THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

Lirilumab (anti-KIR mAb) Combined with Rituximab for Relapsed, Refractory or High-risk Untreated Patients with Chronic Lymphocytic Leukemia (CLL)
2014-0933

Core Protocol Information

Study Chairman:	Nitin Jain
Department:	Leukemia
Phone:	713-745-6080
Unit:	428
Full Title:	Lirilumab (anti-KIR mAb) Combined with Rituximab for Relapsed, Refractory or High-risk Untreated Patients with Chronic Lymphocytic Leukemia (CLL)
Protocol Phase:	Phase II
Version Status:	Terminated 08/15/2019
Version:	07
Document Status:	Final

Abstract

Objectives:

Primary Objectives
1. To determine the efficacy (response rate) of combined lirilumab and rituximab in patients with high-risk CLL as follows:
   a. Cohort 1: refractory to and/or relapsed after at least one prior therapy OR
   b. Cohort 2: untreated patients with high-risk molecular features such as del(17p), mutated *TP53*, del(11q), unmutated *IGHV* gene, or are >65 years of age

Secondary Objectives
1. To determine the safety of lirilumab combined with rituximab in patients with high-risk CLL.
2. To determine the progression-free survival of patients with high-risk CLL treated with lirilumab combined with rituximab.
3. To determine the overall survival of patients with high-risk CLL treated with lirilumab combined with rituximab.

Exploratory Objectives
1. To study immunological and molecular changes in the peripheral blood and bone marrow in response to lirilumab and rituximab therapy.

Rationale: (Be as concise as possible)

Chronic lymphocytic leukemia (CLL): CLL is the most common leukemia in the United States and Western hemisphere.1 It is a disease of the aging population; the median age at diagnosis is 72 and over two-thirds of patients with CLL are over 60 years of age. Both the incidence and prevalence of this disease increase with age. The natural history for individuals with this disease is diverse. Generally, patients with early Rai stage (stage 0, low-risk) have a median expected survival of more than 10 years. Those with evidence of marrow failure manifested by anemia (stage III) or thrombocytopenia (stage IV) (Rai high-risk) have an estimated median survival of only 2 years. In patients with intermediate-risk disease (Rai stage I and II) the estimated median survival is 7 years. There is remarkable clinical diversity in patients with CLL. Following diagnosis, some patients have smoldering, asymptomatic disease that may not progress for many years; others are diagnosed with advanced stage, or early stage disease that rapidly progresses, causing symptoms and/or bone marrow failure and require treatment. Various genetic/molecular markers have been established and validated to help in prognostication and are routinely used in clinical practice. These include b2-microglobulin, cytogenetics, immunoglobulin variable heavy chain gene (*IGHV*) mutational status, zeta chain-associated protein 70 (ZAP-70) expression, and CD38 expression. Presence of deletion 17p (and/or mutated *TP53)* [del(17p)] or deletion 11q [del(11q)] demonstrated by FISH as well as unmutated *IGHV* are associated with inferior clinical outcomes in patients with CLL and considered high-risk disease features. Patients with relapsed/refractory CLL constitute another group of patients with poor prognosis.

Lirilumab: Lirilumab (BMS-986015, IPH2102) is a fully human IgG4 monoclonal antibody (mAb) that is specific for a subset of human KIRs. Lirilumab is a mAb that blocks the KIR/HLA interaction, and lowers the threshold for activation of NK cells without directly activating NK cells. Lirilumab binds specifically and with high affinity to a subset of KIR, namely KIR2DL-1, 2, and 3 and KIR2DS-1 and 2, thus preventing interaction between KIR and HLA-C. Lirilumab also is being developed in combination with the T-cell checkpoint inhibitors, ipilimumab and nivolumab. Nonclinical studies combining anti-Ly49 (5E6 F(ab')2), the murine functional homolog of lirilumab, with the mAbs specific for the murine versions of either cytotoxic T-lymphocyte antigen 4 (CTLA-4) or programmed cell death 1 (PD-1) demonstrated enhanced anti-tumor efficacy. Lirilumab does not bind to NK cells from non-human primate or other species traditionally used for safety testing. Safety testing was performed in mice because Ly49C/I, the murine inhibitory receptors, are functionally homologous to human KIR. Mice treated with lirilumab at 10 mg/kg once weekly for 4 weeks, or the surrogate anti-Ly49 (5E6 F(ab')2) at up to 10 mg/kg twice weekly for 13 weeks, showed no signs of toxicity.

Lirilumab is being developed for immunotherapy in patients with various hematologic malignancies and solid tumors.

Rituximab: Rituxan (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen and is used in the treatment of B-NHL and CLL.

Rationale for Combined Lirilumab and Rituximab

Kohrt et al recently reported the activity of lirilumab in a KIR2DL3 transgenic lymphoma model and of anti-Ly49C/I F(ab')$_2$ in a C57BL/6 syngeneic lymphoma model.[28] In both the models tested, combination of lirilumab with an anti-CD20 monoclonal antibody significantly improved the antitumor efficacy than anti-CD20 monoclonal antibody alone. They reported that anti-Ly49C/I F(ab')$_2$ increased anti-CD20 mAb-mediated NK-cell degranulation and cytotoxicity and potentiated the antilymphoma activity of anti-CD20 mAb in vivo. They also reported that NK cells are required for the antilymphoma activity of the combination treatment. NK-cell depletion, and not macrophage, CD4, or CD8 T-cell depletion, abrogated the therapeutic efficacy of anti-CD20 mAb and anti-Ly49C/I F(ab')$_2$ combination therapy. These findings provide rationale for a clinical trial in B cell malignancies investigating this novel combination of an anti-KIR mAb to tilt the balance of inhibitory and stimulatory NK signals favoring spontaneous cytotoxicity and to further enhance the efficacy of rituximab by the augmentation of ADCC.

We hypothesize that enhanced CLL cell killing and improved clinical responses will be mediated by rituximab by the addition of the anti-KIR monoclonal antibody (lirilumab). The rationale for combining anti-KIR antibody and rituximab include 1) Rituximab induces both NK cell activation (via Fc-FcR engagement). Addition of anti-KIR antibody further enhances NK-cell mediated ADCC. The use of rituximab and anti-KIR antibody has been shown to be synergistic *in vitro* and *in vivo*. 2) Tumor debulking with CD20 monoclonal antibody may synergize or augment the activity of anti-KIR monoclonal antibody 3) Lirilumab and rituximab have non-overlapping and complimentary mechanisms of action and thus may synergize, with no notable increased risk for toxicity. We plan to include patients with relapsed or refractory CLL. In addition, untreated patients with high-risk cytogenetic features such as del(17p), mutated *TP53,* del(11q), unmutated *IGHV*, or are >65 years will be eligible as they have poor outcomes and short progression-free survival with chemoimmunotherapy.

Eligibility: (List All Criteria)

Inclusion:

1) Patients will have a diagnosis of CLL or SLL who meet one or more criteria for active disease as defined by the International Working Group for CLL (IWCLL) and are: a. Cohort 1: refractory to and/or relapsed after at least one prior therapy OR b. Cohort 2: untreated patients with high-risk molecular features such as del(17p), mutated TP53, del(11q), unmutated IGHV gene, or are >65 years of age

2) Age 18 years or older

3) Eastern Cooperative Oncology Group (ECOG) Performance Status </=2

4) Patients must have adequate renal and hepatic function: Serum bilirubin </=1.5 x upper limit of normal (ULN). For patients with Gilbert's disease, serum bilirubin up to </=3 x ULN is allowed provided normal direct bilirubin; Serum creatinine ·1.5 x ULN; ALT and AST </=3 x ULN

5) Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotrophin (Beta-hCG) pregnancy test result within 24 hours prior to the first dose of treatment and must agree to use an effective contraception method during the study and for 12 months following the last dose of the study drugs. Females of non- childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy. Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 31 weeks following the last dose of study drugs.

6) Patients or their legally authorized representative must provide written informed consent.

Exclusion:

1) Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, or localized prostate cancer. If patients have another malignancy that was treated within the last 2 years, such patients may be enrolled if the likelihood of requiring systemic therapy for this other malignancy within 2 years is less than 10%, as determined by an expert in that particular malignancy at MD Anderson Cancer Center and after consultation with the Principal Investigator.

2) Any major surgery, radiotherapy, chemotherapy, biologic therapy, immunotherapy, experimental therapy within 4 weeks prior to the first dose of the study drugs. For oral targeted therapies (such as ibrutinib, idelalisib, venetoclax), a washout of 3 days is allowed. Note: Prior treatment with anti CD20 monoclonal antibody, anti CD52 monoclonal antibody and lenalidomide are allowed. Prior treatment with anti-CTLA-4 and anti-PD1 therapies is allowed after a wash-out of 5 half-lives.

3) Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 2 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.

4) History of stroke or cerebral hemorrhage within 2 months.

5) Patients who have uncontrolled hypertension (defined as sustained systolic blood pressure >/= 160 mmHg or diastolic >/= 100 mmHg).

6) Known evidence of active cerebral/meningeal CLL. Patients may have history of CNS leukemic involvement if definitively treated with prior therapy and no evidence of active disease at the time of registration.

7) Active, uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia requiring steroid therapy.

8) Patients with autoimmune diseases are excluded: Patients with a history of Inflammatory Bowel Disease (including Crohn’s disease and ulcerative colitis) are excluded from this study as are patients with a history of autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis, systemic lupus erythematosus, Wegener’s granulomatosis).

9) Patients with previous allogeneic stem cell transplant (SCT) within 6 months or with active acute or chronic graft-versus host disease are excluded. Patients must be off immunosuppression for GVHD for at least 60 days before Cycle 1 Day 1.

10) Patients with organ allografts (such as renal transplant) are excluded.

11) History of any hepatitis (e.g., alcohol or non-alcohol steatohepatitis (NASH), auto immune, or grade 3-4 drug-related hepatitis).

12) Patients who are on high-dose steroids (doses >10mg/day of prednisone or equivalent) or immune suppression medications. Note: Patients on high-dose steroids (doses >10mg/day of prednisone or equivalent) or immune suppression medications are eligible provided these drugs are discontinued at least 3 days prior to starting on the study drugs.

13) Patients with uncontrolled active infection (viral, bacterial, and fungal) are not eligible.

14) Current or chronic hepatitis B or C infection, or known seropositivity for HIV.

15) Patient is pregnant or breast-feeding.

16) Concurrent use of investigational therapeutic agent

17) Patients may not receive other concurrent chemotherapy, radiotherapy, or immunotherapy. Localized radiotherapy to an area not compromising bone marrow function does not apply.

18) Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that in the opinion of the investigator may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and/or would make the patient inappropriate for enrollment into this study.

Are patients <18 years of age eligible to participate in this study? ○ **Yes** ● **No**

Studies that include children must meet the criteria for inclusion.
http://www.fda.gov/ohrms/dockets/AC/04/briefing/4028B1_05_NIH-Inclusion%20of%20Children.doc
http://www.hhs.gov/ohrp/policy/populations/children.html

Studies that exclude children must have appropriate justification. Please select all that apply:

Phase I or Phase II study targeting cancer that is very unusual in pediatrics (e.g., prostate, lung, breast, chronic lymphocytic leukemia, etc.)

Are participants >65 years of age eligible to participate in this study? ● **Yes** ○ **No**

Are pregnant women eligible to participate in this study? ○ **Yes** ● **No**

Will the recruitment population at M. D. Anderson include persons who are incarcerated at time of enrollment (e.g., prisoners) or likely to become incarcerated during the study?
○ **Yes** ● **No**

Disease Group:

Leukemia

Treatment Agents/Devices/Interventions:

Lirilumab, Rituximab

Proposed Treatment/Study Plan:

Is treatment assignment randomized? ○ **Yes** ● **No**

Is this a blinded or double-blinded study? ○ **Yes** ● **No**

PRETREATMENT EVALUATIONS AND EVALUATIONS DURING THE STUDY

Schedule of Evaluations 11-05-2015.pdf

TREATMENT PLAN

Study Design

This is a phase II open label single-arm study to evaluate combined lirilumab and rituximab in patients with CLL.

	C1D1	C1D8 (±2 days)	C1D15 (±2 days)	C1D22 (±2 days)	C2-C12 D1 (±7 days)	C13-C24 D1 (±7 days)
Rituximab	375 mg/m2	375 mg/m2	375 mg/m2	375 mg/m2	375 mg/m2	–
Lirilumab	3 mg/kg	_	_	_	3 mg/kg	3 mg/kg

Each cycle is 4 weeks. Patients will receive rituximab (375 mg/m2 IV) weekly for the first 4 weeks (Days 1, 8, 15, 22), and then with the start of each course. Lirilumab (3 mg/kg IV) will be given on day 1 of each cycle. Rituximab will be given for the first 12 cycles and lirilumab will continue for up to 24 cycles.

Study Medications

Lirilumab

Preparation and Dispensing of Lirilumab

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Investigator Brochure. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g. required diluents, administration sets).

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. The study drug should be administered shortly after preparation in order to avoid exposure of the prepared drug to room temperature conditions beyond a recommended 4 hour limit. This 4 hour time limit at room temperature includes the time allotted for IV dose administration, which is 60 min. In the event that a delay in use of prepared (diluted) study drug is anticipated, prepared bags may be refrigerated for a maximum of 20 hours. Study drug is to be administered as IV infusion and not IV push or bolus injection.

Lirulumab must be stored at a temperature of 2°C to 8°C and should be protected from light and from freezing. For details on prepared drug storage and use time of lirulumab under room temperature/ light and refrigeration, please refer to the Investigator Brochure.

Rituximab
Rituximab is anti-CD20 monoclonal antibody. Commercial drug supply will be used for this study. Rituximab will be administered as per the institutional guidelines.

DOSE DELAYS AND MODIFICATIONS

Patients who experience Grade 3 or 4 toxicity that can be clearly attributed to either lirilumab or to rituximab may continue treatment with the other agent while the causative agent is delayed until resolution of toxicity to grade </= 1 or baseline. In cases where Grade 3 or 4 toxicity cannot be attributed to a specific study drug, both study drugs should be held regardless of attribution of toxicity until the toxicity is resolved to grade </= 1 or baseline.

Rituximab and lirilumab administration should be delayed and increased monitoring of subjects should ensue if any of the following drug-related adverse event(s) occurs:

- Any Grade >/= 2 ALT, AST, or total bilirubin
- Any Grade >/= 2 non laboratory non-skin drug related adverse event except for fatigue
- Any Grade >/= 2 endocrine drug-related adverse event
- Any Grade >/= 3 skin drug related adverse event
- Any Grade >/= 3 drug-related laboratory abnormality (except lymphopenia or any electrolyte abnormality without any clinical sequelae that is either spontaneously reversible or resolves with clinical management to grade 2 or less within 72 hours)
- Any AE, laboratory abnormality or inter-current illness, which in the judgment of the investigator, warrants delaying the dose of study medication

Discontinuation of lirilumab will occur in the following situations:

- AST, ALT, or T Bili >/= Grade 3
- Grade 2 AST or ALT and symptomatic liver inflammation (e.g., right upper quadrant tenderness, jaundice)
- AST or ALT > 3 x ULN and concurrent total bilirubin > 2 x ULN in the absence of evidence of cholestasis (Hy's law)

CRITERIA FOR RESPONSE

Response will be assessed by the investigator, based on physical examinations, CT scans, laboratory results, and bone marrow examinations, based on the 2008 IWCLL criteria for response for CLL. Overall response (OR) includes complete remission (CR), CR with incomplete marrow recovery (CRi) or partial remission (PR) as determined by investigator assessment using CLL response criteria. Minimal residual disease (MRD) will be assessed in bone marrow by multi-color flow cytometry. Patients with missing or no response assessments will be classified as non-responders by intent to treat analysis.

Study Enrollment:
The study population for this research will consist of participants from:

Only at MDACC

Estimated Accrual:

Total Accrual at MDACC:	48
Estimated monthly accrual at MDACC:	1-2

Accrual Comments:

This study will enroll 48 patients into two cohorts. Cohort 1 will enroll up to 24 CLL patients who are refractory to or have relapsed after at least one prior therapy; cohort 2 will enroll up to 24 untreated CLL patients with high-risk molecular features such as del(17p), mutated TP53, del(11q), unmutated IGHV gene, or are >65 years of age

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Statistical Considerations:

A maximum of 48 patients will be enrolled in this Phase II study. Cohort 1 will enroll up to 24 CLL patients who are refractory to or have relapsed after at least one prior therapy; cohort 2 will enroll up to 24 untreated CLL patients with high-risk molecular features such as del(17p), mutated *TP53*, del(11q), unmutated *IGHV* gene, or are >65 years of age. The primary objective is to evaluate overall response (OR) during the first 6 months of therapy. The primary efficacy endpoint, overall response (OR), is defined as CR, CRi or PR that occurs during the first 6 months of therapy.

EFFICACY

For cohort 1, the target overall response rate is 30%. The Bayesian approach of Thall, Simon, Estey will be implemented for the futility monitoring. The following futility stopping rule will be applied in cohort size of 3, starting from the 9th patient: prob{p(OR)> 0.3) < 0.05, where p(OR) denotes the overall response rate. That is, the trial will be stopped early due to futility, if during the study we determine that there is less than 5% chance that the OR is more than 30%. Assuming that the prior distribution of p(OR) is beta (0.6, 1.4), the stopping boundaries corresponding to this futility monitoring rule are shown below in Table 14.1. The operating characteristics (OCs) for this futility stopping rule are summarized in Table 14.2.

Table 14.1. Futility stopping boundaries for cohort 1, in cohort size of 3.

Number of patients	Stop the trial if there are this many patients achieving OR
9	0
12-15	0-1
18	0-2
21	0-3

Table 14.2. Operating characteristics for the monitoring of OR rate in cohort 1.

True OR Rate	Early Stopping Probability	Average number of patients treated
0.1	0.88	13.8
0.2	0.45	19.4
0.3	0.14	22.6
0.4	0.03	23.7
0.5	0.005	23.9

For cohort 2, the OR rate is ~30% with Rituximab and we target to reach an OR rate of 50%

with the combination therapy. The same Bayesian approach of Thall, Simon, Estey will be implemented for the futility monitoring. The following futility stopping rule will be applied in cohort size of 3, starting from the 9th patient: prob{p(OR)> 0.3+delta) < 0.05, where p(OR) denotes the response rate and delta=0.2. That is, the trial will be stopped early due to futility, if during the study we determine that there is less than 5% chance that the OR rate with the combination therapy will improve from 30% (Rituximab alone) to 50%. Assuming that the prior distribution of p(OR) is beta (0.6, 1.4), the stopping boundaries corresponding to this futility monitoring rule are shown below in Table 14.3. The operating characteristics (OCs) for this futility stopping rule are summarized in Table 14.4.

Table 14.3. Futility stopping boundaries, in cohort size of 3, for cohort 2.

Number of patients	Stop the trial if there are this many patients achieving OR
9	0-2
12	0-3
15	0-4
18	0-5
21	0-7

Table 14.4. Operating characteristics for monitoring of OR rate in cohort 2.

True OR Rate	Early Stopping Probability	Average number of patients treated
0.2	0.97	11.0
0.3	0.78	14.8
0.4	0.44	19.1
0.5	0.16	22.2
0.6	0.04	23.5
0.7	0.005	23.9

TOXICITY

The Bayesian approach of Thall, Simon, Estey will be implemented for toxicity monitoring for patients enrolled in cohorts 1 and 2, where toxicity is defined as any grade 3 or higher non-hematological toxicity which is at least possibly related to the treatment. The toxicity, denoted as TOX will be monitored by the Bayesian stopping boundaries calculated based on beta-binomial distributions. We assume as a priori, p(TOX) ~ beta (0.6, 1.4). The study will be stopped for toxicity if Pr(p(TOX)> 0.30 | data) >0.92. That is, we will stop the trial for new patient enrollment if at any time during the study we determine that there is more than 92% chance that the toxicity rate is more than 30%. The toxicity monitoring rule will be applied starting from the 6th patient, and then in cohort size of 6. The toxicity will be considered continuously throughout the study treatment duration. Stopping boundaries corresponding to this toxicity monitoring rule are shown in Table 14.5 below. The operating characteristics for toxicity monitoring are summarized in Table 14.6.

Table 14.5. Toxicity stopping boundaries in cohort size of 6 for patients enrolled in cohorts 1 and 2.

Number of patients	Stop the trial if there are this

	many patients having toxicity
6	4-6
12	7-12
18	9-18
24	11-24
30	13-30
36	15-36
42	18-42

Table 14.6. Operating characteristics for toxicity monitoring.

True Toxicity Rate	Early Stopping Probability	Average number of patients treated
0.1	0.001	47.9
0.2	0.02	47.1
0.3	0.19	42.3
0.4	0.61	30.5
0.5	0.93	18.2

ANALYSIS PLAN

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. The overall response (OR) rate will be estimated along with the 95% credible interval.

Data from all patients who receive any study drug will be included in the safety analyses. Patients who entered the study and did not take any of the study drugs and had this confirmed will not be evaluated for safety. The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency. The proportion of patients with AEs will be estimated, along with the Bayesian 95% credible interval. Kaplan-Meier method will be used to assess the overall survival (OS) and progression-free survival (PFS) probabilities. The change of biomarkers over time will be assessed through fitting linear or non-linear mixed effect models.

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and wellbeing of the patient requires immediate intervention, based on the judgment of the investigator or his/her designee. In the event of a significant deviation from the protocol, the investigator will notify the MDACC surveillance committee following the institutional guidelines.

Statistical Language for the correlative studies: Descriptive statistics including plots, mean, median and standard deviations will be used to summarize data. For continuous outcomes, t-test and ANOVA will be used to compare outcome measures across patient characteristics. Dunnett's and Tukey's test that properly adjust for multiplicity in multiple tests will be implemented. Pair-wise comparisons will be performed using pre- and post-therapy samples from each patient. The chi-square (c2) test or Fisher's exact test will be used to test the association between two categorical variables such as disease state and performance status. Both univariate and multivariate logistic regressions will be performed to model prognostic factors.

Data Safety Monitoring Board / DSMB at MDACC:

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:
Not Applicable

Please explain:
This is a Phase II study that is not randomized and not blinded.

Protocol Monitoring:

Does this protocol have a schedule for interim and final analysis? No

Provide a rationale for no interim analysis.

This is an exploratory study.

Protocol Monitoring Plan:

This study will be monitored by the MD Anderson IND Office and a protocol-specific monitoring plan will be followed.

Intellectual Property:

1.	Does this study include any agents, devices, or radioactive compound (or drug) manufactured at MD Anderson Cancer Center or by a contract manufacturer?	No

Investigational New Drugs (IND):

Does this protocol require an IND? Yes

Who is the IND Holder/Regulatory Sponsor?
MD Anderson Cancer Center
IND Number: 125496

Please "Compose" an Investigator's Brochure Cover Letter. For technical assistance, contact the PDOL Help Desk, 713-745-7365.

Investigational Device (IDE):

Does this study utilize an Investigational Device? N/A

Sponsorship and Support Information:

Does the Study have a Sponsor, Supporter or Granting Agency? Yes

Sponsor Name: Bristol Myers Squibb
Support Type: Agent Name(s): Lirilumab

This Sponsor/Supporter/Granting Agency will not receive data.

Radioactive Material:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent? Click here for help	N/A

Biosafety:

Does this study involve the use of Recombinant DNA Technology?	No
Does this study involve the use of organisms that are infectious to humans?	No
Does this study involve human/animal tissue other than blood derived hematopoietic stem cells?	No

Questions should be addressed to the Transfusion Medicine Tissue Coordinator at 713-792-8630.

Laboratory Tests:

Is there any biomarker testing in this study being used to determine patient/participant eligibility, treatment assignment, or management of patient/participant care?

- ○ Yes
- ● No
- ○ Not Applicable For This Protocol

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study?	No

Student/Trainee Information:

Is this research being conducted as a partial fulfillment for completion of a degree?	No

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Protocol Page

Lirilumab (anti-KIR mAb) Combined with Rituximab for Relapsed, Refractory or High-risk Untreated Patients with Chronic Lymphocytic Leukemia (CLL)
2014-0933

Core Protocol Information

Short Title	Lirilumab with Rituximab for Relapsed, Refractory or High-risk Untreated CLL Patients
Study Chair:	Nitin Jain
Additional Contact:	Jeannice Y. Theriot William G. Wierda Leukemia Protocol Review Group
Department:	Leukemia
Phone:	713-745-6080
Unit:	428
Full Title:	Lirilumab (anti-KIR mAb) Combined with Rituximab for Relapsed, Refractory or High-risk Untreated Patients with Chronic Lymphocytic Leukemia (CLL)
Protocol Type:	Standard Protocol
Protocol Phase:	Phase II
Version Status:	Terminated 08/15/2019
Version:	07
Submitted by:	Jeannice Y. Theriot--3/15/2016 8:00:48 AM
OPR Action:	Accepted by: Panna B. Shah -- 3/21/2016 11:10:47 AM

Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

Lirilumab and Rituximab in CLL Protocol V2 (2014-0933) 05NOV2015.pdf

Lirilumab (anti-KIR mAb) Combined with Rituximab for Relapsed, Refractory or High-risk Untreated Patients with Chronic Lymphocytic Leukemia (CLL)

Nitin Jain, MD, William Wierda, MD, PhD
Department of Leukemia
MD Anderson Cancer Center

1.0 OBJECTIVES

Primary Objectives

1. To determine the efficacy (response rate) of combined lirilumab and rituximab in patients with high-risk CLL as follows:
   a. Cohort 1: refractory to and/or relapsed after at least one prior therapy OR
   b. Cohort 2: untreated patients with high-risk molecular features such as del(17p), mutated *TP53*, del(11q), unmutated *IGHV* gene, or are >65 years of age

Secondary Objectives

1. To determine the safety of lirilumab combined with rituximab in patients with high-risk CLL.
2. To determine the progression-free survival of patients with high-risk CLL treated with lirilumab combined with rituximab.
3. To determine the overall survival of patients with high-risk CLL treated with lirilumab combined with rituximab.

Exploratory Objectives

1. To study immunological and molecular changes in the peripheral blood and bone marrow in response to lirilumab and rituximab therapy.

2.0 BACKGROUND

2.1 Chronic lymphocytic leukemia (CLL): CLL is the most common leukemia in the United States and Western hemisphere.[1] It is a disease of the aging population; the median age at diagnosis is 72 and over two-thirds of patients with CLL are over 60 years of age. Both the incidence and prevalence of this disease increase with age. The natural history for individuals with this disease is diverse. Generally, patients with early Rai stage (stage 0, low-risk) have a median expected survival of more than 10 years. Those with evidence of marrow failure manifested by anemia (stage III) or thrombocytopenia (stage IV) (Rai high-risk) have an estimated median survival of only 2 years. In patients with intermediate-risk disease (Rai stage I and II) the estimated median survival is 7 years. There is remarkable clinical diversity in patients with CLL. Following diagnosis, some patients have smoldering, asymptomatic disease that may not progress for many years; others are diagnosed with advanced stage, or early stage disease that rapidly progresses, causing symptoms and/or bone marrow failure and require treatment. Various genetic/molecular markers have been

established and validated to help in prognostication and are routinely used in clinical practice.[1] These include β2-microglobulin, cytogenetics, immunoglobulin variable heavy chain gene (*IGHV*) mutational status, zeta chain-associated protein 70 (ZAP-70) expression, and CD38 expression. Presence of deletion 17p (and/or mutated *TP53)* [del(17p)] or deletion 11q [del(11q)] demonstrated by FISH as well as unmutated *IGHV* are associated with inferior clinical outcomes in patients with CLL and considered high-risk disease features.[2-4] Patients with relapsed/refractory CLL constitute another group of patients with poor prognosis.[1,5]

2.2 Immunotherapy in CLL: Immunotherapy has been an important part of CLL therapeutic armamentarium. Several strategies have been employed: a) use of monoclonal antibodies (mAb) such as anti-CD20 mAb (rituximab, ofatumumab, obinutuzumab) and anti-CD52 mAb (alemtuzumab)[6,7]; b) use of lenalidomide[8-10]; c) adoptive immunotherapy with an allogeneic stem cell transplant[11]; d) use of chimeric antigen receptor (CAR).[12] These studies highlight the fact CLL cells are amenable to immune-based therapies.

2.3 T cell dysfunction in CLL: Several studies have shown that CLL development and progression is associated with functional immune-defects in the T cell compartment.[7,9,10,13-17] Ramsay et al. showed that T cells isolated from patients with CLL have functional defects in F-actin polymerization leading to impaired formation of immunological synapses with antigen presenting cells (APCs).[9] Riches et al. reported that T cells from patients with CLL exhibit features of T cell exhaustion, which results in progressive loss of T cell proliferative and cytotoxicity capacity.[10] Motta et al. reported increased expression of both surface and cytoplasmic cytotoxic T lymphocyte-associated antigen (CTLA-4, also known as CD152) in both CD4+ and CD8+ T cells from treatment naïve patients with CLL compared to normal donors.[14] Riches et al. recently reported increased expression of programmed death-1 (PD-1, also known as CD279) receptor in T cells of patients with CLL.[10] They also reported that PD-1 is preferentially expressed on $CD3^{+}CD8^{+}CCR7^{-}$ effector T cells. Unlike CTLA-4 whose predominant role is at the time of T cell activation, PD-1 predominantly regulates effector T cell function in the peripheral tissues.[18-20] PD-L1 (ligand for PD-1) is also over expressed in the CLL B cells.[13] The increased expression of CTLA-4 and PD-1 on T cells of patients with CLL and PD-L1 on the CLL cells contributes to impaired T cell function.

2.4 Natural killer (NK)-cell function in CLL: NK cells constitute 15% of peripheral blood lymphocytes and play an important role in the ability of the innate immune system to fight off viral infections and also cancer.[21] NK cells bind to target cells through multiple receptors and binding of ligand to receptor results in activation of the NK cell, release of preformed granules containing perforin and granzymes into the target cell, and apoptosis. The activation of NK cells is regulated by a variety of activating and inhibitory receptors that are expressed by the transformed target cells. Activating receptors include NKp30, NKp44, NKp46, NKG2D, and DNAM-1. For effective activation of NK-cells tumor cells must express stress or activation ligands for activating receptors. Negative regulators of NK activating receptors include killer Ig-like receptor (KIR), CD94/NKG2A, and leukocyte Ig-like receptor-1, which recognize MHC-class 1 molecules. NK cells have the capability of binding every

cell in the body. Binding of normal cells does not result in cytotoxic activity because of the ability of NK cells to simultaneously utilize a different set of receptors to bind major histocompatibility complex (MHC) class I molecules. Binding to HLA is used as a mechanism to distinguish self from non-self, and this recognition controls the activation state of NK cells. Thus, KIR/HLA interaction directly impacts NK cell responsiveness. There are both inhibitory and activating KIR, which is one factor that results in diversity of KIR inheritance and expression. KIR is also expressed on NK cells and a small subset of T cells. Thus, mechanistically, blockade of inhibitory KIR could induce anti-tumor effects by allowing for NK cell (and possibly some T cell) activation.

Lack of KIR-HLA class I interactions have been associated with potent NK-mediated antitumor efficacy and increased survival in AML patients undergoing haploidentical stem cell transplantation from KIR-mismatched donors.[22] Romagne et al. developed a monoclonal antibody that cross-reacts with KIRDL1, -2 and -3 receptors thereby blocking inhibitory signaling via these receptors. This resulted in augmented NK cell mediated lysis of tumor cells but did not induce killing of normal peripheral blood mononuclear cells, suggesting a preferential NK cell activity against AML cells.[23] Intriguingly inoculation of NK cells alone did not protect against autologous implanted AML in immunodeficient mice, however preadministration with KIR monoclonal antibody induced anti-AML activity with long-term survival.

Several studies have reported that the cytotoxic function of NK cells in patients with CLL is defective.[24-27] Palmer et al. evaluated peripheral blood T cell and NK cell at diagnosis in 166 consecutive patients with newly diagnosed CLL treated at Mayo clinic.[27] They reported at 45% of the patients with CLL had an increase in the absolute NK cell number (upper limit of normal 0.6 x 10^9/l) at diagnosis. Similarly, 54% of the patients with CLL had an increase in the absolute T cell number (upper limit of normal 2.0 x 10^9/l) at diagnosis. This observational cohort study found wide inter-patient variation in size of the normal T cell and NK cell compartment at the time of diagnosis. It was found that smaller size of the blood T/NK cell compartments relative to the size of the circulating leukemic B-cell clone was associated with more advanced stage at diagnosis as well as unmutated *IGHV* status, raising the possibility that CLL patients with greater host immunity may experience a more indolent disease course. Both the ratio of NK:MBC (monoclonal B cell) and T:MBC correlated with time to first treatment.[27] Huergo-Zapico et al. evaluated NK cells in the peripheral blood at diagnosis in a group of 99 patients with CLL and 50 healthy matched controls.[24] Patients with CLL had significantly higher NK cell number than controls. They also reported that compared to controls, NK2GD receptor expression on NK cells was markedly decreased in patients with CLL. CD107a degranulation assay showed that NK cells of patients with CLL had diminished cytotoxic activity compared with healthy controls.[24]

2.5 Lirilumab: Lirilumab (BMS-986015, IPH2102) is a fully human IgG4 monoclonal antibody (mAb) that is specific for a subset of human KIRs. Lirilumab is a mAb that blocks the KIR/HLA interaction, and lowers the threshold for activation of NK cells without directly activating NK cells. Lirilumab binds specifically and with high affinity to a subset of KIR,

namely KIR2DL-1, 2, and 3 and KIR2DS-1 and 2, thus preventing interaction between KIR and HLA-C. Lirilumab also is being developed in combination with the T-cell checkpoint inhibitors, ipilimumab and nivolumab. Nonclinical studies combining anti-Ly49 (5E6 F(ab')2), the murine functional homolog of lirilumab, with the mAbs specific for the murine versions of either cytotoxic T-lymphocyte antigen 4 (CTLA-4) or programmed cell death 1 (PD-1) demonstrated enhanced anti-tumor efficacy. Lirilumab does not bind to NK cells from non-human primate or other species traditionally used for safety testing. Safety testing was performed in mice because Ly49C/I, the murine inhibitory receptors, are functionally homologous to human KIR. Mice treated with lirilumab at 10 mg/kg once weekly for 4 weeks, or the surrogate anti-Ly49 (5E6 F(ab')2) at up to 10 mg/kg twice weekly for 13 weeks, showed no signs of toxicity.

Lirilumab is being developed for immunotherapy in patients with various hematologic malignancies and solid tumors. As of the data cut-off for this IB (29-Jul-2014), 293 subjects have been treated in 1 concluded and 3 ongoing trials: 1 monotherapy Phase 1 trial, 1 monotherapy placebo-controlled Phase 2 trial, and 2 combination therapy Phase 1 trials. Thirty-seven subjects received lirilumab monotherapy in a Phase 1 trial for patients with advanced solid tumors and hematological malignancies (IPH2102-101). One hundred fifty subjects received either lirilumab or placebo in a 2:1 ratio in a Phase 2 trial for patients with AML (IPH2102-201). IPH2102-201 is a double blind trial; thus, approximately 100 subjects received lirilumab. Eighty-eight subjects with advanced solid tumors received lirilumab in combination with nivolumab in a Phase 1 trial (CA223001). Eighteen subjects with advanced solid tumors received lirilumab in combination with ipilimumab in a Phase 1 trial (CA223002). As of 29-Jul-2014, the majority of adverse events (AEs) in these 4 ongoing trials were mild or moderate (Grade 1 or 2), self-limiting, and manageable. The most common related AEs were asthenia, fatigue, pruritus, infusion-related reaction, chills, and headache.

The first (IPH2102-101) is a monotherapy, dose escalation, Phase 1 trial to determine the maximum tolerated dose (MTD). As of the data cut-off date (July 29, 2014) a total of 37 patients have receive lirilumab on this trial. Of the 20 subjects treated with lirilumab monotherapy during the dose escalation period of IPH2102-101, 3 subjects were treated with lirilumab 0.015 mg/kg, 3 subjects with 0.3 mg/kg, 4 subjects with 1 mg/kg, 4 subjects with 3 mg/kg, 3 subjects with 6 mg/kg, and 3 subjects with 10 mg/kg every 4 weeks. There were no DLTs, and the MTD was not reached. Of the 17 subjects treated with lirilumab monotherapy during the cohort expansion period of the study, 9 subjects were treated with lirilumab at 0.015 mg/kg and 8 subjects at 3 mg/kg every 4 weeks. A total of 245 AEs were reported by 36 of 37 (97%) exposed subjects. Overall, most of these AEs were mild (CTCAE Grade 1) or moderate (CTCAE Grade 2). For the 18 (48.6%) subjects who discontinued prematurely, reasons for discontinuation were disease progression (13 subjects, related AEs (3 subjects), subject's decision (1 subject), and Sponsor's decision (1 subject). AEs leading to discontinuation included urticaria, hypersensitivity, abnormal liver function test (LFT), increased gamma-glutamyl transferase (GGT), increased blood bilirubin, and papular rash, all considered to be related to study drug by the investigator.

The second (IPH2102-201) is a double-blind, placebo-controlled, Phase 2 trial of lirilumab in patients with AML who are in complete remission but ineligible for allogeneic transplant. One-third of subjects in this study will be receiving placebo. The doses of lirilumab evaluated in this maintenance AML trial were 0.1 mg/kg every 12 weeks and 1.0 mg/kg every 4 weeks. A total of 100 patients have been treated with lirilumab on this trial as of the data cut-off date (July 29, 2014). One hundred one (67%) subjects have treatment ongoing and 50 (33%) subjects discontinued prematurely. In these 50 subjects, the main (or only) reason for study discontinuation was relapse of disease (43 subjects), AEs of pancytopenia (1 subject) and acute febrile neutrophilic dermatosis (1 subject), withdrawal of consent (2 subjects), investigator decision (2 subjects), and suspicion of disease progression (2 subjects). An independent Data and Safety Monitoring Board completed safety analysis of 86 randomized subjects enrolled in this trial. On 11-Mar-2014, the members of this committee recommended continuation of the study without any modification. Adverse events were reported by 121 of 150 (81%) subjects exposed to either lirilumab or placebo. Most of these AEs were mild (Grade 1) or moderate (Grade 2). Thirty-three (22%) subjects reported Grade 3 or Grade 4 AEs (irrespective of causality) including thrombocytopenia in 5 (3%), arthralgia in 1 (<1%), neutropenia in 7 (5%), fatigue in 1 (<1%), weight increase in 2 (1%), and urinary tract infection in 1 (1%) patients. One subject reported Grade 5 pulmonary embolism, and 1 subject reported Grade 5 general physical health deterioration (corresponding to disease progression). Both of the Grade 5 events were considered by the investigator to be unrelated to study drug. Sixty-six of 150 (44%) subjects had AEs considered to be related to the study drug (either lirilumab or placebo). Most related AEs were mild or moderate in severity. Nine (6%) subjects had related Grade 3 AEs (neutropenia in 3 subjects and acute febrile neutrophilic dermatosis, sciatica, myalgia, thrombocytopenia, increased amylase, and bronchospasm in 1 subject each). One subject (0.7%) had a related Grade 4 AE of neutropenia that occurred on Cycle 1/Day 8. Adverse events evaluated as related to study drug and reported in >/= 3% of subjects were asthenia in 15 (10%) subjects, pruritus in 13 (9%) subjects, chills in 7 (5%) subjects, pyrexia in 6 (4%) subjects, and neutropenia in 5 (3%) of subjects. Five (3%) subjects reported AEs that led to study discontinuation: 4 subjects reported single events that were unrelated to study drug (lirilumab or placebo), and 1 subject reported Grade 3 acute febrile neutrophilic dermatosis that was considered related to study drug. Seventeen (11%) subjects reported SAEs during the study. The only Grade 3 or Grade 4 SAE'a (irrespective of causality) seen in more than 1 subject was urinary tract infection in 2 (1%). Only 4 of 20 SAEs were considered to be related to study drug by the investigator, including one case each of Grade 4 neutropenia, Grade 3 myalgia, Grade 3 sciatica, and Grade 3 acute febrile neutrophilic dermatosis.

The third (CA223001) and fourth (CA223002) are Phase 1 trials of lirilumab in combination with either the anti-PD1 antibody nivolumab or the anti-CTLA-4 antibody ipilimumab, respectively, to determine if coordinate modulation of the innate and adaptive immune systems results in greater clinical benefit. A total of 88 subjects have received combination therapy of nivolumab and lirilumab in clinical trial CA223001 as of the data cut-off date (July

29, 2014) including 4 with lirilumab 0.1 mg/kg + nivolumab 3 mg/kg (completed), 13 with lirilumab 0.3 mg/kg + nivolumab 3 mg/kg (ongoing), 9 with lirilumab 1 mg/kg + nivolumab 3 mg/kg, and 62 with lirilumab 3 mg/kg + nivolumab 3 mg/kg. The objective of the study is to evaluate the safety of lirilumab in combination with nivolumab in subjects with advanced refractory solid tumors. Lirilumab 3mg/kg every 4 weeks in combination with nivolumab was well tolerated and was the dose administered to the majority of patients (62 of the 88 patients) on this trial (see lirilumab investigator brochure). As of the data cut-off date (29-Jul-2014), preliminary data include 18 subjects who have been treated with the combination of lirilumab and ipilimumab in clinical trial CA223002. 3 with lirilumab 0.1 mg/kg + ipilimumab 3 mg/kg (completed), 8 with lirilumab 0.3 mg/kg + ipilimumab 3 mg/kg, 6 with lirilumab 1 mg/kg + ipilimumab 3 mg/kg, and 1 with lirilumab 3 mg/kg + ipilimumab 3 mg/kg (ongoing). Two dose levels of ipilimumab (3 mg/kg and 10 mg/kg) and 4 dose levels of lirilumab (0.1, 0.3, 1, and 3 mg/kg) are being evaluated in CA223002, with 3 subjects per dose level if there is no DLT. The 5 dose cohorts are as follows (lirilumab dose + ipilimumab dose): Cohort 1: 0.1 mg/kg + 3 mg/kg; Cohort 2: 0.3 mg/kg + 3 mg/kg; Cohort 3: 1 mg/kg + 3 mg/kg; Cohort 4: 3 mg/kg + 3 mg/kg; Cohort 5: 3 mg/kg + 10 mg/kg. Subjects receive lirilumab in combination with ipilimumab every 3 weeks for a total of 4 doses (induction) and then every 12 weeks for an additional 4 doses starting at Week 24 (maintenance).

Summary of Safety: Mainly safety data are available, efficacy data available only for the IPH2102-101 and no responses observed as of the data cutoff date. As the first clinical trials with lirilumab are ongoing or recently concluded, data on safety presented herein are preliminary and subject to change. Up until 29-Jul-2014, AEs were reported by 36 of 37 (97%) subjects treated with lirilumab monotherapy (doses ranging from 0.015 mg/kg to 10 mg/kg); 121 of 150 (81%) subjects treated with blinded therapy (lirilumab or placebo [2:1]); 63 of 88 (72%) subjects treated with lirilumab 0.1, 0.3, 1, or 3 mg/kg in combination with nivolumab 3 mg/kg; and 17 of 18 (94%) subjects treated with lirilumab 0.1 mg/kg or 0.3 mg/kg in combination with ipilimumab 3 mg/kg. The majority of AEs were mild or moderate (Grades 1 or 2). To date, 12 SAEs were considered to be related to study treatment. Additional detailed safety data is available in the Lirilumab investigator brochure.

Blockade of inhibitory KIR by lirilumab is thus a promising mechanism to promote killing of tumor cells by the innate immune system. IPH2101 is the first fully-human anti-KIR monoclonal antibody, and lirilumab is the second generation. Both products bind to the same KIR subtypes with similar affinities. Functionally and biologically, the 2 antibodies are similar with the following exceptions: 1) IPH2101 is a non-recombinant protein that is produced by a murine hybridoma cell line; whereas, lirilumab is a recombinant product produced in CHO cells. 2) Lirilumab has a single amino acid substitution of a serine to a proline in the IgG4 heavy chain, resulting in greater stability of the compound by reducing the formation of half antibodies. IPH2101 studies were done prior to lirilumab studies and safety, efficacy, PKs, and immunologic correlates of IPH2101 in a phase 1 trial in elderly AML in first remission have been published (Vey N, et al., Blood, 2012 Nov 22;120(22):4317-23).[28] Patients received escalating doses (0.0003-3 mg/kg) of IPH2101 following a 3 + 3 design. The doses that elicited full occupancy were: 1 week = 0.075 mg/kg,

2 weeks = 1 mg/kg, and for at least 4 weeks = 3 mg/kg. There was a clear correlation between mAb exposure and KIR occupancy. The maximum tolerated dose was not reached, although full KIR saturation (> 90%) was sustained for 4 weeks only at the 3 mg/kg. Lirilumab dose of 3 mg/kg every 4 weeks is also the highest dose to be tested in BMS study of lirilumab in combination with elotuzumab for multiple myeloma: A Phase I Open Label Dose Escalation and Randomized Cohort Expansion Study of the Safety and Tolerability of Elotuzumab (BMS-901608) Administered in Combination With Either Lirilumab (BMS-986015) or Urelumab (BMS-663513) in Subjects With Multiple Myeloma" (study identifier: NCT02252263). Based on this data and the tolerability of lirilumab in combination with other agent (namely nivolumab) in the CA223001 trial we would like to evaluate lirilumab at the dose of 3.0 mg/kg every 4 weeks in this study.

For details of lirilumab preclinical studies, clinical studies, toxicities, pharmacokinetics, and adverse events please see the Lirilumab Investigator Brochure.

2.6 Rituximab: Rituxan (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen and is used in the treatment of B-NHL and CLL.[1]

2.7 Rationale for Combined Lirilumab and Rituximab

Kohrt et al recently reported the activity of lirilumab in a KIR2DL3 transgenic lymphoma model and of anti-Ly49C/I $F(ab')_2$ in a C57BL/6 syngeneic lymphoma model.[29] In both the models tested, combination of lirilumab with an anti-CD20 monoclonal antibody significantly improved the antitumor efficacy than anti-CD20 monoclonal antibody alone. They reported that anti-Ly49C/I $F(ab')_2$ increased anti-CD20 mAb-mediated NK-cell degranulation and cytotoxicity and potentiated the antilymphoma activity of anti-CD20 mAb in vivo. They also reported that NK cells are required for the antilymphoma activity of the combination treatment. NK-cell depletion, and not macrophage, CD4, or CD8 T-cell depletion, abrogated the therapeutic efficacy of anti-CD20 mAb and anti-Ly49C/I $F(ab')_2$ combination therapy. These findings provide rationale for a clinical trial in B cell malignancies investigating this novel combination of an anti-KIR mAb to tilt the balance of inhibitory and stimulatory NK signals favoring spontaneous cytotoxicity and to further enhance the efficacy of rituximab by the augmentation of ADCC.

We hypothesize that enhanced CLL cell killing and improved clinical responses will be mediated by rituximab by the addition of the anti-KIR monoclonal antibody (lirilumab). The rationale for combining anti-KIR antibody and rituximab include 1) Rituximab induces both NK cell activation (via Fc-FcR engagement). Addition of anti-KIR antibody further enhances NK-cell mediated ADCC. The use of rituximab and anti-KIR antibody has been shown to be synergistic *in vitro* and *in vivo*. 2) Tumor debulking with CD20 monoclonal antibody may synergize or augment the activity of anti-KIR monoclonal antibody 3) Lirilumab and rituximab have non-overlapping and complimentary mechanisms of action and thus may synergize, with no notable increased risk for toxicity. We plan to include patients with relapsed or refractory CLL. In addition, untreated patients with high-risk cytogenetic features such as

del(17p), mutated *TP53,* del(11q), unmutated *IGHV*, or are >65 years will be eligible as they have poor outcomes and short progression-free survival with chemoimmunotherapy.

3.0 STUDY POPULATION

3.1 Inclusion Criteria

1. Patients will have a diagnosis of CLL or SLL who meet one or more criteria for active disease as defined by the International Working Group for CLL (IWCLL) and are:
    a. Cohort 1: refractory to and/or relapsed after at least one prior therapy OR
    b. Cohort 2: untreated patients with high-risk molecular features such as del(17p), mutated *TP53*, del(11q), unmutated *IGHV* gene, or are >65 years of age
2. Age 18 years or older
3. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2
4. Patients must have adequate renal and hepatic function
    - Serum bilirubin ≤1.5 x upper limit of normal (ULN). For patients with Gilbert's disease, serum bilirubin up to ≤3 x ULN is allowed provided normal direct bilirubin.
    - Serum creatinine ≤1.5 x ULN
    - ALT and AST ≤3 x ULN
5. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotrophin (β-hCG) pregnancy test result within 24 hours prior to the first dose of treatment and must agree to use an effective contraception method during the study and for 12 months following the last dose of the study drugs. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy. Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 31 weeks following the last dose of study drugs.
6. Patients or their legally authorized representative must provide written informed consent.

3.2 Exclusion Criteria

1. Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, or localized prostate cancer. If patients have another malignancy that was treated within the last 2 years, such patients may be enrolled if the likelihood of requiring systemic therapy for this other malignancy within 2 years is less than 10%, as determined by an expert in that particular malignancy at MD Anderson Cancer Center and after consultation with the Principal Investigator.
2. Any major surgery, radiotherapy, chemotherapy, biologic therapy, immunotherapy, experimental therapy within 4 weeks prior to the first dose of the study drugs. For oral targeted therapies (such as ibrutinib, idelalisib, venetoclax), a washout of 3 days is allowed. Note: Prior treatment with anti CD20 monoclonal antibody, anti CD52 monoclonal antibody and lenalidomide are allowed. Prior treatment with anti-CTLA-4 and anti-PD1 therapies is allowed after a wash-out of 5 half-lives.
3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias,

congestive heart failure, or myocardial infarction within 2 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.

4. History of stroke or cerebral hemorrhage within 2 months.
5. Patients who have uncontrolled hypertension (defined as sustained systolic blood pressure ≥ 160 mmHg or diastolic ≥ 100 mmHg).
6. Known evidence of active cerebral/meningeal CLL. Patients may have history of CNS leukemic involvement if definitively treated with prior therapy and no evidence of active disease at the time of registration.
7. Active, uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia requiring steroid therapy.
8. Patients with autoimmune diseases are excluded: Patients with a history of Inflammatory Bowel Disease (including Crohn's disease and ulcerative colitis) are excluded from this study as are patients with a history of autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis, systemic lupus erythematosus, Wegener's granulomatosis).
9. Patients with previous allogeneic stem cell transplant (SCT) within 6 months or with active acute or chronic graft-versus host disease are excluded. Patients must be off immunosuppression for GVHD for at least 60 days before cycle 1 day 1.
10. Patients with organ allografts (such as renal transplant) are excluded.
11. History of any hepatitis (e.g., alcohol or non-alcohol steatohepatitis (NASH), auto immune, or grade 3-4 drug-related hepatitis).
12. Patients who are on high-dose steroids (doses >10mg/day of prednisone or equivalent) or immune suppression medications. Note: Patients on high-dose steroids (doses >10mg/day of prednisone or equivalent) or immune suppression medications are eligible provided these drugs are discontinued at least 3 days prior to starting on the study drugs.
13. Patients with uncontrolled active infection (viral, bacterial, and fungal) are not eligible.
14. Current or chronic hepatitis B or C infection, or known seropositivity for HIV.
15. Patient is pregnant or breast-feeding.
16. Concurrent use of investigational therapeutic agent
17. Patients may not receive other concurrent chemotherapy, radiotherapy, or immunotherapy. Localized radiotherapy to an area not compromising bone marrow function does not apply.
18. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that in the opinion of the investigator may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and/or would make the patient inappropriate for enrollment into this study.

4.0 TREATMENT PLAN

4.1 Study Design

This is a phase II open label single-arm study to evaluate combined lirilumab and rituximab in patients with CLL.

	C1D1	C1D8 (±2 days)	C1D15 (±2 days)	C1D22 (±2 days)	C2-C12 D1 (±7 days)	C13-C24 D1 (±7 days)
Rituximab	375 mg/m2	375 mg/m2	375 mg/m2	375 mg/m2	375 mg/m2	–
Lirilumab	3 mg/kg	_	_	_	3 mg/kg	3 mg/kg

Each cycle is 4 weeks. Patients will receive rituximab (375 mg/m2 IV) weekly for the first 4 weeks (Days 1, 8, 15, 22), and then with the start of each course. Lirilumab (3 mg/kg IV) will be given on day 1 of each cycle. Rituximab will be given for the first 12 cycles and lirilumab will continue for up to 24 cycles.

5.0 STUDY MEDICATIONS

5.1 Lirilumab

5.1.1 Preparation and Dispensing of Lirilumab

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Investigator Brochure. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g. required diluents, administration sets).

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. The study drug should be administered shortly after preparation in order to avoid exposure of the prepared drug to room temperature conditions beyond a recommended 4 hour limit. This 4 hour time limit at room temperature includes the time allotted for IV dose administration, which is 60 min. In the event that a delay in use of prepared (diluted) study drug is anticipated, prepared bags may be refrigerated for a maximum of 20 hours. Study drug is to be administered as IV

infusion and not IV push or bolus injection.

Lirilumab must be stored at a temperature of 2°C to 8°C and should be protected from light and from freezing. For details on prepared drug storage and use time of lirilumab under room temperature/ light and refrigeration, please refer to the Investigator Brochure.
Unused or expired lirilumab vials will be disposed per MDACC guidelines.

5.1.2 Administration of Lirilumab
Please refer to the Investigator Brochure

5.2 Rituximab

Rituximab is anti-CD20 monoclonal antibody. Commercial drug supply will be used for this study. Rituximab will be administered as per the institutional guidelines.

6.0 DOSE DELAYS AND MODIFICATIONS

Patients who experience Grade 3 or 4 toxicity that can be clearly attributed to either lirilumab or to rituximab may continue treatment with the other agent while the causative agent is delayed until resolution of toxicity to grade ≤1 or baseline. In cases where Grade 3 or 4 toxicity cannot be attributed to a specific study drug, both study drugs should be held regardless of attribution of toxicity until the toxicity is resolved to grade ≤1 or baseline.

Rituximab and lirilumab administration should be delayed and increased monitoring of patients should ensue if any of the following drug-related adverse event(s) occurs:

- Any Grade ≥ 2 ALT, AST, or total bilirubin
- Any Grade ≥ 2 non laboratory non-skin drug related adverse event except for fatigue
- Any Grade ≥ 2 endocrine drug-related adverse event
- Any Grade ≥ 3 skin drug related adverse event
- Any Grade ≥ 3 drug-related laboratory abnormality (except lymphopenia or any electrolyte abnormality without any clinical sequelae that is either spontaneously reversible or resolves with clinical management to grade 2 or less within 72 hours)
- Any AE, laboratory abnormality or inter-current illness, which in the judgment of the investigator, warrants delaying the dose of study medication

Discontinuation of lirilumab will occur in the following situations:

- AST, ALT, or T Bili ≥ Grade 3
- Grade 2 AST or ALT and symptomatic liver inflammation (e.g., right upper quadrant tenderness, jaundice)
- AST or ALT > 3 x ULN and concurrent total bilirubin > 2 x ULN in the absence of evidence of cholestasis (Hy's law)

7.0 CONCOMITANT THERAPY

7.1 Allowed concomitant therapy

All concomitant medications will be documented in the medical record. Patients should receive full supportive care during study participation, including hematopoietic growth factors, transfusion of blood products, fluid and electrolyte replacement, and antibiotics when appropriate.

7.2 Excluded concomitant therapy

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Immunotherapy (outside of this study)
- Any therapies intended for the treatment of lymphoma/leukemia whether FDA-approved or experimental (outside of this study)
- Steroid therapy for anti-neoplastic intent. Inhaled steroids for asthma, topical steroids, steroids as part of premedication, or replacement/stress corticosteroids are permitted.

8.0 PRETREATMENT EVALUATIONS

1. Pretreatment evaluation will include a complete history and physical examination including vital signs ECOG performance status, height and weight and recording of concurrent medications (within 7 days of the first dose)
2. Complete blood count (hemoglobin, white blood cell count, platelet count, white blood count differential) (within 7 days of the first dose)
3. Clinical laboratory evaluation will include serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, β-2 microglobulin, serum immunoglobulins, lipase, amylase (within 7 days of the first dose)
4. B, T, NK cell counts and subset analyses on the peripheral blood (within 7 days of the first dose)
5. PT, aPTT (within 7 days of the first dose)
6. Urinalysis (within 7 days of the first dose)
7. HIV Ab, Hepatitis C ab, HBsAg, anti-HBcAb (within 30 days of the first dose)
8. TSH, Free T4 (within 30 days of the first dose)
9. Women of childbearing potential must have a negative serum or urine β-hCG pregnancy test result within 24 hours prior to the first dose of study drugs.
10. 12-lead EKG (within 30 days of the first dose)
11. Bone marrow aspiration and biopsy (within 60 days of the first dose if no intervening treatment for CLL given)
12. CT scan of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast, within 30 days of the first dose. Patients with palpable cervical lymphadenopathy noted at screening physical examinations should have imaging of the neck included in their screening imaging studies and at subsequent time points for response assessment. Note: PET scan may be used instead of the CT scan imaging.

9.0 EVALUATIONS DURING THE STUDY

Cycle 1 Day 1 (Rituximab and Lirilumab)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH
2. Vital signs, history and physical examination (Note: history and physical examination within 3 days prior to the Day 1 is acceptable)

Cycle 1 Day 8 (Rituximab) (+/- 2 day)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH
2. Vital signs, history and physical examination

Cycle 1 Day 15 (Rituximab) (+/- 2 day)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH
2. Vital signs, history and physical examination

Cycle 1 Day 22 (Rituximab) (+/- 2 day)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH
2. Vital signs, history and physical examination

Cycle 2 Day 1 (Rituximab and Lirilumab) (+/- 1 week)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, serum immunoglobulins, TSH, Free T4
2. B, T, NK cell counts and subset analyses on the peripheral blood
3. Serum or urine β-hCG pregnancy test (for women of childbearing potential)
4. Vital signs, history and physical examination

Cycle 2 Day 8 (no mAb) (+/- 2 day)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH

Cycle 2 Day 15 (no mAb) (+/- 2 day)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH
2. Vital signs, history and physical examination

Cycle 2 Day 22 (no mAb) (+/- 2 day)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH

Cycle 3 Day 1 (Rituximab and Lirilumab) (+/- 1 week)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, serum immunoglobulins, TSH, Free T4
2. B, T, NK cell counts and subset analyses on the peripheral blood
3. Serum or urine β-hCG pregnancy test (for women of childbearing potential)
4. Vital signs, history and physical examination

Cycle 3 Day 15 (no mAb) (+/- 3 day)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH
2. Vital signs, history and physical examination

End of Cycle 3 (response assessment) (+/- 1 week)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, β-2 microglobulin, serum immunoglobulins
2. Vital signs, History and Physical Examination
3. B, T, NK cell counts and subset analyses on the peripheral blood
4. TSH, Free T4
5. Serum or urine β-hCG pregnancy test (for women of childbearing potential)
6. Bone marrow aspiration and biopsy with multi-color flow cytometry for MRD evaluation
7. CT scan of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast. PET scan may be used instead of the CT scan imaging.

Cycle 4 Day 1 (Rituximab and Lirilumab) (+/- 1 week)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH
2. Serum or urine β-hCG pregnancy test (for women of childbearing potential)
3. Vital signs, history and physical examination

Cycle 4 Day 15 (no mAb) (+/- 3 day)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH
2. Vital signs, history and physical examination

Cycle 5 Day 1 (Rituximab and Lirilumab) (+/- 1 week)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, serum immunoglobulins, TSH, Free T4
2. B, T, NK cell counts and subset analyses on the peripheral blood
3. Serum or urine β-hCG pregnancy test (for women of childbearing potential)
4. Vital signs, history and physical examination

Cycle 5 Day 15 (no mAb) (+/- 3 day)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH
2. Vital signs, history and physical examination

Cycle 6 Day 1 (Rituximab and Lirilumab) (+/- 1 week)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, serum immunoglobulins, TSH, Free T4
2. B, T, NK cell counts and subset analyses on the peripheral blood
3. Serum or urine β-hCG pregnancy test (for women of childbearing potential)
4. Vital signs, history and physical examination

Cycle 6 Day 15 (no mAb) (+/- 3 day)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH
2. Vital signs, history and physical examination

End of Cycle 6 (response assessment) (+/- 1 week)

1. CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, β-2 microglobulin, serum immunoglobulins
2. Vital signs, History and Physical Examination
3. B, T, NK cell counts and subset analyses on the peripheral blood
4. TSH, Free T4
5. Serum or urine β-hCG pregnancy test (for women of childbearing potential)
6. Bone marrow aspiration and biopsy with multi-color flow cytometry for MRD evaluation
7. CT scan of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast. PET scan may be used instead of the CT scan imaging.

Cycle 7 onwards (All evaluations can be +/- 1 week) (Rituximab on day 1 of cycles 7-12; Lirilumab on day 1 of cycles 7-24)

1. CBC, platelet count and differential; serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH at least monthly.
2. Complete history and physical examination including vital signs at least monthly.
3. Quantitative immunoglobulin levels every month
4. B, T, NK cell counts and subset analyses on the peripheral blood every 3 months
5. TSH, Free T4 every 3 months
6. Serum or urine β-hCG pregnancy test (for women of childbearing potential) before dose of lirilumab
7. Urinalysis every 3 months
8. Bone marrow aspiration and biopsy with multi-color flow cytometry for MRD evaluation every 3 months
9. CT scan of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast every 3 months. PET scan may be used instead of the CT scan imaging.

End of Study Visit – Patients, who are taken off study for any reason, will have an end of study visit. The end of study visit will occur 30 days (+/- 1 week) after the last dose of the study drugs. At this visit, the patient will have labs (CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH), history and physical examination, serum immunoglobulins, B, T, NK cell counts and subset analyses on the peripheral blood, bone marrow aspiration and biopsy with multi-color flow cytometry for MRD evaluation (if the previous bone marrow evaluation was >3 months ago), and CT or PET imaging (if the previous CT or PET imaging was >3 months ago).

After completion of all protocol related treatments, patients will be followed for at least one year with at least monthly labs (CBC, platelet count and differential, sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH), at least monthly history and physical examination, serum immunoglobulins every 3 months, B, T, NK cell counts and subset analyses on the peripheral blood every 3 months, bone marrow aspiration and biopsy with multi-color flow cytometry for MRD evaluation every 3-6 months, and CT or PET imaging every 3-6 months. All evaluations can be +/- 1 week. Note: This post-protocol follow-up period of one year will end early if the patient starts another treatment for their CLL/SLL. Inability to comply with these post-protocol follow-up evaluations will not be considered a protocol-deviation.

NOTE: All treatments with lirilumab and rituximab must be administered at the MDACC. During the first cycle all laboratory evaluations will be done at MDACC. Subsequently, the patient may have laboratory work and physical examination done at a local clinic and the results reported to the research nurse for the study. The laboratory work done at a local clinic will be

forwarded to the patient's attending physician at MDACC, or PI of the study, who will sign off on the labs to verify that the results have been reviewed.

Outside Physician Participation During Treatment

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record

2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix D)

3. Protocol required evaluations outside MDACC will be documented by fax. Faxed evaluations will be dated and signed by the MDACC physician/investigator indicating that they have reviewed it.

4. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.

5. Documentation to be provided by the local physician will include progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.

6. The home physician will be requested to report to the MDACC physician/investigator all life threatening events within 24 hours of documented occurrence.

10.0 CRITERIA FOR RESPONSE

Response will be assessed by the investigator, based on physical examinations, CT scans, laboratory results, and bone marrow examinations, based on the 2008 IWCLL criteria for response for CLL. Overall response (OR) includes complete remission (CR), CR with incomplete marrow recovery (CRi) or partial remission (PR) as determined by investigator assessment using CLL response criteria.[30] Minimal residual disease (MRD) will be assessed in bone marrow by multi-color flow cytometry. Patients with missing or no response assessments will be classified as non-responders by intent to treat analysis.

11.0 ADVERSE EVENT REPORTING

11.1 Leukemia-specific Adverse Event Recording and Reporting Guidelines

These guidelines serve to bring the Department of Leukemia in compliance with the institutional policy on Reporting of Serious Adverse Events.

Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment. Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.
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 patients enrolled on the trial.

11.1.1 PDMS/CORe will be used as the electronic case report form for this protocol. Adverse events will be documented in the medical record and entered into PDMS/CORe.

11.1.2 These guidelines will be followed for the recording and reporting of adverse and serious adverse events.

a. Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event.
    i. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed
        a. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
        b. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.
b. The maximum grade of the adverse event will be captured per course or protocol defined visit date.
c. These adverse events will be recorded in the case report form:
    i. Any grade adverse event that is possibly, probably, or definitely related to the study drug(s).
    ii. All serious adverse events regardless of attribution to the study drug(s).
    iii. Any grade adverse event regardless of attribution to the study drug(s) that results in any dose modification.
d. Hematologic adverse events will not be recorded or reported for studies in patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:
    i. Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g. marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.
e. Serious adverse events will be reported according to institutional policy.
f. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the

protocol and Leukemia-specific adverse event recording and reporting guidelines.

11.1.3 Abnormal hematologic values will not be recorded on the case report form. For abnormal chemical values, the apogee or nadir (whichever is appropriate) will be reported per course on the case report form.

11.1.4 All events that are not listed as expected in section 11.1.2 will be collected for the purpose of grading, and determining attribution to study drug by the PI.

11.1.5 Serious Adverse Event Reporting (SAE)
An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical 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 (21 CFR 312.32). Pregnancy, drug overdose, and secondary malignancy will be handled as SAE.

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

"Serious Adverse Event Reporting (SAE) for M. D. Anderson-Sponsored IND Protocols":

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

Investigator Communication with Supporting Companies:

- Any individual expedited SAE reports required by the FDA will be reported to BMS.
- **All Serious Adverse Events must be reported to BMS Worldwide Safety**
  - All SAEs, whether related or unrelated to lirilumab and all pregnancies must be reported to BMS (by the investigator or designee) within 24 hours.
  - All SAEs should be reported via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:
    SAE Email Address: Worldwide.Safety@BMS.com
    SAE Fax Number: 609-818-3804

12.0 DISCONTINUATION OF STUDY TREATMENT

A patient's treatment with study drugs may be discontinued for any of the following reasons:

- Clinically significant progressive disease
- Adverse events that are not manageable with dose adjustments and/or optimal medical management, or that, in the opinion of the investigator, pose an unacceptable risk for the patient.
- Investigator decision
- Patient decision (e.g., withdrawal of consent)
- Study termination by Sponsor

Patients who experience toxicity that can be clearly attributed to either lirilumab or rituximab may continue treatment with the other agent. If toxicity cannot be clearly attributed to a single agent, treatment with both agents should be discontinued. Patients who discontinue treatment for reasons other than progressive disease should remain on study and continue to have disease assessments per protocol.

13.0 CORRELATIVE STUDIES

Correlative studies relating to immunologic response will be collected on a separate IRB-approved Protocol (PA13-0291).

Approximately 20cc of peripheral blood will be collected at the following time-points (pretreatment, C1D1, C1D8, C2-24D1) and stored in the Leukemia Research Bank. This testing is optional and failure to collect these studies at any of the specified time-points is not a protocol deviation. Approximately 3cc of bone marrow aspirate will be collected at the following time-points (pretreatment, after C3, after C6, after C9, after C12, after C15, after C18, after C21, after C24) and stored in the Leukemia Research Bank. This testing is optional and failure to collect these studies at any of the specified time-points is not a protocol deviation.

Immune Function Studies (Katy Rezvani MD, PhD, MDACC) – This testing is optional and failure to collect these studies at any of the specified time-points is not a protocol deviation. We use 14 color multiparameter flow cytometry to comprehensively analyze NK cell frequencies, phenotype, function (both KIR-ligand mediated and ADCC), homing to sites of tumor (bone marrow and lymph node where available) using the assays described below and in table below. PBMC will be collected on Day 1 (prior to the study drugs) and Day 2 of each cycle (cycles 1-12). In addition, PBMC will be collected on day 8 of cycle 1. Approximately 3cc of bone marrow aspirate will be collected at the following time-points (pretreatment, after C3, after C6, after C9, after C12). To determine whether treatment with a combination of rituximab and lirilumab will enhance CD16 mediated ADCC, NK cells will be stimulated with antibodies against CD20 (Rituximab) to trigger ADCC responses against CD20+ cell lines (Raji and Daudi), in the presence or absence of lirilumab. Function will be assessed using a combination of degranulation (CD107a), effector cytokine production (IFN-γ and TNF-α) and 51chromium release. Each patient will be used as his / her own control and the effect of rituximab and lirilumab combination therapy on NK cell frequency, phenotype and function will be assessed longitudinally. A total of 25 samples will be analyzed per patient. Samples will be sent to the laboratory of Dr. Katy Rezvani, MDACC.

Table 13.1. Flow cytometric parameters that will be used to evaluate the impact of rituximab + lirilumab on NK cell phonotype and function

Cell type	Markers & transcription factors	Effector molecules
NK cells NK subsets (may be $^{+}$ or $^{-}$) NK activation markers KIR receptors Adhesion / migration Costimulatory molecules	$CD45^{+}$ $CD56^{+}$ $CD3^{-}$ $NKp46^{+}$ IL-2R$\alpha^{+/-}$ IL-12Rβ^{+} IL-15R$\beta^{+/-}$ IL-18R^{+} T-bet$^{+ \text{ or } -}$ Eomes$^{+ \text{ or } -}$ CD16, CD27, CD57, CD94, CD141, CD161, KLRG-1, 2B4, 4-1BB, NKG2A, -C, -D, DNAM-1, NKp30, NKp44, KIRs, CD132 CD25, CD69, down-regulation of CD27 & KLRG-1, Ki67, Lag3, CD107a KIR2DL1 (clone 143211, KIR2DS1 (clone 11PB6), KIR2DL3 (clone REA147), KIR2DSL2/3 (clone GL183), KIR3DL1 (clone DX9), KIR3DSL11 (CLONE z27.3.7) CX3CR1, CCR9, α4β7, CD62L, CCR7, CCR8, CXCR3, CLA PD1, PDL1, PDL2, Lag 3 (to assess exhaustion)	Perforin, Granzymes, TNFα, INFγ Cytotoxicity CD107a

14.0 STATISTICAL CONSIDERATIONS

A maximum of 48 patients will be enrolled in this Phase II study. Cohort 1 will enroll up to 24 CLL patients who are refractory to or have relapsed after at least one prior therapy; cohort 2 will enroll up to 24 untreated CLL patients with high-risk molecular features such as del(17p), mutated *TP53*, del(11q), unmutated *IGHV* gene, or are >65 years of age. The primary objective is to evaluate overall response (OR) during the first 6 months of therapy. The primary efficacy endpoint, overall response (OR), is defined as CR, CRi or PR that occurs during the first 6 months of therapy.

EFFICACY

For cohort 1, the target overall response rate is 30%. The Bayesian approach of Thall, Simon, Estey will be implemented for the futility monitoring.[31] The following futility stopping rule will be applied in cohort size of 3, starting from the 9th patient: prob{p(OR)> 0.3) < 0.05, where p(OR) denotes the overall response rate. That is, the trial will be stopped early due to futility, if during the study we determine that there is less than 5% chance that the OR is more than 30%. Assuming that the prior distribution of p(OR) is beta (0.6, 1.4), the stopping boundaries corresponding to this futility monitoring rule are shown below in Table 14.1. The operating characteristics (OCs) for this futility stopping rule are summarized in Table 14.2.

Table 14.1. Futility stopping boundaries for cohort 1, in cohort size of 3.

Number of patients	Stop the trial if there are this many patients achieving OR
9	0

12-15	0-1
18	0-2
21	0-3

Table 14.2. Operating characteristics for the monitoring of OR rate in cohort 1.

True OR Rate	Early Stopping Probability	Average number of patients treated
0.1	0.88	13.8
0.2	0.45	19.4
0.3	0.14	22.6
0.4	0.03	23.7
0.5	0.005	23.9

For cohort 2, the OR rate is ~30% with Rituximab and we target to reach an OR rate of 50% with the combination therapy. The same Bayesian approach of Thall, Simon, Estey will be implemented for the futility monitoring.[31] The following futility stopping rule will be applied in cohort size of 3, starting from the 9th patient: prob{p(OR)> 0.3+delta) < 0.05, where p(OR) denotes the response rate and delta=0.2. That is, the trial will be stopped early due to futility, if during the study we determine that there is less than 5% chance that the OR rate with the combination therapy will improve from 30% (Rituximab alone) to 50%. Assuming that the prior distribution of p(OR) is beta (0.6, 1.4), the stopping boundaries corresponding to this futility monitoring rule are shown below in Table 14.3. The operating characteristics (OCs) for this futility stopping rule are summarized in Table 14.4.

Table 14.3. Futility stopping boundaries, in cohort size of 3, for cohort 2.

Number of patients	Stop the trial if there are this many patients achieving OR
9	0-2
12	0-3
15	0-4
18	0-5
21	0-7

Table 14.4. Operating characteristics for monitoring of OR rate in cohort 2.

True OR Rate	Early Stopping Probability	Average number of patients treated
0.2	0.97	11.0
0.3	0.78	14.8
0.4	0.44	19.1
0.5	0.16	22.2

0.6	0.04	23.5
0.7	0.005	23.9

TOXICITY

The Bayesian approach of Thall, Simon, Estey will be implemented for toxicity monitoring for patients enrolled in cohorts 1 and 2, where toxicity is defined as any grade 3 or higher non-hematological toxicity which is at least possibly related to the treatment.[31] The toxicity, denoted as TOX will be monitored by the Bayesian stopping boundaries calculated based on beta-binomial distributions. We assume as a priori, p(TOX) ~ beta (0.6, 1.4). The study will be stopped for toxicity if Pr(p(TOX)> 0.30 | data) >0.92. That is, we will stop the trial for new patient enrollment if at any time during the study we determine that there is more than 92% chance that the toxicity rate is more than 30%. The toxicity monitoring rule will be applied starting from the 6th patient, and then in cohort size of 6. The toxicity will be considered continuously throughout the study treatment duration. Stopping boundaries corresponding to this toxicity monitoring rule are shown in Table 14.5 below. The operating characteristics for toxicity monitoring are summarized in Table 14.6.

Table 14.5. Toxicity stopping boundaries in cohort size of 6 for patients enrolled in cohorts 1 and 2.

Number of patients	Stop the trial if there are this many patients having toxicity
6	4-6
12	7-12
18	9-18
24	11-24
30	13-30
36	15-36
42	18-42

Table 14.6. Operating characteristics for toxicity monitoring.

True Toxicity Rate	Early Stopping Probability	Average number of patients treated
0.1	0.001	47.9
0.2	0.02	47.1
0.3	0.19	42.3
0.4	0.61	30.5
0.5	0.93	18.2

ANALYSIS PLAN

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. The overall response (OR) rate will be estimated along with

the 95% credible interval.

Data from all patients who receive any study drug will be included in the safety analyses. Patients who entered the study and did not take any of the study drugs and had this confirmed will not be evaluated for safety. The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency. The proportion of patients with AEs will be estimated, along with the Bayesian 95% credible interval. Kaplan-Meier method will be used to assess the overall survival (OS) and progression-free survival (PFS) probabilities. The change of biomarkers over time will be assessed through fitting linear or non-linear mixed effect models.

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and wellbeing of the patient requires immediate intervention, based on the judgment of the investigator or his/her designee. In the event of a significant deviation from the protocol, the investigator will notify the MDACC surveillance committee following the institutional guidelines.

Statistical Language for the correlative studies: Descriptive statistics including plots, mean, median and standard deviations will be used to summarize data. For continuous outcomes, t-test and ANOVA will be used to compare outcome measures across patient characteristics. Dunnett's and Tukey's test that properly adjust for multiplicity in multiple tests will be implemented. Pair-wise comparisons will be performed using pre- and post-therapy samples from each patient. The chi-square (c2) test or Fisher's exact test will be used to test the association between two categorical variables such as disease state and performance status. Both univariate and multivariate logistic regressions will be performed to model prognostic factors.

15.0 REFERENCES

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

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INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

Lirilumab (anti-KIR mAb) Combined with Rituximab for Relapsed, Refractory or High-risk Untreated Patients with Chronic Lymphocytic Leukemia (CLL)
2014-0933

Subtitle: BMS-Combination of Lirilumab with Rituximab in CLL Patients

Study Chair: Nitin Jain

1. _____ _____
Participant's Name Medical Record Number

You are being asked to take part in this clinical research study at The University of Texas MD Anderson Cancer Center ("MD Anderson"). This consent and authorization form explains why this research study is being done and what your role will be if you choose to take part. This form also describes the possible risks connected with being in this study. After reviewing this information with the person responsible for your enrollment, you should know enough to be able to make an informed decision on whether you want to take part in the study.

You are being asked to take part in this study because you have chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL).

2. PURPOSE OF STUDY

The goal of this clinical research study is to learn if lirilumab in combination with rituximab can help to control either CLL or SLL. The safety of the drug combination will also be studied.

3. DESCRIPTION OF STUDY

Screening Tests

Signing this consent form does not mean that you will be able to take part in this study. The following screening tests will help the doctor decide if you are eligible:

- You will have a physical exam.
- You will have an electrocardiogram (EKG) to check your heart function.
- Urine will be collected for routine tests.
- Blood (about 3-5 tablespoons) will be drawn for routine tests and to test for hepatitis B, C, and HIV (the AIDS virus). This routine blood draw will include a pregnancy test if you can become pregnant. This pregnancy test may also be a urine test. To take part in this study, you cannot be pregnant.
- You will have a bone marrow biopsy and/or aspirate to test for tumor markers. Tumor markers may be related to the status of the disease. To collect a bone marrow biopsy/aspirate, an area of the hip or other site is numbed with anesthetic, and a small amount of bone marrow and bone is withdrawn through a large needle.
- You will have a computed tomography (CT) scan or a positron emission tomography (PET) scan to check the status of the disease. You will be given a contrast dye to help the study staff "see" the images better.

The study doctor will discuss the screening test results with you. If the screening tests show that you are not eligible to take part in the study, you will not be enrolled. Other treatment options will be discussed with you.

Study Treatment

Each study cycle is 28 days.

You will receive rituximab by vein over about 4-6 hours on Days 1,8, 15, and 22 of Cycle 1. After Cycle 1, you will receive rituximab on Day 1 of Cycles 2-12.

You will also receive lirilumab by vein over about 1 hour on Day 1 of each cycle.

Study Visits

On **Days 1, 8, 15, and 22 of Cycles 1 and 2** and then **about every 2 weeks during Cycles 3-6**:

- You will have a physical exam. You will not have this exam on Days 8 and 22 of Cycle 2.
- Blood (about 2 tablespoons) will be drawn for routine tests. If the doctor thinks it is needed, more blood may need to be drawn and you may need to have these tests performed more often. The study doctor will tell you if more blood will be drawn or if you will have this blood draw repeated.

On **Day 1 of each cycle**, if you can become pregnant, blood (about 1 tablespoon) or urine will be collected for a pregnancy test.

On **Day 28 of Cycles 3 and 6:**

- You will have physical exam.
- Blood (about 2 tablespoons) will be drawn for routine tests. This routine blood draw may include a pregnancy test if you can become pregnant. Urine may also be collected for this pregnancy test.
- You will have a bone marrow aspiration/biopsy to check the status of the disease.
- You will have a CT or PET scan.

At least **1 time each month after Cycle 7:**

- You will have physical exam.
- Blood (about 2 tablespoons) will be drawn for routine tests.

At least 1 time **every 3 months after Cycle 7:**

- Urine will be collected for routine tests. This routine urine collection will include a pregnancy test, if you can become pregnant. Blood (about 1 tablespoon) may also be drawn for this pregnancy test.
- You will have a bone marrow aspiration/biopsy to check the status of the disease.
- You will have a CT or PET scan.

Any time that the doctor thinks it is needed while you are on study, you will have blood draws, CT or PET scans, and/or bone marrow aspirations/biopsies to check the status of the disease and/or to monitor your health.

If the doctor thinks it is acceptable, you may be able to have some of these tests, such as routine blood and urine collections, performed at a local lab or clinic closer to your home. The results will be sent to the study doctor for review. Ask the study staff or study doctor about this possibility.

Length of Study

You may receive up to 12 cycles of rituximab and up to 24 cycles of lirilumab. You will no longer be able to take the study drugs if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

Your participation on the study will be over after about 1 year of follow-up visits.

End-of-Study Visit

Within 30 days after your last dose of study drug:

- You will have a physical exam.
- Blood (about 2-3 tablespoons) will be drawn for routine tests.
- If the doctor thinks it is needed, you will have a bone marrow aspirate to check the status of the disease.

- If the doctor thinks it is needed, you will have a CT or PET scan.

Follow-Up Visits
After your end-of-study visit, you will have the following tests and procedures performed.

One (1) time each month for up to 1 year:
- You will have a physical exam.
- Blood (about 2-3 tablespoons) will be drawn for routine tests.

One (1) time every 3-6 months for up to 1 year, if the doctor thinks it is needed:
- You will have a bone marrow aspirate to check the status of the disease.
- You will have a CT scan or a PET scan.

If you start a new type of anticancer treatment during the year after your last dose of study drugs, you will stop having these follow-up visits.

Other Testing
The study staff may ask you to take part in other MD Anderson clinical research study (PA13-0291) for additional research testing. The study doctor will discuss this with you and, if you decide to take part, you will sign a separate consent document.

This is an investigational study. Lirilumab is not FDA approved or commercially available. Rituximab is FDA approved and commercially available for the treatment of CLL. The use of these drugs in combination to treat CLL/SLL is considered investigational. The study doctor can explain how the drugs are designed to work.

Lirilumab will be provided at no cost to you while you are on the study. You and/or your insurance provider will be responsible for the cost of rituximab.

Up to 48 participants will be enrolled in this study. All will take part at MD Anderson.

4. RISKS, SIDE EFFECTS, AND DISCOMFORTS TO PARTICIPANTS

While on this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after treatment is stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even result in hospitalization and/or death.

Tell the study staff about any side effects you may have, even if you do not think they are related to the study drugs/procedures.

Lirilumab and rituximab may each cause low blood cell counts (red blood cells, platelets, and/or white blood cells):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Lirilumab Side Effects

This is an early study of lirilumab in humans, so the side effects are not well known. Based on other early studies, lirilumab may cause the following side effects:

● headache ● weakness ● fatigue ● fever ● chills ● itching ● sweating ● nausea	● skin rash ● loss of appetite ● vomiting ● constipation ● abnormal digestive blood test (possible inflammation of the pancreas) ● low blood cell counts (red, white, platelets)	● abnormal liver tests (possible liver damage) ● infusion reaction (possible chills and/or hives) ● immune response that causes the body to attack itself

Rituximab Side Effects

Common (occurring in more than 20% of patients)

● fever ● fatigue ● chills	● nausea ● low blood cell counts (red, white, platelet)	● weakness ● infection

Rituximab may commonly cause life-threatening infusion reactions (such as difficulty breathing, tissue swelling, sudden stopping of the heart, and shock caused by heart damage).

Because rituximab is a mouse antibody that has been changed to make it similar to a human antibody, treatment with rituximab may commonly cause the body to make human antibodies to the mouse-based antibody. These antibodies are called HAMA or HACA. The potential response of your body to rituximab may lead to decreasing the effectiveness of mouse-based antibody therapies for you in the future. If you receive other drugs in the future that contain mouse proteins, you could develop an

allergic reaction to those drugs.

Occasional (occurring in 3-20% of patients)

● high blood pressure ● swelling (such as arm/leg and/or tissue) ● flushing ● anxiety ● headache ● difficulty sleeping ● dizziness ● skin rash ● itching ● night sweats	● hives ● high blood sugar (possible diabetes) ● diarrhea ● abdominal pain ● weight gain ● vomiting ● upset stomach ● abnormal liver and/or bone tests (possible liver damage)	● pain (such as back, joints, and/or muscle) ● muscle spasms ● difficulty breathing (possibly due to narrowing of the airways) ● cough ● runny nose ● nosebleed ● sore throat

Rare but serious (occurring in fewer than 3% of patients)

● sudden stopping of the heart ● fast and/or irregular heartbeat ● chest pain due to heart trouble ● heart failure ● heart attack ● low blood pressure (possible dizziness/fainting) ● blood vessel inflammation (possible bleeding, bruising, and/or rash) ● shock caused by heart damage ● inflammation of the brain and spinal cord (possible altered consciousness) ● progressive multifocal leukoencephalopathy (PML – a disease with brain damage that may likely result in paralysis and/or coma, which may be permanent, or death)	● severe and/or painful blisters ● severe skin rash ● very severe blistering skin disease (with ulcers of the skin and digestive tract) ● very severe blistering skin disease (loss of large portion of skin) ● blockage and/or hole in the intestines (possibly leaking contents into the abdomen) ● anemia due to destruction of red blood cells ● thick blood (possible blockage of blood flow) ● decreased bone marrow function and inability to make red blood cells ● condition that looks like lupus (an immune system disease) ● immune system reaction (possible organ damage)	● muscle inflammation and weakness ● abnormal sensation (such as pins and needles) ● kidney damage/failure ● inflammation inside the eye and/or of an eye nerve ● bronchiolitis obliterans (damage of the small airways with difficulty breathing) ● lung inflammation causing chest pain ● life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) ● worsening of existing cancer (Kaposi's syndrome) ● breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle

● brain damage (possible headache, confusion, seizures, and/or vision loss)	● liver failure ● liver damage due to inflammation	cramps, kidney damage, and/or other organ damage)

In people who have ever been infected with hepatitis B virus, there is a risk that the virus can flare up during treatment with drugs that affect your immune system, such as rituximab. This could lead to liver failure. The risk of hepatitis B virus flaring up may continue for several months after you stop taking rituximab. If you become jaundiced (yellowing of the skin and eyes) or develop viral hepatitis while taking rituximab or after stopping treatment, you should tell your study doctor right away. Your study doctor will discuss this risk with you and explain what testing is recommended to check for hepatitis.

Rituximab may also cause other viruses to reactivate. This includes JC virus (PML), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C.

Rituximab may cause you to develop another type of cancer (such as acute myelogenous leukemia [AML], a type of blood cancer.).

Talk to the study doctor before receiving any vaccines (for example, vaccines for measles, mumps, rubella, or polio). Receiving a vaccine while taking rituximab may increase the risk of serious infection or make the vaccine less effective.

Other Risks

Using the study drugs together may cause side effects that are not seen when each is given alone. The study drug combination may also increase the frequency and/or severity of the side effects listed above.

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **bone marrow aspirations/biopsies** performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site. An allergic reaction to the anesthetic may occur. A scar may form at the site.

This study may involve unpredictable risks to the participants.

Pregnancy Related Risks

4a. Because taking part in this study can result in risks to an unborn or breast-feeding baby, you should not become pregnant, breast-feed a baby, or father a child while on this study. You must use birth control during the study

and for at least 12 months (females) or 31 weeks (males) after your last dose of study drug, if you are sexually active.

Birth Control Specifications: Talk to the study doctor about appropriate methods of birth control to use while on study.

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away.

Getting pregnant will result in your removal from this study.

5. POTENTIAL BENEFITS

The study drugs may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

6. ALTERNATIVE PROCEDURES OR TREATMENTS

You may choose not to take part in this study. You may choose to receive treatment with other chemotherapy. You may choose to receive treatment with other targeted therapies, if available. You may choose to receive rituximab without being part of this study. You may choose to receive other investigational therapy, if available. You may choose not to have treatment for cancer at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

OPTIONAL PROCEDURES FOR THE STUDY

Optional Procedure #1: If you agree, extra blood (about 4 teaspoons) will be drawn before your dose of study drug on Days 1 and 8 of Cycle 1 and Day 1 of Cycles 2-4, and stored in a research bank at MD Anderson for use in future research related to cancer.

Before your samples can be used for research, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson. The IRB is a committee of doctors, researchers, and community members. The IRB is responsible for protecting study participants and making sure all research is safe and ethical.

Your samples will be given a code number. No identifying information will be directly linked to your samples. Only the researcher in charge of the bank will have access to the code numbers and be able to link the samples to you. This is to allow medical data related to the samples to be updated as needed.

Optional Procedure #2: If you agree, blood (about 6 teaspoons each time) will be drawn on Days 1, 2, and 8 of Cycle 1 and Days 1 and 2 of Cycles 2-12 to learn if the study drug affects your immune system.

Optional Procedure #3: If you agree, extra aspirate/bone marrow will be collected during regularly scheduled aspirates/biopsies (before you begin treatment and after Cycles 3, 6, 9, and 12) to learn about the effectiveness of the study drug(s).

Optional Procedure #4: If you agree, aspirates/biopsies scheduled after Cycles 15, 18, 21, and 24 will be stored in the Leukemia Research Bank at MD Anderson for use in future research related to cancer.

There are no benefits to you for taking part in the optional procedures. You may stop taking part at any time. There will be no cost to you for taking part in the optional procedures.

You do not have to agree to take part in the optional procedures in order to receive treatment on this study.

Optional Procedure Risks:

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **aspirates/biopsies** performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the aspiration. An allergic reaction to the anesthetic may occur. A scar may form at the aspiration site.

MD Anderson and others can learn about cancer and other diseases from your **banked samples**. In the future, people who may do research with these samples may need to know more information about your health. This information may be collected from your medical record. MD Anderson will make reasonable efforts to preserve your privacy, but cannot guarantee complete privacy. Sometimes your samples may be used for genetic research about diseases that are passed on in families. The type of genetic testing being performed in this study will not provide you or your doctor information about diseases that are passed down in families. It will not tell the study researchers anything that will prevent you from getting health insurance, and it will not tell the study researchers anything about any diseases or conditions you may get in the future.

If you withdraw your consent to the storage of leftover samples in the tissue bank, then they will no longer be collected for storage. Any of your samples that remain in the tissue bank will no longer be used for research and will be destroyed.

However, if any of your de-identified samples were already released for research purposes before you withdrew consent, MD Anderson will not be able to destroy them.

CONSENT/PERMISSION/AUTHORIZATION FOR OPTIONAL PROCEDURES

Circle your choice of "yes" or "no" for each of the following optional procedures:

Optional Procedure #1: Do you agree to allow additional blood to be drawn and stored in a research bank at MD Anderson for use in future research related to cancer?

YES **NO**

Optional Procedure #2: Do you agree to allow extra blood to be drawn to learn if the study drug affects your immune system?

YES **NO**

Optional Procedure #3: Do you agree to allow extra aspirate/bone marrow to be collected during regularly scheduled aspirates/biopsies to learn about the effectiveness of the study drug(s)?

YES **NO**

Optional Procedure #4: Do you agree to allow aspirate/biopsies scheduled during Cycles 15, 18, 21, and 24 to be collected and stored in a research bank at MD Anderson for use in future research related to cancer?

YES **NO**

Additional Information

7. You may ask the study chair any questions you have about this study. You may contact the study chair, Dr. Nitin Jain, at 713-745-6080. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-2933 with any questions that have to do with this study or your rights as a study participant.

8. Your participation in this research study is strictly voluntary. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor. If you withdraw from this study, you can still choose to be treated at MD Anderson.

9. This study or your participation in it may be changed or stopped at any time by the study chair, Bristol Myers Squibb, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP - a regulatory agency that oversees research in humans), or the IRB of MD Anderson.

10. You will be informed of any new findings that might affect your willingness to continue taking part in the study.

11. MD Anderson may benefit from your participation and/or what is learned in this study.

12. This study is supported by: Bristol Myers Squibb.

13. The MD Anderson Conflict of Interest policy states that MD Anderson employees may not serve as the study chair or co-chair on a research study if they have received funds that are greater than the amount allowed by the policy or own stock in the sponsoring or supporting companies.

    The MD Anderson Conflict of Interest policy and the IRB require that you be told about significant financial relationships that the study staff and MD Anderson officials may have with the study sponsor(s).

    At this time, no significant financial relationships with the study sponsor(s) have been disclosed by any of the study staff.

14. In a medical emergency, you may be cared for by someone who has a financial interest with the study sponsor(s). If you have any questions about this, you may call the IRB at 713-792-2933.

STUDY COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson or Bristol Myers Squibb for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-2933 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs, including hospitalization, nausea, vomiting, low blood cell counts, and dehydration. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

OUTSIDE CARE

If the IRB has allowed and you and the study doctor choose, part of your care may be provided outside of MD Anderson by your home doctor(s). The care that is provided by your home doctor(s) will become a part of your study participation. Before you return home, your home doctor(s) will be told about the study, your participation in the study, and the guidelines that they will need to follow while you are on the study. Your home doctor(s) will receive relevant documents and parts of your medical/research records so that they can provide proper care for you and comply with clinical research requirements. Your home doctor(s) will also be responsible for providing the MD Anderson research team with any documents and records about your care. This is necessary for compliance with study requirements. If your home doctor(s) is/are unable or unwilling to provide the care or the documentation required, you may need to return to MD Anderson for all study-related treatments and tests. Your participation in the study may also need to be reconsidered.

Authorization for Use and Disclosure of Protected Health Information:

A. During the course of this study, the research team at MD Anderson will be collecting and using your protected health information. This information may include personal identifying information about you (such as your name, race, date of birth, gender, city, and zip code), your medical history, study schedule, and the results of any of your tests, therapies, and/or procedures. The purpose of collecting and sharing this information is to learn about how the study procedures may affect the disease and any study-related side effects. Your doctor and the research team may share your study information with the parties named in Section D below.

   Blood and urine samples will be sent to the laboratory of Dr. Katy Rezvani, Professor at MD Anderson Cancer Center.

B. Signing this consent and authorization form is optional. However, if you refuse to provide your authorization to use and disclose your protected health information for this study, you will not be able to participate in this research project.

C. MD Anderson will take appropriate steps to keep your protected health information private when possible, and it will be protected according to state and federal law. However, there is no guarantee that your information will remain confidential, and it may be re-disclosed at some point. Federal agencies (such as the FDA, OHRP, or National Cancer Institute [NCI]), Bristol Myers Squibb, and the IRB of MD Anderson might view or receive your record in order to collect data and/or meet legal, ethical, research, and safety-related obligations. In some situations, the FDA could be required to reveal the names of participants.

D. Your protected health information may be shared with the following parties:

- Bristol Myers Squibb (and/or any future sponsors of the study)
- Federal agencies that require reporting of clinical study data (such as the FDA, NCI, and OHRP)
- The IRB of MD Anderson
- Officials of MD Anderson
- Clinical study monitors who verify the accuracy of the information
- Individuals with medical backgrounds who determine the effect that the treatment procedures may have on the disease
- Individuals who put all the study information together in report form

E. There is no expiration date for the use of your protected health information. You may withdraw your authorization to share your protected health information at any time in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP). You may contact the IRB Staff at 713-792-2933 with questions about how to find the NPP. If you withdraw your authorization, you will be removed from the study, and the study chair and staff will no longer use or disclose your protected health information in connection with this study, unless the study chair or staff needs to use or disclose some of your research-related personal health information to preserve the scientific value of the study. Data collected about you up to the time you withdrew will be used and included in the data analysis. The parties listed in Section D above may use and disclose any study data that were collected before you canceled your authorization.

F. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Please Do Not Use for Patient Consent

Go to the PDOL Homepage to access the Informed Consent Printer Database

CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS _____ _____

SIGNATURE OF PARTICIPANT DATE

LEGALLY AUTHORIZED REPRESENTATIVE (LAR)

The following signature line should only be filled out when the participant does not have the capacity to legally consent to take part in the study and/or sign this document on his or her own behalf.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS _____ _____

SIGNATURE OF LAR DATE

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS _____

RELATIONSHIP TO PARTICIPANT

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under Protocol **2014-0933**.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS _____ _____

SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) DATE

A witness signature is only required for vulnerable adult participants. If witnessing the assent of a pediatric participant, leave this line blank and sign on the witness to assent page instead.

PERSON OBTAINING CONSENT

I have discussed this clinical research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF STUDY CHAIR
OR PERSON AUTHORIZED TO OBTAIN CONSENT

DATE

TRANSLATOR

I have translated the above informed consent as written (without additions or subtractions) into _____ and assisted the people
(Name of Language)
obtaining and providing consent by translating all questions and responses during the consent process for this participant.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

NAME OF TRANSLATOR | SIGNATURE OF TRANSLATOR | DATE

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line below.)

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF WITNESS TO THE VERBAL TRANSLATION (OTHER THAN TRANSLATOR, PARENT/GUARDIAN, OR STUDY CHAIR) | DATE