rationale for Use of Ofatumumab in CLL

The rationale for evaluating the activity of ofatumumab in elderly patients with CLL is based on the experience with rituximab. Two clinical studies have been conducted at our center evaluating the activity of monotherapy with rituximab as initial treatment of patients with CLL. One study focused on the activity of rituximab in patients without indications for treatment, but with high-risk for progression based on beta2 microglobulin level. In this subset of patients the overall response (OR) rate was 82% and the duration of response was 23 months (Ferrajoli et al., Cancer 2011). In a subsequent study, we treated 32 patients age 70 or older with rituximab in association with GM-CSF. All patients had indication for treatment and patients with poor performance status were allowed to participate. In this group the OR rate was 69% and the median duration of response was 18 months (Ferrajoli, et al. Leuk and Lymph, 2009). This elderly group tolerated the treatment well, with toxicity limited to infusion reactions.

Ofatumumab therefore, with its favorable toxicity profile, its clinical activity in the relapsed/refractory setting, and in vitro studies suggest that ofatumumab has greater complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicty compared to rituximab, is an attractive therapeutic option for elderly patients with CLL requiring initial therapy.

2.0 Objectives

Primary Objective:

1.1 To evaluate the overall response rate of ofatumumab in the upfront setting in elderly, unfit patients with CLL. [Unfit patients in this trial are: patients with and ECOG/WHO performance status of 2-3 (usually defined as “slow-go or no-go”) or patients with an ECOG/WHO performance status of 0-1 and a CIRS or Charlson (Charlson, 1987 J Chronic Dis 40(5): 373-83) co-morbidity score of 2 or higher.]

Secondary Objectives:

1.2. To determine the overall survival with ofatumumab in the upfront setting in elderly, unfit CLL patients.
1.3. To evaluate the complete response rate and time to progression after repeated doses of ofatumumab in elderly, unfit patients with CLL.
1.4. To determine the plasma levels of ofatumumab in elderly, unfit patients.
1.5. To evaluate predictive capability of miRNAs detection in plasma samples.

3.0 Study Design

This is a single center open label phase II study to evaluate the efficacy and safety of ofatumumab as initial treatment of elderly, unfit patients with CLL and indications for treatment according to NCI-WG guidelines.

Treatment Plan:

The administration of ofatumumab will be four weekly IV infusions at the dose of 300 mg during week 1, then 2000 mg in weeks 2, 3 and 4, then monthly during months 2-12.

Pre-medication before each ofatumumab infusion must be given within 30 minutes to 2 hours prior to each treatment:
• Acetaminophen (PO) 1000 mg or equivalent
• Diphenhydramine (IV) 50 mg
• Glucocorticoid (IV) equivalent to 50 mg prednisolone. The dose of glucocorticoid can be decreased at the time of subsequent doses if grade 3 or greater infusion reaction did not occur with the preceding dose.

First Infusion of 300 mg Ofatumumab:

The initial rate of the first infusion of 300 mg ofatumumab (0.3 mg/ml) should be 12 ml/h. If no infusion reactions occur the infusion rate should be increased every 30 minutes, to a maximum of 400 ml/h, according to Table 1. If this schedule is followed, the infusion duration will be approximately 4.5 hours. If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If, however, the infusion rate was 12 mL/hour before the pause, the infusion should be restarted at 12 mL/hour. Hereafter, the infusion rate may be increased according to the judgment of the investigator, in the manner described in this section.

Subsequent infusions of 2000 mg ofatumumab:

If the previous infusion has been completed without grade ≥ 3 infusion-associated AEs, the subsequent infusion of **2000** mg (2 mg/ml) can start at a rate of 25 mL/hour and should be doubled every 30 minutes up to a maximum of 400 ml/h, according to Table 2.

Duration of the infusion will be approximately 4 hours if this schedule is followed. If a Grade ≥3 AE related to the infusion occurs, the infusion must be interrupted. When the AE decreases to grade <3, the investigator may restart the infusion.

Table 1. Infusion rate at 1st Ofatumumab infusion.

Time	mL/hour
0 – 30 minutes	12
31 – 60 minutes	25
61 – 90 minutes	50
91 – 120 minutes	100
121 - 150 minutes	200
151 - 180 minutes	300
181+ minutes	400

Table 2. Infusion rate at subsequent Ofatumumab infusion.

Time	mL/hour
0 – 30 minutes	25
31 – 60 minutes	50
61 – 90 minutes	100
91 – 120 minutes	200
121+ minutes	400

During infusion the patient should be monitored closely and appropriate measurements should be performed whenever judged necessary. Allopurinol 300 mg/day will be given during the first 14 days of treatment for tumor lysis prophylaxis.

Dose Reduction: DOSE REDUCTION GUIDELINES FOR OFATUMUMAB.
No dose reduction is planned for ofatumumab. Its administration will be held for grade 3 or higher hepatic toxicity and can be omitted if clinically indicated.

Precautions with Ofatumumab Treatment:

Chronic obstructive pulmonary disease, moderate to severe (unapproved use); risk of grade 3 bronchospasm during infusion. Cytopenias, including prolonged severe neutropenia and thrombocytopenia may occur; monitoring recommended.

Hepatitis B infection, carriers or at risk of infection; risk of hepatitis B reactivation with fulminant hepatitis, hepatic failure, and death; evaluate for evidence of infection before beginning treatment and closely monitor for reactivation for 6 to 12 months following therapy; discontinue therapy if viral hepatitis occurs.

Infusion reactions, some serious (e.g. bronchospasm, dyspnea, laryngeal edema, pulmonary edema, angioedema, cardiac ischemia/infarction) have been reported; especially during first 2 infusions; premedication is recommended; depending on the severity of the reaction, adjustment in infusion rate, interruption, and/or discontinuation of therapy is recommended. Obstruction of small intestinal may occur. Progressive multifocal leukoencephalopathy (PML) including fatalities, may occur; new onset or changes in preexisting neurological signs and symptoms may be indicative of PML; discontinue therapy if PML occurs.

Viral live vaccination; do not use in patients who recently received ofatumumab therapy.

Potential Side Effects of Ofatumumab:

Common
Dermatologic: rash (all grades, 14% to 17%; grade 3 or greater, less than 1% to 2%). Gastrointestinal: diarrhea (18% to 19%), nausea (11% to 12%). Hematologic: anemia (all grades, 16% to 17%; grade 3 or greater, 5% to 8%).
Respiratory: bronchitis (all grades, 11% to 19%; grade 3 or greater, less than 1% to 2%), cough (19%), dyspnea (all grades, 14% to 19%; grade 3 or greater, 2% to 5%), pneumonia (all grades, 23% to 25%; grade 3 or greater, 14% to 15%), upper respiratory infection (3% to 11%).
Other: fatigue (15%), Fever (all grades, 20% to 25%; grade 3 or greater, 3% to 5%)

Serious
Gastrointestinal: bowel obstruction.
Hematologic: neutropenia, Grade 3 or greater (42%).
Hepatic: relapsing type B viral hepatitis.
Immunologic: infectious disease (all grades, 70%; grade 3 or greater, 29%), sepsis (all grades, 8% to 10%; grade 3 or greater, 8% to 10%).
Neurologic: progressive multifocal leukoencephalopathy.

Other: complication of infusion (first infusion, 44%; second infusion, 29%).

Further information can be found in the Ofatumumab Investigator's Brochure.

Supplier
GlaxoSmithKline (GSK) will supply commercial ofatumumab for this study.

Receipt of Study Drug
The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator or designee will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to GSK or its representative.

Storage
The study drug will be stored refrigerated (2-8^{o}C) in a safe and secure place. The study drug will not be frozen. A temperature log with daily readings will be kept.

Recommended Concomitant Therapy
Allopurinol 300 mg/day will be given during the first 14 days of treatment for tumor lysis prophylaxis. Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, and anti-emetics when/if appropriate. Use of filgrastim (G-CSF), erythropoietin to treat for neutropenia and anemia respectively is permitted while on study.

4.0 Patient Eligibility

Inclusion Criteria: Patients will be eligible for inclusion in the study if they meet all of the following criteria:

1) Patients with chronic lymphocytic leukemia requiring treatment >65 at the time of signing informed consent.

2) ECOG/WHO performance status of 2-3 or patients with chronic lymphocytic leukemia requiring treatment age >65 years at the time of signing informed consent and ECOG/WHO performance status of 0-1 and a CIRS or Charlson co-morbidity score of 2 or higher.

3) Adequate renal and hepatic function (creatinine <2mg/dL and eGFR more than 30cc/minute, bilirubin <2mg/dL). Patients with renal or liver dysfunction due to organ infiltration by lymphocytes may be eligible after discussion with the study chairman. Patients with Gilbert's syndrome are eligible.

Exclusion Criteria:

1. Patients with documented prolymphocytic leukemia (prolymphocytes more than 55% in the blood).

2. Known positivity for HIV.

3. Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HB DNA test will be performed and if positive the subject will be excluded.

4. Prior treatment for CLL.

5. Concurrent chemotherapy, radiotherapy, or immunotherapy, including other monoclonal antibodies. Localized radiotherapy to an area not compromising bone marrow function does not apply.

Patients with malignancies with indolent behavior such as prostate cancer treated with radiation or surgery can be enrolled in the study as long as they have a reasonable expectation to have been cured with the treatment modality received.

6. Any serious medical condition, laboratory abnormality, or psychiatric illness that places the subject at unacceptable risk if he/she were to participate in the study.

7. Any known hypersensitivity to ofatumumab or its components.

5.0 Criteria for Removal from Study:

Treatment with study drug is discontinued and the patient will be removed from study when any of the following occurs:

1. Lack of therapeutic effect.

2. Adverse event(s) that, in the judgment of the Investigator or the patient, may cause severe or permanent harm or which rule out continuation of the study drug.

3. Withdrawal of consent.

4. Lost to follow up.

6.0 Visit Schedule and Assessments:

Pretreatment evaluation

Pretreatment evaluation will include a physical examination, height and weight and recording of concurrent medications (within 7 days of registration).

Chemistry: Clinical laboratory evaluation will include serum chemistry. This will include sodium, potassium, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, uric acid, and TSH. Beta-2-microglobulin (within 7 days of registration).

Hematology: Complete CBC and differential and peripheral blood lymphocyte subset and immunoglobulin levels (within 7 days of registration).

Bone marrow aspiration and biopsy within one month from registration. Bone marrow will be evaluated by flow cytometry for clonality and for IgVH mutation studies (unless known) ZAP-70 expression (unless known), cytogenetic and genomic abnormalities (unless known).

HIV, Hepatitis B and C screening (if not performed within 3 months from registration).

Evaluation During Study

Monitoring will consist of biweekly (every other week ±3 days) blood counts and SMA12 during treatment, then every 3 months (±2 weeks) during follow-up until alternative treatment for CLL or death, whichever occurs first. For patients who are HBsAg-, HBcAb+, HBsAb+/-, and HBV DNA- on enrollment and proceeded with treatment, HBV DNA PCR testing will be done every 2 months while on treatment and maintenance, then every 3 months during follow-up for 6 months.

A physician will see patients at least monthly (±5 days) during treatment, then every 6 months (±2 weeks) during follow-up. All patients will be followed for survival.

CD4+, CD8+ and peripheral blood lymphocyte subset, beta-2-microglobulin will be analyzed after month 6 and every six months thereafter. Bone marrow biopsy and aspiration will be performed as clinically indicated after month 6 and every six months thereafter.

7.0 Criteria for Response

The 2008 NCI Working Group criteria for response will be used. Response will be assessed after month 3, month 6 and every 6 months thereafter.

8.0 Evaluation of Toxicity

Toxicity will be scored using CTC Version 4.0 for toxicity and adverse event reporting according to the M.D. Anderson guidelines. Hematologic toxicity will be assessed, graded, and summarized according to the 2008 IWCLL Guidelines (See Table 3). Adverse events will be documented in the medical record and entered into the case report form according to the Leukemia-Specific Adverse Event Recording and Reporting Guidelines (Appendix D). PDMS/CORe will be used as the electronic case report form for this protocol. The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

Table 3. 2008 IWCLL Grading for Hematological Toxicity Grade	**Decrease in PLT* or HGB** (nadir) from pretreatment value, %**	**Absolute neutrophil count (ANC)/l*** (nadir)**
0	10%	2000
1	11 – 24%	1500 – < 2000
2	25 – 49%	1000 – < 1500
3	50 – 74%	500 – < 1000
4	75%	< 500

If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

M.D. Anderson (Sponsor) Reporting Requirements for Serious Adverse Events and Dose Limiting Toxicities:

As per MDACC and Leukemia phase II-III studies.

Serious Adverse Event (SAE) Definition

A serious adverse event is one that at any dose (including overdose):

Results in death.

Is life-threatening[1].

Requires inpatient hospitalization or prolongation of existing hospitalization.

Results in persistent or significant disability or incapacity[2].

Is a congenital anomaly or birth defect.

Is an important medical event[3].

Suspected Positive Pregnancy

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.
[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.
[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

Serious Adverse Events Reporting: The principal investigator has the obligation to report all serious adverse events to The University of Texas, M. D. Anderson Cancer Center (MDACC) IRB, GSK and NCCN within 24 hours.

Email Krulewicz@gsk.com or

Fax SAEs to: 1.610.917.6715

AND

Email: ORPReports@nccn.org or fax 215-358-7699

All serious adverse events not requiring expedited reporting should be reported to MDACC IRB within 5 business days. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 24 hours of knowledge regardless of the attribution. SAEs beyond 4 weeks after the end of study drug administration will be reported if thought to be drug related, in compliance with MDACC IRB, GSK and NCCN required SAE reporting requirements.

Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements. Serious Adverse Events Reporting: The principal investigator has the obligation

to report all serious adverse events to MDACC IRB, GSK and NCCN within 24 hours.

Annual Reports

All adverse experience reports must include the patient number, age, sex, severity of reaction (mild, moderate, severe), relationship to study drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to MDACC IRB, GSK and NCCN as described below.

Expedited reporting by Principal Investigator to GSK

Serious adverse events (SAE) are defined above. The investigator should inform GSK and NCCN of any SAE within 24 hours of being aware of the event. The date of awareness should be noted on the report. This must be documented on an M. D. Anderson SAE form. This form must be completed and supplied to MDACC IRB, NCCN and GSK within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the study drug. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up M. D. Anderson SAE form. A final report to document resolution of the SAE is required. The GSK protocol number (115857) should be included on SAE reports to GSK and NCCN. A copy of the fax transmission confirmation of the SAE report to GSK and NCCN should be attached to the SAE and retained with the patient records.

Report of Adverse Events to the Institutional Review Board

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

Sponsor Reporting to the FDA

Adverse drug reactions that are Serious, Unlisted/unexpected, and at least possibly associated to the drug, and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA). A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

The sponsor shall notify the FDA by telephone or by fax of any unexpected fatal or life threatening experience associated with the use of the drug. As soon as possible, but no later than 7 calendar days after the sponsors initial receipt of the information. Each phone call or fax shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND if applicable.

Adverse event updates and safety reports

1.GSK shall notify the Investigator via a Safety Report of the following information:

2.Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.

3.Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

4.The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

5.The Investigator must keep copies of all AE information, including correspondence with GSK and the IRB/EC, on file.

Protocol amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed by NCCN and GSK. Amendments should only be submitted to IRB/EC after consideration of NCCN and GSK review. Written verification of IRB/EC approval will be obtained before any amendment is implemented.

Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the IRB/EC in writing of such deviation from protocol.

9.0 Optional Correlative Studies

Ofatumumab serum levels

Ofatumumab serum levels will be measured at baseline, 1 week, and month 3, 6, 9 and 12. Samples will be collected and shipped to GSK for analysis as ofatumumab assays are proprietary to GSK and must be used through them.

miRNA plasma levels and profiling

Selected miRNA plasma levels in CLL patients will be determined.

Genome-wide profiling study on plasma samples collected from all the patients before the start of the treatment and we will further perform follow-up studies at specific time points (month 3, 6, 9 and 12) will be conducted by quantitative RT-PCR (Rossi et al., Blood 116, 945-952 2010).

10.0 Statistical design

This is a phase II trial to assess the activity and tolerability of ofatumumab in elderly (age 65 or greater), unfit patients with previously untreated CLL.

Response will be assessed after month 3, month 6 and every 6 months thereafter using the 2008 NCI-WG criteria. Toxicity will be score using CTCAE v4.0. The first time point to evaluate efficacy and toxicity will be at completion of month 6 of treatment. Toxicity will be monitored during the entire treatment.

The primary endpoint of this study is OR (CR + PR) and a Simon's two-stage optimum design will be used for this study. A sample size of 34 is chosen to differentiate between a good response rate of 70% and a poor response rate of 40% with 95% power at a significance level of 0.05. The trial will stop early due to lack of efficacy if there are 6 or fewer patients with OR in the first 14 patients. Lack of efficacy will also occur if there are 18 or fewer responses in 34 patients. Secondary endpoints are progression-free survival (PFS) and CR rate. PFS is defined as time from start of therapy to death or progression of disease and it will be calculated using Kaplan Meier estimates. Responses will be assessed by Fisher's exact test with intention to treatment analysis by pre-treatment characteristics. Potential relationships between ofatumumab plasma concentrations and clinical outcomes (e.g. OR) will be explored using regression analyses.

For the correlative studies, we will assess the association between survival data and miRNA marker expression using proportional hazards models and estimate the distributions of time-to-event outcomes using the Kaplan and Meier method. We will then compare these distributions among treatment or cohort groups using the log-rank test. We will compare the proportions of complete responses between positively and negatively expressed miRNAs that are therapeutic markers in various trials. Fifty-eight samples (2-3 sequential samples from each patient) will be required to achieve 80% power at a 2-sided significance level of 0.05 and Bonferroni adjustment for testing 10 markers, assuming that 50%

patients are marker positive and that the response rates in the positively and negatively expressed markers are 75% and 25%, respectively.

11.0 Study Monitoring and Auditing

Investigator responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

The Investigator will permit study-related monitoring visits and audits by NCCN, GSK or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and made available to NCCN and GSK representatives so that the accuracy and completeness may be checked.

12.0 Regulatory Considerations

Institutional Review Board/Ethics Committee approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

Informed consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

Premature discontinuation of study

Single center

The responsible local clinical Investigator as well as NCCN and GSK have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center. Possible reasons for termination of the study could be but are not limited to:

· Unsatisfactory enrollment with respect to quantity or quality.
· Inaccurate or incomplete data collection.
· Falsification of records.
· Failure to adhere to the study protocol.

Study as a whole

NCCN and GSK reserves the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

13.0 Data Confidentiality Plan

All laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

14.0 References

Calin GA and Croce CM. MicroRNA signatures in human cancers. Nature Reviews Cancer 6, 857-866, 2006.

Calin GA and Croce CM. Chronic lymphocytic leukemia: interplay between noncoding RNAs and protein coding genes. Blood 114(23):4761-4770. Epub 2009 Sep 10, 2009.

Chanan-Khan et al. Blood 106(11): Abstract 447, 2005.

Cheson, BD: Ofatumumab, a novel anti-CD20 monoclonal antibody for the treatment of B-cell malignancies. J Clin Oncol 28:3525-3530, 2010.

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic co-morbidity in longitudinal studies: development and validation. J Chronic Dis 40(5):373-383, 1987.

Ferrajoli A, Keating MJ, O'Brien S, Cortes J, Thomas DA. Experience with rituximab immunotherapy as an early intervention in patients with Rai stage 0 to II chronic lymphocytic leukemia. Cancer, e-Pub 1/2011.

Ferracin M, Zagatti B, Rizzotto L, Cavazzini F, Veronese A, Ciccone M, Saccenti E, Lupini L, Grilli A, De Angeli C, Negrini M, Cuneo A. MicroRNAs involvement in fludarabine refractory chronic lymphocytic leukemia. Mol Cancer, 9:123, 2010.

Ferrajoli A, O'Brien S., Wierda W, Lerner S, Faderl S, Kantarjian H, Keating MJ. Treatment of patients with CLL 70 years old and older: A single center experience of 142 patients. Leuk & Lymph 46 (Suppl.1):S86, 2005.

Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 376(9747):1164-1174, 2010.

Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol 23:4079-4088, 2005.

Liu CG, Calin GA, Volinia S and Croce CM. MicroRNA expression profiling using microarrays. Nature Protocols 3:563-578, 2008.

Liu CG, Calin GA, Meloon B, Gamliel N, Sevignani C, Ferracin M, Dumitru CD,Shimizu M, Zupo S, Dono M, et al. An oligonucleotide microchip for genome-wide microRNA profiling in human and mouse tissues. Proc Natl Acad Sci U.S.A. 101, 9740-9744, 2004.

Moussay E, Wang K, Cho JH, van Moer K, Pierson S, Paggetti J, Nazrov PV, Palissot V, Hood LE, Berchem G, Galas DJ. MicroRNA as biomarkers and regulators in B-cell chronic lymphocytic leukemia. Proc Natl Acad Sci U.S.A. 108(16): 6573-6578, 2011.

Rossi S, Shimizu M, Barbarotto E, Nicoloso MS, Dimitri F, Sampath D, Fabbri M, Lerner S, et al. A microRNA fingerprinting of CLL patients with chromosome 17p deletion identify a miR-21 score that stratifies early survival. Blood 116:945-952, 2010.

Teeling JL, Mackus WJM, Wiegman LJJM, van den Brakel JHN, Beers SA, French RR, van Meerten T, Ebeling S, Vink T, Slootstra JW, Parren PWHI, Glennie MJ, van de Winkel JGJ. The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. J Immunol 177:362-371, 2006.

Teeling JL, French RR, Cragg MS, van den Brakel J, Pluyter M, Huang H, Chan C, Parren P, Hack CE, Dechant M, Valerius T, van de Winkel JJ and Glennie MJ. Characterization of new human CD20 monoclonal antibodies with potent cytolytic activity against non-Hodgkin lymphomas. Blood 104(6):1793-1800, 2004

Vasilescu C, Rossi S, Shimizu M, Tudor S, Veronese A, Ferracin M, Nicoloso MS, Barbarotto, E, Popa M, et al. MicroRNA fingerprints identify miR-150 as a plasmaprognostic marker in patients with sepsis. PLoS ONE 4, e7405, 2009.

Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, Visone R, Lorio M, Roldo C, Ferracin M, et al. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci U.S.A. 103:2257-2261, 2006.

Yanaihara N, Caplen N, Bowman E, Kumamoto K, Okamoto A, Yokota J, Tanaka T, Calin GA, Liu CG, Croce CM, et al. A microRNA signature in lung cancer diagnosis and prognosis. Cancer Cell 9:189-198, 2006.

Flinn IW, Harwin WN, Ward P, Doss HH, Papish SW, Hainsworth JD, Berdeja JG, Byrd JC. Phase II Trial of Ofatumumab (OFA) for older Patients and Patients who refuse Fludarabine-Based Regimens with Previously untreated Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL). Blood 120(21), 2012.