



Protocol Page

An Open-label Phase II Study of Lirilumab (BMS-986015) in Combination with 5-azacytidine (vidaza) for the Treatment of Patients with Refractory/Relapsed Acute Myeloid Leukemia
2014-0862

Core Protocol Information

Short Title	An Open-label Phase II Study of Lirilumab (BMS-986015) in Combination with 5-azacytidine (vidaza) for the Treatment of Patients with Refractory/ Relapsed Acute Myeloid Leukemia
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- The Clinical Research Committee - (CRC)

Protocol Body



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An Open-label Phase II Study of Lirilumab (BMS-986015) in
Combination with 5-azacytidine (vidaza) for the Treatment of
Patients with Refractory/ Relapsed Acute Myeloid Leukemia

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1.0 OBJECTIVES

1.1 Primary Objectives

Part a. Lead-in phase:

1. To determine the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of lirilumab in combination with 5-azacytidine in patients with refractory/ relapsed (AML).

Part b. Phase II:

1. To determine the overall response rate (ORR) of lirilumab in combination with 5-azacytidine in patients with refractory/ relapsed AML.

1.2 Secondary Objectives:

1. To determine the duration of response, disease-free survival (DFS), and overall survival (OS) of patients with refractory/ relapsed AML treated with this combination.
2. To determine the safety of lirilumab in combination with 5-azacytidine in patients with refractory/ relapsed AML.

1.3 Exploratory Objectives:

1. To study immunological and molecular changes in the peripheral blood and bone marrow in response to lirilumab and 5-azacytidine therapy.
2. To determine induction of hypomethylation and DNA damage during therapy with this combination and its correlation with response.

2.0 BACKGROUND

2.1 Acute myeloid leukemia

AML is a malignancy of immature granulocytes or monocytes. The malignancy is characterized by accumulation of leukemic blastocytes and blockade of normal bone marrow production resulting in thrombocytopenia, anemia, and neutropenia. . There are approximately 13,000 new cases of AML per year in the United States, with an estimated 10,000 deaths occurring in the same time period[1]. Almost all newly diagnosed cases, as well as deaths, will be in adults[2]. Standard treatment for AML includes systemic combination chemotherapy to control bone marrow and systemic disease. Treatment is generally divided into an induction phase, to attain remission, and a maintenance phase[2]. Approximately 60% to 70% of adults with AML can be expected to attain complete remission status following appropriate induction therapy. Remission rates in adult AML are inversely related to age, with an expected remission rate of >65% for those younger than 60 years. Increased morbidity and mortality during induction appear to be directly related to age[3-5].

2.2 Relapsed/ Refractory AML

Approximately, 30-40% of adults with AML fail to achieve CR with 1 or 2 cycles of induction chemotherapy, and are deemed primary refractory. The outcome of patients with acute myeloid leukemia (AML) who are refractory to induction therapy are dismal, with low response rates to salvage chemotherapy and poor long-term survival [6-8]. We have

previously reported a dismal median OS of 3.8 months for patients with AML who are refractory to HiDAC-containing induction therapy (defined as $\geq 1\text{gm/m}^2$ cytarabine per dose)[7]. Salvage therapy in such patient populations yielded a response rate of 18% and median response duration of 9 months.

These results emphasize the need to explore alternate salvage regimens for patients with relapsed/refractory AML. The development of novel and effective anti-AML agents and/or combinations is crucial to improving the outcome of AML.

2.3 **Role of PD-1/PD-L1 interactions and NK-cells in AML**

PD-1 and CTLA-4 are well known negative regulators of CTL survival and effector function in both solid tumors and leukemia [9]. It has been clearly demonstrated that blocking ligation of PD-1 and CTLA-4 prevents deletion of CTLs [10, 11]. A third component of the negative regulatory pathway is the inhibitory-cell killer immunoglobulin-like receptors (KIR) [12]. Inhibitory-cell KIR receptors negatively regulate natural killer (NK) cell-mediated killing of HLA class I-expressing tumors. NK cells play a crucial role in anti-tumor responses by killing transformed cells. The activation of NK-cells is regulated by a variety of activating and inhibitory receptors that are expressed by the transformed target cells [13]. Activating receptors include NKp30, NKp44, NKp46, NKG2D, and DNAM-1 [14]. For effective activation of NK-cells tumor cells must express stress or activation ligands for activating receptors. Negative regulators of NK activating receptors include KIR, CD94/NKG2A, and leukocyte Ig-like receptor-1, which recognize MHC-class 1 molecules [15]. Effective NK-cell activity occurs when the target cells express stress ligands with reduced expression of MHC class 1 ligands. Persistent expression of MHC class 1 ligands may result in tumors evading NK-cell mediated immunosurveillance [16]. Lack of KIR-HLA class I interactions has been associated with potent NK-mediated antitumor efficacy and increased survival in AML patients upon haploidentical stem cell transplantation from KIR-mismatched donors [17]. 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 [12]. 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. Lirilumab (IPH2102/BMS-986015) is a fully human monoclonal antibody blocking interaction between Killer-cell immunoglobulin-like receptors (KIR) on NK cells with their ligands.

2.4 **Lirilumab (IPH2102/BMS-986015):**

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. Once activated, NK cells release preformed cytotoxic granules into the target cell leading to direct killing of cancer cells. The concurrent release of cytokines and chemokines also results in a micro-environmental milieu that recruits other immune cells.

Lirilumab is the second anti-KIR antibody. IPH2101 is the first anti-KIR antibody. IPH2101

and lirilumab have identical target specificities. The differences are that IPH2101 is a native IgG4 antibody produced from a hybridoma cell line, whereas lirilumab has a single amino acid mutation to stabilize the hinge region of the molecule and is produced by Chinese hamster ovary (CHO) cells. No additional clinical trials will be conducted with IPH2101. Lirilumab is being developed for treatment of patients with hematologic and solid tumor malignancies. Lirilumab is currently being tested in 4 clinical trials and will be used in all subsequent trials.

Evidence in support of NK cell involvement in the anti-tumor response comes from the hematopoietic stem cell transplant setting. Given the diversity of both KIR and HLA, it is not surprising that KIR on donor NK cells may not recognize host HLA, referred to as KIR mismatch. The finding that patients with acute myeloid leukemia (AML) transplanted with KIR-mismatched donor NK cells had lower relapse rates (3% versus 47%, $p < 0.01$) and reduced risk of relapse (relative risk: 0.48, 95% confidence interval (CI) [0.29, 0.78]) compared to patients transplanted with KIR-matched donor NK cells gave scientific support for the role of NK cells in the anti-tumor response[17].

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. Surface plasmon resonance analysis demonstrated that the mean (standard deviation [SD]) monovalent affinity of lirilumab for recombinant soluble KIR2DL1 was 2.04×10^{-8} (0.31×10^{-8}) M and for KIR2DL3 was 3.01×10^{-10} (0.41×10^{-10}) M.

The scientific rationale for the clinical development of lirilumab was based on the following findings:

- 1) Blockade of inhibitory KIR resulted in killing of AML blasts by KIR-mismatched NK cells but not by KIR-matched NK cells in vitro.
- 2) NOD/SCID mice infused with AML cells and NK cells died of disease within $\dagger 60$ days. In contrast, all mice treated with KIR blockade survived at Day 75 ($p < 0.01$)[12].

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. A total of 243 subjects have received lirilumab in 3 Phase 1 studies (1 concluded and 2 ongoing) and 1 ongoing phase 2 study.

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 received 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).

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 $\geq 3\%$ 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's (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,

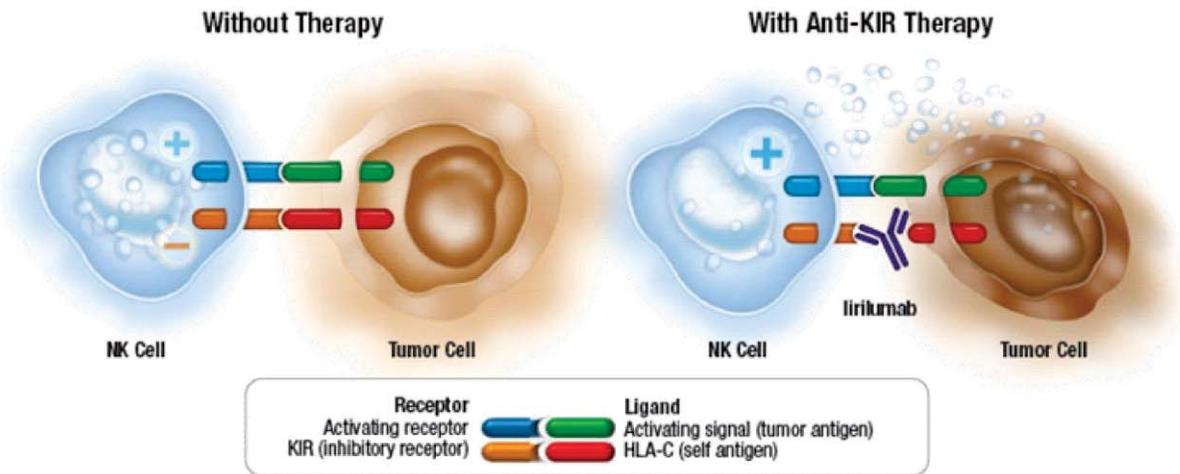
Grade 3 myalgia, Grade 3 sciatica, and Grade 3 acute febrile neutrophilic dermatosis.

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 on this trial (lirilumab investigator brochure, Appendix E).

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 (Appendix E).

Figure 2-1: Lirilumab Augments NK-mediated Killing of Tumor Cells by Blocking the Negative Signaling that Normally Results



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). 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 escalating doses of lirilumab to a maximum potential 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 most recent version of the Lirilumab Investigator Brochure (Appendix E).

2.5 5-azacytidine (Vidaza):

5-azacytidine, an analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, and deoxyribonucleic acid (DNA) synthesis and metabolism. Since the early 1970s, 5-azacytidine has been investigated primarily in

the US for the treatment of acute leukemia. Clinical studies have focused mainly on patients with disease refractory to conventional chemotherapy. Results of these investigations demonstrated activity of 5-azacytidine in the treatment of AML. Clinical studies subsequently evaluated the effects of 5-azacytidine in a variety of other malignant and hematologic disorders, including solid tumors, hemoglobinopathies (eg, thalassemia and sickle cell anemia), and MDS. In 1984, the Cancer and Leukemia Group B (CALGB) began a series of clinical studies with 5-azacytidine in patients with MDS. These studies, in addition to other supportive data, led to the approval of Vidaza® (5-azacytidine) in May 2004 for the treatment of MDS.

5-azacytidine inhibits the methylation of newly synthesized DNA by inhibiting DNA methyltransferase (DNMT).[18-20] Increased methylation of DNA (hypermethylation) may result in the silencing of critical genes responsible for cell growth control and differentiation. Hypermethylation of CpG islands spanning the promoter regions of tumor suppressor genes is commonly associated with cancers.[21] It is now widely recognized that hypermethylation of DNA is frequently associated with myelodysplastic syndromes and other cancers,[22-24] such as renal,[25] melanoma,[26] breast,[27] colorectal,[28] non-small cell lung[29] and hematologic malignancies.[30] 5-azacytidine is believed to exert its antineoplastic effects through hypomethylation and cytotoxicity on abnormal hematopoietic cells in the bone marrow.[31-35] Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation.[21, 36, 37] The cytotoxic effects of 5-azacytidine cause the death of rapidly dividing cells, including cancer cells that are no longer responsive to normal growth control mechanisms.[31, 38-40]

The cytotoxicity of 5-azacytidine is proportional to dose and exposure time.[31, 32] Although the mechanisms of cytotoxicity are complex and multifaceted, there is general agreement that incorporation of 5-azacytidine into DNA and ribonucleic acid (RNA), and inhibition of protein synthesis, are critically important.[41] Cytotoxicity is greatest in cells that are proliferating (S phase) and metabolically active.[31] Cytotoxic effects may also be mediated through induction of the DNA damage response pathways.[40] Non-proliferating cells are relatively insensitive to 5-azacytidine.[31]

Toxicology studies have been conducted in mice, rats, dogs, and Rhesus monkeys.[42] Most of the studies were performed during the 1970s and early 1980s according to existing guidelines and standards in place during that period. The preclinical studies identified the bone marrow, liver, kidneys, and lymphoid tissues (spleen, lymph nodes, and thymus) as the main target organs of toxicity for 5-azacytidine.[42] In single-dose studies, the lethal dose of 5-azacytidine after intravenous (IV) administration in mice, rats, and dogs was approximately 250 mg/m². Repeated daily dosing appears to increase the toxicity of 5-azacytidine.[42] The genotoxicity of 5-azacytidine is consistent with that of other nucleoside analogs that interact with nucleic acids.[42] Likewise, similar to other agents with cytostatic properties, 5-azacytidine was embryotoxic and reduced the reproductive performance in mice and rats.[42]

Limited 5-azacytidine pharmacokinetic data are currently available. Based on human plasma concentrations of total radioactivity (which represents parent drug plus circulating metabolites), 5-azacytidine is rapidly absorbed when given subcutaneously (SC), with maximum plasma concentrations found 0.5 to 2 hours after dosing.[42] 5-azacytidine and/or its by-products are then rapidly cleared by the kidneys. The half-lives and percent radioactivity recovered in urine are similar following IV and SC routes of administration. The effects of renal or hepatic impairment, gender, age, or race on the pharmacokinetics of 5-azacytidine have not been studied.[42] A single dose (75 mg/m²) SC versus IV crossover study in 6 MDS subjects[43] revealed an approximate bioavailability of 89% for the SC dose (range 52% to 128%) with mean half-lives of 0.69 hour and 0.36 hour after SC and IV administration, respectively. These results demonstrated that 5-azacytidine is rapidly and nearly completely absorbed after SC administration and that elimination is also rapid. The apparent SC clearance (167 L/h or 2791 mL/min) and systemic IV clearance (147 L/h) of 5-azacytidine exceeded the glomerular filtration rate (approximately 125 mL/min) and total renal blood flow (1200 mL/min) in healthy subjects. This indicates that non-renal elimination (eg, metabolism, hydrolysis, and/or degradation) plays a role in the elimination of parent 5-azacytidine. In addition, 5-azacytidine 75 mg/m² was generally well-tolerated after single SC injection or IV infusion over 10 minutes.[43]

A number of studies have looked at different parenteral doses and schedules of 5-azacytidine, finding maximum tolerated doses of up to 500 mg/m² when administered weekly.[44]

During the two decades between the start of the CALGB studies and the approval of 5-azacytidine, a new understanding of MDS has developed, such as the World Health Organization (WHO) diagnostic criteria, the International Prognostic Scoring System (IPSS), and the International Working Group (IWG) response criteria. Silverman et al. reevaluated the combined data (N = 309) from 3 of the CALGB studies using the WHO classification system for MDS and AML and the IWG response criteria.[45] Using the IWG response criteria in MDS patients, response rates were between 40% and 70% in 5-azacytidine treated patients. Ten to 17% of patients achieved a complete remission; partial remission was rare; and 23% to 36% of patients had a hematologic improvement. In patients with AML (N = 103), 35% to 48% had hematologic improvement or better responses. The median survival time for 27 patients assigned to 5-azacytidine was 19.3 months compared with 12.9 months for the 25 patients assigned to observation.[45]

A randomized international Phase III trial (Study 5-azacytidine PH GL 2003 CL 001) for higher-risk MDS patients, classified by FAB as RAEB, RAEB-T, or CMML with 0-29% marrow blasts, with an IPSS of Intermediate -2 or High by central pathology/cytogenetic review was recently reported.[46] Patients were randomized to 5-azacytidine (75 mg/m²/day x 7days in 28 day cycles) or conventional care regimens (CCR), where CCR was pre-selected by the Investigator as best supportive care (transfusions, antibiotics, and G-CSF for neutropenic infection), low-dose

cytarabine (20 mg/m²/day x 14 days in 28 day cycles); or standard chemotherapy (conventional induction/consolidation). Patients were stratified by FAB/IPSS and randomized 1:1 to 5-azacytidine or CCR. This trial did not allow erythropoietin. Three hundred fifty eight patients (70% male) were randomized at 79 centers to 5-azacytidine (N=179) or CCR (N=179): best supportive care only (N=105, 59%), low-dose cytarabine (N=49, 27%), or standard chemotherapy (N=25, 14%). Median age was 69 years (range 38-88 years). The 5-azacytidine and CCR groups were comparable for baseline patient characteristics. At baseline, 95% of patients were higher risk: RAEB (58%), RAEB-T/WHO AML (34%), CMML (3%), and other (5%). By IPSS, 87% were higher risk: Intermediate -2 (40%), High (47%), and 13% Indeterminate/other. 5-azacytidine was administered for a median of 9 cycles; low-dose cytarabine for 4 cycles. Median follow-up for the survival analysis was 21.1 months. 5-azacytidine demonstrated statistically superior overall survival compared to CCR, with a median overall survival of 24.4 months vs. 15 months for CCR (stratified log-rank p=0.0001, hazard ration 0.58). Two-year survival approximately doubled in the 5-azacytidine arm compared to CCR: 51% vs. 26% (p<0.0001). 5-azacytidine was well tolerated with safety data consistent with previous reports.

Further details can be found in the 5-azacytidine Drug Information (Appendix F), which contains comprehensive pharmacology, toxicology, pharmacokinetics, pharmacodynamics, metabolism, preclinical, and clinical efficacy and safety data information.[42]

2.6 Rationale for study:

NK cells play a crucial role in anti-tumor responses by killing transformed cells. Inhibitory-cell KIR receptors negatively regulate natural killer (NK) cell-mediated killing of HLA class I-expressing tumors. Negative regulators of NK activating receptors include KIR, CD94/NKG2A, and leukocyte Ig-like receptor-1, which recognize MHC-class 1 molecules [15]. Lack of KIR-HLA class I interactions has been associated with potent NK-mediated antitumor efficacy and increased survival in AML patients upon haploidentical stem cell transplantation from KIR-mismatched donors [17]. 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 [12]. Intriguingly inoculation of NK-cells alone did not protect against autologous implanted AML in immunodeficient mice, however pre-administration with KIR monoclonal antibody induced anti-AML activity with long-term survival. Lirilumab (IPH2102/BMS-986015) is a fully human monoclonal antibody blocking interaction between Killer-cell immunoglobulin-like receptors (KIR) on NK cells with their ligands. Hypomethylating agents may alter immune regulation [47]. Yang et al have recently demonstrated that hypomethylating therapy leads to up regulation of PD-L1, PD-1, and PD-L2 gene expression [48]. Patients resistant to hypomethylating therapy had higher increments in gene expression suggesting that PD-1 up-regulation may promote resistance to hypomethylating agents. Hypomethylating agents also possess anti-leukemia activity when given on their own. Blockade of the KIR-receptors by lirilumab may improve

response rates and abrogate immune-mediated resistance to hypomethylating agents in AML via reactivation of NK-cell mediated leukemic cell lysis.

In this initial trial, we propose to investigate whether the lirilumab in combination with 5-azacytidine improve the response rates in patients with refractory/ relapsed AML. In this proposal we propose to introduce lirilumab blockade early, when there are still leukemia cells that can prime the immune competent cells for eventual eradication. If the combination proves to be well tolerated and results in improved response rates, we would expand the use of this approach in the frontline setting for AML.

3.0 STUDY DESIGN

- This will be a phase II, single-arm, open-label, non-randomized study with a safety lead-in phase.
- Patients will receive 5-azacytidine subcutaneously or intravenously daily for the first 7 days of each treatment cycle. For the lead-in portion, the length of the cycle will be at least 28 days to evaluate DLT. Subsequently cycles will be repeated approximately every 28 days (+/-7 days), and therapy will be continued until clinically significant disease progression or documentation of unacceptable toxicity.
- Patients will receive therapy with lirilumab IV infusion on Day 8 (+/-2 days) of each 5-azacytidine cycle.
- The historical experience in relapsed/refractory AML patient population is that response with single agent hypomethylator therapy (5-azacytidine or decitabine), when available, is 10-15%. In many instances (eg, patients with relapsed/refractory AML beyond first salvage) no standard therapy is available. Thus, an overall response rate of 30% will be considered significant.

4.0 PATIENT SELECTION

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to initiating treatment or any study-specific procedures. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.1 Inclusion Criteria

- 4.1.1 Patients with AML or biphenotypic or bilineage leukemia who have failed at least one prior therapy. Patients with AML should have failed prior therapy

or have relapsed after prior therapy.

- 4.1.2 Patients should not be eligible or able to receive approved therapy of confirmed clinical benefit in this patient population
- 4.1.3 Patients with MDS or CMML who received therapy for the MDS or CMML and progress to AML are eligible at the time of diagnosis of AML regardless any prior therapy for AML. The WHO classification will be used for AML.
- 4.1.4 Prior therapy with hydroxyurea, chemotherapy, biological or targeted therapy (e.g. FLT3 inhibitors, other kinase inhibitors), or hematopoietic growth factors is allowed.
- 4.1.5 Age ≥ 18 years.
- 4.1.6 Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2 .
- 4.1.7 Adequate organ function: total bilirubin ≤ 2 times upper limit of normal (\times ULN) ($\leq 3 \times$ ULN if considered to be due to leukemic involvement or Gilbert's syndrome); aspartate aminotransferase or alanine aminotransferase $\leq 2.5 \times$ ULN ($\leq 5.0 \times$ ULN if considered to be due to leukemic involvement); serum creatinine $\leq 2 \times$ ULN or GFR ≥ 50
- 4.1.8 Patients must provide written informed consent
- 4.1.9 In the absence of rapidly progressing disease, the interval from prior treatment to time of initiation of 5-azacytidine and lirilumab will be at least 2 weeks OR at least 5 half-lives for cytotoxic/noncytotoxic agents. Use of one dose of cytarabine (up to 2 g/m²) is allowed prior to the start of study therapy or hydroxyurea for patients with rapidly proliferative disease is allowed before the start of study therapy and while the patient is on active study treatment, as needed, for clinical benefit and after discussion with the PI. Concurrent therapy for CNS prophylaxis or continuation of therapy for controlled CNS disease is permitted
- 4.1.10 Females must be surgically or biologically sterile or postmenopausal (amenorrheic for at least 12 months) or if of childbearing potential, must have a negative serum or urine pregnancy test within 72 hours before the start of the treatment
- 4.1.11 Women of childbearing potential must agree to use an adequate method of contraception during the study and until 3 months after the last treatment. Males must be surgically or biologically sterile or agree to use an adequate method of contraception during the study until 3 months after the last treatment.

Adequate methods of contraception include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
- Combination of any of the two following (a+b or a+c or b+c)
 - a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
 - b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
 - c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception, women should have been stable on the same pill before taking study treatment.

Note: Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

4.2 Exclusion Criteria

- 4.2.1 Patients with known allergy or hypersensitivity to lirilumab, 5-azacytidine, or any of their components. Patients who have previously been treated with lirilumab in combination with 5-azacytidine will be excluded.
- 4.2.4 Patients with a known history of severe interstitial lung disease or severe pneumonitis or active pneumonitis that is uncontrolled in the opinion of the

treating physician.

- 4.2.5 Patients with a known history of any of the following autoimmune diseases are excluded: (a) patients with a history of inflammatory bowel disease (including Crohn's disease and ulcerative colitis) (b) patients with a history of rheumatoid arthritis, systemic progressive sclerosis [scleroderma], Systemic Lupus Erythematosus, autoimmune vasculitis [e.g., Wegener's Granulomatosis]).
- 4.2.6 Patients with organ allografts (such as renal transplant) are excluded
- 4.2.7 Patients with allogeneic stem cell transplantation within the last 6 months or patients with active GVHD will be excluded
- 4.2.8 Ongoing immunosuppressive therapy, including cyclosporine and tacrolimus. Patients who are on high dose steroid. Note: Subjects may be using systemic corticosteroids (daily doses ≤ 10 mg of prednisone or equivalent) or topical or inhaled corticosteroids.
- 4.2.9 Patients with symptomatic CNS leukemia or patients with poorly controlled CNS leukemia.
- 4.2.10 Active and uncontrolled disease/ (active uncontrolled infection, uncontrolled hypertension despite adequate medical therapy, active and uncontrolled congestive heart failure NYHA class III/IV, clinically significant and uncontrolled arrhythmia) as judged by the treating physician.
- 4.2.11 Patients with active and uncontrolled Human Immunodeficiency Virus (HIV) infection will be excluded. However, patients with well controlled HIV infection will be considered.
- 4.2.12 Patients known to be positive for hepatitis B by surface antigen expression. Patients known to have active hepatitis C infection (positive by polymerase chain reaction or on antiviral therapy for hepatitis C within the last 6 months)
- 4.2.13 Any other medical, psychological, or social condition that may interfere with study participation or compliance, or compromise patient safety in the opinion of the investigator
- 4.2.14 Patients unwilling or unable to comply with the protocol.
- 4.2.15 Pregnant or breastfeeding
- 4.2.16 Acute promyelocytic leukemia (APL).

5 TREATMENT PLAN

5.1 General

All patients will be registered through CORE. The objective will be to administer lirilumab and 5-azacytidine at full dose. We will first treat 6 patients at dose level -1. Other dose levels will be used for dose adjustments for toxicity during therapy.

5.2 Schedule

The Investigator is responsible for completing the cohort summary template and submitting to the IND office Medical Monitor for review and approval prior to advancing subjects to the next protocol specified cohort/dose level. A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence". This should be submitted after the first six patients.

5.2.1 Patients will be treated according to the following schedule:

- 5-azacytidine will be administered subcutaneously (SQ) or intravenously (IV) for 7 days of every cycle (Days 1-7) as determined by treating physician. Both SQ and IV forms of administration are FDA approved and considered interchangeable. Patients may start receiving 5-azacytidine by one route and changed to the other at any time as needed based on patient and/or physician preference.
- Lirilumab will be administered as an approximately 60 minute IV infusion on Day 8 (+/-2 days) of each 5-azacytidine cycle. Lirilumab will be administered every cycle with no interruptions unless there are adverse events as described in Section 5.3. The dosing calculations should be based on the body weight. All doses should be rounded to the nearest milligram. There will be no dose reductions (only interruptions when indicated) allowed for lirilumab on this trial.
- 5-azacytidine at a dose of 75 mg/m² on days 1-7 has been shown to be safe in combination with multiple agents including lenalidomide[49], bortezomib[49], and vorinostat[50, 51]. 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). 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 the maximum dose for this trial of lirilumab 3.0 mg/kg every 4 weeks is the recommended phase 2 dose (RP2D) from ongoing Phase 2 study (IPH2102-101). We propose the starting dose level of 5-azacytidine 75 mg/m² x 7 days and lirilumab 1.0 mg/kg on day 8 of each 28 (+/- 7) day cycle to be escalated or de-escalated based on occurrence of DLTs as described below. The lead-in phase is to ensure that the combination is well tolerated with no unexpected side effects.

5.2.1.1 The starting dose will be dose level -1.

Table 1. Dose levels of 5-azacytidine and lirilumab during the lead-in phase (part a)

Dose level	5-azacytidine (mg/m ² /d, Days 1-7)	Lirilumab (mg/kg, day 8)
-4	25	0.3
-3	50	0.3
-2	75	0.3
-1	75	1.0 (Starting dose)
0	75	3.0

5.2.1.2 The goal of the lead-in phase is to identify the dose at which <2/6 patients experience DLT. During the lead-in phase the dose’s of 5-azacytidine and lirilumab may be reduced if 2 or more patients experience DLT at any given dose. After the lead in phase the dose of lirilumab may not be reduced in the phase II portion of the study. For potential lirilumab related AEs in the phase II portion of the study only dose interruptions of lirilumab will be permitted. Dose reductions or escalations of 5-azacytidine will continue to be permitted in the phase II portion of the study and dose reductions or escalations of 5-azacytidine beyond those mentioned in table 5 or different to the doses specified should be discussed with the PI and documentation of the justification recorded in the chart.

5.2.1.3 The dose and /or schedule of administration is subject to modification pending information from ongoing clinical trials of lirilumab as a single agent and in combination with other drugs.

DLT is defined as clinically significant non-hematologic adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and occurring during the first cycle on study that meets any of the following criteria:

- CTCAE Grade 3 AST (SGOT) or ALT (SGPT) for ≥ 7 days
- CTCAE Grade 4 AST (SGOT) or ALT (SGPT) of any duration
- All other clinically significant non-hematological adverse event that is Grade 3 or 4 according to the NCI common terminology criteria version 4.0 with the following exceptions:
 - Grade 3 or 4 nausea, vomiting and diarrhea will be considered DLT only if not controlled by optimal therapy.
 - Grade 3 biochemical abnormalities (e.g., lipase or bilirubin elevation) will only be considered DLT if accompanied by clinical consequences. Grade 3 or 4 electrolyte abnormalities will only be considered DLT if possibly related to study drug and not corrected by optimal replacement therapy.

5.2.1.4 We will first treat 6 patients at dose level -1 in the lead-in phase. If DLT occurs in $\geq 2/6$ patients, this dose level would exceed the MTD, and 6 patients will be treated at the next lower dose level (i.e. dose level -2). If DLT is observed in the first 28 days of treatment in 0 or 1/6 at dose level -1, then dose level 0 will be evaluated. The dose adjustment (Table 1) will continue in cohorts of 6 until we reach a dose level at which $< 2/6$ patients experience a DLT in the first 28 days. The dose level at which 0-1/6 patients experience a DLT in the first 28 days of treatment will be the MTD and will be used to treat an additional 34 patients in the phase II portion of the study. If $\geq 2/6$ patients experience DLT at dose level -4, the study will be revised to consider additional lower dose levels (based on potential synergistic toxicity).

5.2.1.5 Patients that are removed from study before day 28 for any reason other than toxicity and have not experienced DLT will be replaced.

5.2.2 One cycle of therapy is defined as 28 days. Patients will receive one cycle of therapy every 28 days (+/- 7 days).

5.2.2.1 In the phase II part of the study (once the MTD dose has been defined) cycles may be started early (but not earlier than day 21) for patients with active disease if judged in the best interest of the patient.

For the lead-in cohort, DLT defining period is 28 days. As such, cycle 2 should not be started before 28 days for the patients being treated on the lead-in cohort.

5.2.2.2 Subsequent cycles may be delayed for recovery of toxicity or other medical conditions (e.g. infections). Delays in start of subsequent cycles greater than 8 weeks will be acceptable only for patients who are deriving clinical benefit and after discussion with the principal investigator of potential risk/benefit ratio.

5.2.2.3 In instances where one drug has to be discontinued transiently because of safety, the administration of the other drug may continue as scheduled. If the drug that is held can resume at a later time, no doses will be made up and the administration will follow the originally defined schedule calendar according to the drug that was continued.

5.2.2.4 Subsequent courses of 5-azacytidine and lirilumab may be administered regardless of peripheral blood counts during the first 4 cycles and/or in the presence of residual leukemia.

If prolonged myelosuppression (more than 8 weeks) WITH evidence of a hypocellular marrow (marrow cellularity less than 5% without evidence of leukemia) is observed, 5-azacytidine and lirilumab will be discontinued. Delays in start of subsequent cycles greater than 8 weeks will be acceptable only for patients who are deriving clinical benefit and after discussion with the principal investigator of potential risk/benefit ratio. If the peripheral counts do not recover (ANC $<1 \times 10^9/L$ and/or platelets $<30 \times 10^9/L$) but there is evidence of residual leukemia in the bone marrow, subsequent cycles can be administered at the discretion of the treating physician not earlier than 21 days after the prior cycle.

5.2.2.4 For patients who discontinue therapy, the reason for treatment discontinuation will be captured.

5.3 Dose Adjustments

5.3.1 Lirilumab and 5-azacytidine dose adjustments for drug-related hematological AEs:

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE version 4.0 (Appendix C) of the toxicity and the guidelines provided below.

- Patients with acute leukemia's usually present with abnormal peripheral blood counts at the time therapy is started and myelosuppression is an expected event during the course of therapy for acute leukemias. Thus, no dose adjustments or treatment interruptions for myelosuppression will be planned for the first 4 cycles and/or in the presence of residual leukemia. After that, treatment interruptions and dose adjustments may be considered according to the following guidelines only when there is no evidence of active leukemia (e.g., only if <5% blasts in the bone marrow or cytopenias not considered to be related to leukemia).
 1. Patients with a response (e.g., only if <5% blasts in the bone marrow or cytopenias not considered to be related to leukemia) and pre-cycle counts of neutrophils $>1 \times 10^9/L$ and platelets $>50 \times 10^9/L$ who have sustained low counts of neutrophils $<0.5 \times 10^9/L$ or a platelet count $<20 \times 10^9/L$ for more than 2 consecutive weeks in the current cycle, may have the treatment with 5-azacytidine interrupted at the discretion of the treating physician after discussing with the PI until neutrophils recover to $\geq 1 \times 10^9/L$ and platelets to $\geq 50 \times 10^9/L$. Lirilumab has not been associated with neutropenia and/or thrombocytopenia in prior studies and should generally not be interrupted for myelosuppression.
 2. If there are persistent peripheral blood blasts, or the bone marrow shows >5% blasts or evidence of leukemia, treatment may be continued regardless of neutrophil and platelet count with supportive care as needed. Dose-interruptions of 5-azacytidine in these patients should be considered on an individual case and discussed with the PI.
 3. Patients with a response (no marrow evidence of leukemia) and pre-cycle counts of neutrophils $<1 \times 10^9/L$ and platelets $<50 \times 10^9/L$ may be continued regardless of neutrophil and platelet count with supportive care as needed. Dose-interruptions in these patients should be considered on an individual case and discussed with the PI.
 4. Investigators should, whenever possible, determine which medication is causing the toxicity and interrupt or dose reduce 5-azacytidine and/or interrupt lirilumab, as applicable. No dose reductions are permitted for lirilumab. Lirilumab has not been associated with neutropenia and/or thrombocytopenia in prior studies and should generally not be interrupted or discontinued for myelosuppression.

5.3.2 Lirilumab and 5-azacytidine dose adjustments for non-hematologic drug-related AEs

Investigators should, whenever possible, determine which medication is causing the toxicity and interrupt or dose reduce 5-azacytidine and/or interrupt lirilumab, as applicable. No dose reductions (only interruptions) are permitted for lirilumab. Dose reductions of azacytidine will be as per Table 1. Thus, if dose level 0 is established as the MTD, one and two dose level reductions of azacytidine will be azacytidine 50 mg/m² x 7 days and azacytidine 25 mg/m² x 7 days, respectively. If the MTD is below dose level 0 further dose reduction levels of 5-azacytidine will be defined before moving to the phase II portion of the study.

Table 2 Dose adjustments for non-hematologic drug-related adverse events, clinically significant in the opinion of the investigator

Grade	Occurrence	Dose modification
1 or 2	Any time	No dose reduction.
3 or 4 (Persistent grade 2: Consider similar dose adjustments if persistent and not responding to optimal management in the opinion of PI and treating physician)	1st and 2nd time	Hold lirilumab and 5-azacytidine. Resume lirilumab and 5-azacytidine at prior dose if recovery to ≤ Grade 1 occurs within 14 days. If toxicity persists for 15-28 days, hold therapy and resume at ONE dose level below current dose for 5-azacytidine and prior dose of lirilumab ONLY after recovery to ≤ Grade 2. Dose re-escalation to prior dose of 5-azacytidine is permitted in accordance with the dose-escalation guidelines in section 5.3.6.
	3 rd and 4th time	Hold lirilumab and 5-azacytidine. Follow until toxicity ≤ Grade 2. Resume lirilumab at prior dose and 5-azacytidine at ONE dose level below current dose. Dose re-escalation of 5-azacytidine to prior dose is permitted in accordance with the dose-escalation guidelines in section 5.3.6.
	5th time	Hold lirilumab and 5-azacytidine. Follow until toxicity ≤ Grade 2. Resume lirilumab at prior dose and 5-azacytidine at TWO dose levels below current dose. Dose re-escalation of 5-azacytidine by ONE dose level every 4 weeks is permitted in accordance with the dose-escalation guidelines in section 5.3.6.

5.3.3 Lirilumab dose delay/interruption for immune-oncology drug-related AEs, clinically significant in the opinion of the investigator

Lirilumab administration should be delayed for the following drug-related AEs, clinically significant in the opinion of the investigator:

- Any Grade ≥2 non -skin AE, except that
 - Grade 2 fatigue or laboratory abnormalities do not require delay, however
 - ◆ For a subject with baseline AST, ALT, or total bilirubin within normal limits, delay dosing for drug-related Grade ≥2 values
- Any Grade 3 skin AE, or Grade 3 laboratory abnormality, with the following exceptions:

- Grade 3 lymphopenia or leukopenia does not require dose delay.
- If a subject has Grade 1 baseline AST, ALT, or total bilirubin, delay dosing for drug-related Grade 3 toxicity
 - Any AE, laboratory abnormality, or intercurrent illness, which in the judgment of the investigator, warrants delaying the dose of study medication.
 - Lirilumab dose reductions are not permitted in this study (only dose delays when indicated).

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Discontinuation Section below) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

If the criteria to resume treatment are met, the subject should restart treatment at the same dose at the next scheduled timepoint per protocol. The next scheduled time point for 5-azacytidine is the projected day 1 of the next cycle. The next scheduled time point for Lirilumab is the projected day 8 of the next cycle. These will be the next scheduled time points irrespective of the patients current dose level. However, if the treatment is delayed past the next scheduled timepoint per protocol, the next scheduled timepoint will be delayed until dosing resumes. Patients who receive combination therapy in whom continuation of 5-azacytidine is considered to be inadequate, or inappropriate (e.g., because of pancytopenia) can discontinue 5-azacytidine and continue with lirilumab only.

If treatment is delayed > 8 weeks, the subject must be permanently discontinued from study therapy, except as specified in discontinuation section.

5.3.4 Lirilumab Discontinuation Criteria

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR lasting > 7 days with systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis,

pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reactions, and infusion reactions:

- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below:
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation: AST or ALT > 8 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
 - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
 - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any dosing interruption lasting > 8 weeks with the following exceptions:
 - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 8 weeks the Investigator must be consulted. Tumor/Leukemia assessments should continue as per protocol even if dosing is interrupted.
 - Dosing interruptions > 8 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 8 weeks the Investigator must be consulted. Tumor/Leukemia assessments should continue as per protocol even if dosing is interrupted.

5.3.5 Detailed management algorithms for immune-oncology drug-related adverse events (including gastrointestinal, renal, pulmonary, hepatic, endocrine, skin and neurological) are provided in Appendix G. These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor in specific cases.

5.3.6 Intra-patient dose re-escalation of 5-azacytidine for patients who have had dose-reductions due to hematological or non-hematological toxicity:

Once the MTD has been established in the lead-in, the lirilumab dose will not be reduced or escalated during the phase II. Intra-patient dose re-escalation of 5-azacytidine (in accordance with the dosing schema in table 1) will be permitted provided:

- Patient has completed ≥ 1 cycle at their current dose level
- Patient has not experienced any grade 3 or higher non-hematologic drug-related toxicity, and
- Patient has not experienced drug-related hematologic DLT, and
- At least 6 patients have been treated at the next higher dose level and followed for at least 28 days without experiencing DLT.
- The dose may be escalated by one dose level per cycle (per table 1) provided such dose level does not exceed the established MTD or dose level 0, whichever is lower. Dose level 0 is the maximum dose allowed on this study. No dose escalation beyond dose level 0 will be permitted.

5.3.7 Modifications of dose schedules other than the above will be allowed within the following guidelines:

5.3.7.1 Further dose reductions can be made to keep clinically significant toxicities grade ≤ 2 .

5.3.7.2 Dose adjustments by more than 1 dose level at a time (e.g., from 5-azacytidine 75 mg/m² to 25 mg/m²) can be considered when judged in the best interest of the patient (e.g. severe myelosuppression) when toxicity has resolved. The reason for this reduction will be discussed with the PI or Co-PI and documented in the medical record.

5.3.7.3 A patient who has had a dose reduction because of any of the reasons mentioned above may have their dose escalated provided the patient has remained free of toxicity requiring dose adjustments as defined above for at least 1 month. Escalation will be made by 1 dose-level increment only, and not more frequent than every month.

5.3.7.4 Treatment interruptions and dose modifications other than the ones mentioned above for either study drug related toxicity and/or events that are unrelated to study drug, for example but not limited to hospitalization for reasons unrelated to study drug can be considered after discussion with the PI, and proper documentation of the rationale. Dose adjustment/delay of only one of the agents is permissible if the toxicity is most likely judged to be related to one of the agents by the investigator (e.g., in patients with autoimmune thyroiditis or autoimmune hepatitis this would be likely secondary to lirilumab and 5-azacytidine dose could be escalated, in patients with cytopenia's this would be likely secondary to 5-azacytidine and lirilumab dose could be escalated).

5.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

1. Clinically significant progressive disease, or
2. Intercurrent illness that prevents further administration of treatment, or
3. Patient request, or
4. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator, or
5. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy.
 - 5.4.1 It is planned that up to a total of 24 cycles of therapy will be administered for patients deriving benefit from this regimen. Continuation of therapy for patients completing 24 cycles of therapy may be considered on a case-by-case basis after discussion with the principal investigator.
 - 5.4.2. A minimum of 1 full course (defined as the administration of 5-azacytidine for 7 days and one dose of lirilumab) will be required for a patient to be considered as having received an adequate trial to evaluate efficacy. All patients receiving at least one dose of any of the two drugs will be considered evaluable for toxicity.

5.5 Supportive Care:

Supportive care measures including blood products, infection prophylaxis and growth factors will be administered according to institutional and Leukemia Department guidelines.

Supportive care measures including blood products, infection prophylaxis and growth factors will be administered according to institutional and Leukemia Department guidelines.

Management Algorithms for Treatment of Lirilumab Related Adverse Events

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Lirilumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents such as lirilumab may mitigate severe toxicity. Lirilumab has a known safety profile however, a general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated. Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events, and lirilumab is no exception. The oral equivalent of the recommended IV doses may be considered for

ambulatory patients with low-grade toxicities. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Management Algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: **Endocrinopathy, Gastrointestinal, Hepatic, Neurological Pulmonary, Renal and Skin**. These algorithms are found in the “Lirilumab Investigator Brochure” (Appendix E) and “Management algorithms for immuno-oncology drug-related adverse events” (Appendix G) of this protocol. The guidance provided in these algorithms should not replace the Investigator’s medical judgment but should complement it.

Finally, consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is highly recommended.

5.6 Concomitant Medications:

Consistent with subject safety and comfort, administration of any prescription or over-the-counter drug products other than study medication should be minimized during the study period. Subjects should be discouraged from use of street drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol during the clinical study.

If considered necessary for the subject’s wellbeing, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The investigator’s decision to authorize the use of any drug other than study drug should take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study.

Subjects should be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the-counter, or illicit) before and during the course of the study.

Recommendations with regard to specific types of concomitant therapies, supportive care, diet and other interventions are as follows:

Concomitant medications are recommended as prophylaxis for nausea, vomiting, and infections, and are allowed for managing myelosuppression as shown in Table 3. Myelosuppression is expected in patients with AML due to underlying disease, as well as due to chemotherapy (such as 5-azacytidine), or both. Most patients have neutropenia, thrombocytopenia, or both at study entry. Significant or life-threatening myelosuppression may be managed with growth factor support including G-CSF, GM-CSF and platelet growth factors and erythropoietin/darbopoetin/blood transfusion according to institutional standard of

care, American Society of Clinical Oncology (ASCO) Practice Guidelines, and/or NCCN Practice Guidelines.

Infections secondary to myelosuppression are common in patients with AML, and may be related to underlying disease, chemotherapy, or both. Therefore, the use of prophylactic antibiotics, antifungal agents, and antiviral agents is recommended according to institutional standards.

Since the effect of both lirilumab and 5-azacytidine may be delayed for up to 4 weeks, patients with high WBC counts may receive hydroxyurea and up to 1 dose of cytarabine (up to 2 g/m²) prior to study entry. Hydroxyurea is allowed while the patient is on active study treatment, as needed, for clinical benefit and after discussion with the PI. Hydrea and cytarabine use would be recorded in the CRF. Concurrent therapy for CNS prophylaxis or continuation of therapy for controlled CNS disease is permitted. With the exception of these agents, concomitant systemic chemotherapy or radiation therapy is not permitted. Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

Subjects may be receiving systemic corticosteroids (daily doses ≤10 mg of prednisone or equivalent if indicated for adrenal replacement or antiemetic therapy), topical, or inhaled corticosteroids at study enrollment. They may receive systemic, topical, inhaled, or enteric corticosteroids while on study without limitation if they develop conditions that require corticosteroid therapy; such subjects are not required to discontinue study participation.

All ongoing medications and therapies (including herbal products, nutritional supplements, and nontraditional medications) at screening will be considered prior medications. Concomitant medication data will not be collected or entered into the case report form other than hydrea and cytarabine as mentioned above; however, the subject's medication record will contain a list of concomitant medications. If a prohibited medication is inadvertently administered/ taken by the patient, the patient may remain on study as long as the prohibited medication is discontinued as soon as feasible. If a prohibited medication is considered essential for the patient well being, continuation on study with concomitant administration of such medication(s) will need to be discussed with and approved by principal investigator and medical monitor. Prohibited medications are shown in Table 3.

Table 3: Instructions for the use of concomitant medications and therapies

Category of Use	Medication	Comment on Use	Restriction on Use
Recommended	Prophylactic antibiotics, antifungal agents, and antiviral agents	Strongly encouraged	None
	Antiemetic agents	According to standard of care at MDACC	None
Allowed	Oral allopurinol or rasburicase	At investigators discretion	None
	Leukapheresis	According to standard of	Before induction 1 day 1

		care at MDACC	only
	Red blood cell transfusion	None	None
	Platelet transfusion	None	None
	White blood cell transfusion	At investigators discretion according to standard of care at MDACC	None
	Myeloid growth factors or platelet growth factor	At investigators discretion according to standard of care at MDACC	None
	Erythropoietin or darbepoetin	At investigators discretion	None
	Any other medication for supportive care	At investigators discretion according to standard of care at MDACC	None

MDACC = MD Anderson Cancer Center

6.0 STUDY MEDICATIONS

6.1 **Lirilumab (Anti-KIR)**

For details regarding dose-calculation of lirilumab, preparation and dispensing of lirilumab, administration of lirilumab, patient monitoring during infusion and treatment of lirilumab related infusion reactions please see the dosing procedure manual (Appendix I).

6.2 **Azacytidine:**

5-azacytidine is commercially available. Commercial supply will be used for purposes of this study. Standard procedures should be used for preparation and administration of 5-azacytidine. The following guidelines are suggested:

Vidaza® (5-azacytidine) (is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Vidaza® (5-azacytidine) suspensions.

If reconstituted Vidaza® (5-azacytidine) comes into contact with the skin, immediately and thoroughly wash with soap and water. If it comes into contact with mucous membranes, flush thoroughly with water.

The Vidaza® (5-azacytidine) vial is single-use and does not contain any preservatives. Unused portions of each vial should be discarded properly. Do not save any unused portions for later administration.

6.2.1 Preparation for Subcutaneous Administration: Vidaza® (5-azacytidine) should be reconstituted aseptically with 4 mL sterile water for injection. The diluent should be injected slowly into the vial. Vigorously shake or roll the vial until a uniform suspension is achieved. The suspension will be cloudy. The resulting suspension will contain 5-azacytidine 25 mg/mL.

6.2.1.1 Preparation for Immediate Subcutaneous Administration: Doses greater than 4 mL should be divided equally into 2 syringes. The product may be held at room temperature for up to 1 hour, but must be administered within 1 hour after reconstitution.

6.2.1.2 Preparation for Delayed Subcutaneous Administration: The reconstituted product may be kept in the vial or drawn into a syringe. Doses greater than 4 mL should be divided equally into 2 syringes. The product must be refrigerated immediately, and may be held under refrigerated conditions (2°C–8°C, 36°F–46°F) for up to 8 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

6.2.1.3 Subcutaneous Administration: To provide a homogeneous suspension, the contents of the syringe must be re-suspended by inverting the syringe 2–3 times and vigorously rolling the syringe between the palms for approximately 30 seconds immediately prior to administration. Vidaza® (5-azacytidine) suspension is administered subcutaneously. Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate sites. Rotate sites for each injection (thigh, abdomen, or upper arm). New injections should be given at least 1 inch from an old site and never into areas where the site is tender, bruised, red, or hard.

6.2.1.4 Suspension Stability: 5-azacytidine reconstituted for subcutaneous administration may be stored for up to 1 hour at 25°C (77°F) or for up to 8 hours between 2°C and 8°C (36°F and 46°F).

6.2.2 Preparation for Intravenous Administration: Reconstitute the appropriate number of Vidaza® (5-azacytidine) vials to achieve the desired dose. Reconstitute each vial with 10 mL sterile water for injection. Vigorously shake or roll the vial until all solids are dissolved. The resulting solution will contain 5-azacytidine 10mg/mL. The solution should be clear. Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Withdraw the required amount of Vidaza® (5-azacytidine) solution to deliver the desired dose and inject into a 50-100 mL infusion bag of either 0.9% Sodium Chloride Injection or Lactated Ringer's Injection.

6.2.2.1 Intravenous Solution Incompatibility: Vidaza® (5-azacytidine) is incompatible with 5% Dextrose solutions, Hespan, or solutions that contain bicarbonate. These solutions have the potential to increase the rate of degradation of Vidaza® (5-azacytidine) and should therefore be avoided.

6.2.2.2 Intravenous Administration: Vidaza® (5-azacytidine) solution is administered intravenously. Administer the total dose over a period of 10-40 minutes. The administration must be completed within 1 hour of reconstitution of the VIDAZA vial.

6.2.2.3 Solution Stability: Vidaza® (5-azacytidine) reconstituted for intravenous administration may be stored at 25°C (77°F), but administration must be completed within 1 hour of reconstitution.

6.2.3 Storage: Store unreconstituted vials at 25° C (77° F); excursions permitted to 15°-30° C (59°-86° F) (See USP Controlled Room Temperature). There is no need to protect 5-azacytidine from exposure to light.

6.2.4 Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be applied.

6.3 Variations in infusion times of lirilumab or 5-azacytidine due to minor differences in IV bag overfill/underfill and institutional procedure on flushing chemotherapy lines will not result in protocol deviation. All infusion times are considered approximate.

7.0 PATIENT EVALUATION

Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in schedule of events and other protocol requirements that do not affect the rights and safety of the patient will not be considered as deviations. Such variations may include laboratory assessments completed outside of schedule, occasional missed required research samples such correlative assays.

7.1 Pre-Treatment Evaluation

All pretreatment studies should be obtained within 14 days of entry into the trial, unless otherwise stated.

7.1.1 A complete history and physical, documentation of all measurable disease, concomitant medications and performance status.

7.1.2 CBC, platelet count, differential (differential can be omitted if WBC is $\leq 0.5 \times 10^9/L$).

7.1.3 Creatinine, total bilirubin, ALT or AST.

- 7.1.4 Pregnancy test (urine or plasma) in females of childbearing potential should be performed within 72 hours before initiation of study.
- 7.1.5 Bone marrow aspirate during the last 28 days preceding study initiation. Cytogenetics will be obtained prior to therapy (results from prior analysis can be used for this purpose).
- 7.1.6 Pretreatment optional correlative studies (see below)

7.2 Evaluation During Treatment

- 7.2.1 Physical exam at the start of each cycle (\pm 4 days) and documentation of all concomitant medications.
- 7.2.2 CBC, platelet count, differential once weekly (\pm 4 days) for the first 3 cycles, then every 2-4 weeks (differential can be omitted if WBC is $\leq 0.5 \times 10^9/L$)
- 7.2.3 Creatinine, total bilirubin, ALT once weekly (\pm 4 days) for the first 3 cycles, then every 2-4 weeks.
- 7.2.4 Bone marrow aspiration on day 28 (\pm 7 days), then every 1-3 cycles. Bone marrow tests can be ordered more frequently if mandated by development of peripheral blood counts. No repeat bone marrow is necessary if nonresponse or progressive disease can be unequivocally diagnosed from peripheral blood tests or, in patients with a WBC < 0.3 if the bone marrow test is considered noncontributory by the investigator at any time point.
- 7.2.5 Concomitant medication data will not be collected or entered into the case report form except for concomitant hydroxyurea and cytarabine; however, the subject's medication record will contain a list of concomitant medications.
- 7.2.6 Correlative Studies relating to immunologic response: Tumor tissue, blood samples and bone marrow aspirate will be collected on a separate IRB approved laboratory protocol for immune monitoring as previously published[52-55], under the supervision of the Immunotherapy Platform (MDACC Protocol PA13-0291). Patients will be consented separately on the IRB approved consent for protocol PA 13-0291. Patients may participate in protocol 2014-0862 irrespective of whether they choose to participate on protocol PA 13-0291. In tumor tissues, immunohistochemical studies will be performed to evaluate tumor and immunological cell markers such as CD4 and CD8 T cells. In peripheral blood, we will also evaluate tumor and immune cell populations including but not limited to CD4 and CD8 T cells in pre and post therapy samples.
- 7.2.7

Peripheral blood up to 20 mL (within 24 hours) will be collected under an IRB-approved laboratory protocol for testing of biomarkers at the following time points

- Baseline (prior to 5-azacytidine dose), on day 8 (prior to lirilumab dose), and between days 21 to 28 on cycle 1 (done at MD Anderson).
- In each subsequent cycle blood samples will be obtained on day 1 (prior to 5-azacytidine dose) and day 8 (prior to lirilumab dose) when possible.
- Samples will be collected at progression whenever possible.

Bone Marrow:

- Bone marrow samples will be collected under an IRB-approved laboratory protocol for testing of biomarkers at baseline, at day 28 (+/-7 days), then every 1-3 cycles, and at progression whenever possible.

All these samples can be obtained +/- 3 days. Missed samples for correlative studies will not constitute protocol deviations. All correlative samples are optional.

- 7.2.8 For patients that remain on study with no significant toxicity for more than 6 months, subsequent evaluations during study may be modified after discussion with the principal investigator. These include a decrease in frequency of bone marrow aspirations to every 6-12 months (or as clinically indicated), correlative studies to every 6-12 months (or suspension of sample collection for correlative studies), other laboratory tests to once every cycle.
- 7.2.9 ALL treatments with lirilumab must be administered at the MDACC outpatient clinic. The first cycles of azacytidine must be administered at the MDACC outpatient clinic. Subsequently, patients will have the option of receiving 5-azacytidine injections or infusions at the MDACC outpatient clinic or local ambulatory treatment center. If the local treatment center cannot accommodate 7 consecutive day administration on Days 1-7 of 5-azacytidine, it is allowable to be administered on a 5+2 (days off) + 2 schedule (For example, Administer Monday through Friday, omit Saturday and Sunday, Resume/Administer Monday and Tuesday). In the event that the 5+2+2 schedule is utilized, the Lirilumab will be administered on Day 10, which is allowable by schedule window or +/- 2 days from Day 8. We do not intend for the subjects to receive lirilumab at an outside physician's office. During the first cycle all the laboratory evaluations will be done at MDACC. Subsequently, the patient may have the laboratory work done at a local clinic and the results reported to the research nurse for the study. The laboratory work done at the 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 H)
 3. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
 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.
 7. All follow-up visits will be performed at MDACC. Patients will return to MDACC for physical examination at the start of each cycle i.e. approximately every 28 days (+/-7).
- 7.2.10 End of Treatment Visit to be completed 30 days (+/-7 days) after the last dose of study drug. Blood (about 2-3 teaspoons) will be drawn for CBC, platelet count, differential, creatinine, total bilirubin, ALT. No other procedures or labs will be needed.
- 7.2.11 Patients with an objective response at completion of active study treatment will be followed for survival at MD Anderson Cancer Center (MDACC) for up to 90 days after completion of active treatment and while still on study. If the patient is unable to return to MDACC the follow-up visits may be conducted via telephone.

Data regarding adverse events will be collected during the study. Please see **Appendix D** regarding data capturing of adverse events and adverse events source documentation. Protocol specific data will be entered into PDMS/CORE. PDMS/CORE will be used as the electronic case report form for this protocol. Only unexpected AEs will be recorded in the Case Report Form (CRF). The Principal Investigator will sign and date the AE log per each

patient at the completion of each course. Following signature, the AE log will be used as source documentation for the adverse events for attribution.

Treatment may be discontinued for a variety of reasons, including patient withdrawal, investigator decision, and reasons specified by the protocol. Reasons for discontinuation of treatments are described below.

7 CRITERIA FOR RESPONSE:

Response Criteria for AML

Response criteria will be modified from the International Working Group for AML (JCO 2003; 21: 4642-9)[56]. Responders are patients who obtain a CR, CRi, or PR, with or without cytogenetic response, hematologic improvements, and morphologic leukemia-free state. Briefly, criteria are as follows:

8.1.1 Complete remission (CR):

- ◆ Peripheral blood counts:
No circulating blasts
Neutrophil count $\geq 1.0 \times 10^9/L$
Platelet count $\geq 100 \times 10^9/L$
- ◆ Bone marrow aspirate and biopsy:
 $\leq 5\%$ blasts
No Auer rods
No extramedullary leukemia

8.1.2 Complete Remission with Incomplete Platelet Recovery (CRp):

For patients to be classified as being in CRp, they must achieve CR except for incomplete platelet recovery ($< 100 \times 10^9/L$).

8.1.3 Complete remission with incomplete blood count recovery (CRi):

- ◆ **Peripheral blood counts:**
No circulating blasts
Neutrophil count $< 1.0 \times 10^9/L$, or
Platelet count $< 100 \times 10^9/L$
- ◆ **Bone marrow aspirate and biopsy:**
 $\leq 5\%$ blasts
No Auer rods
No extramedullary leukemia

8.1.4 Partial remission:

- ◆ All CR criteria if abnormal before treatment except:
- ◆ $\geq 50\%$ reduction in bone marrow blast but still $> 5\%$

8.1.5 Morphologic leukemia-free state:

- ◆ Bone marrow: $\leq 5\%$ myeloblasts

8.1.6 Hematologic Improvement (HI): Hematologic response must be described by the number of positively affected cell lines.

- ◆ **Erythroid response (E)** (pretreatment Hgb < 11 g/dL)
Hgb increase by ≥ 1.5 g/dL
- ◆ **Platelet response (P)** (pretreatment platelets $< 100 \times 10^9/L$)
Absolute increase of $\geq 30 \times 10^9/L$ for patients starting with $> 20 \times 10^9/L$ platelets
Increase from $< 20 \times 10^9/L$ to $> 20 \times 10^9/L$ and by at least 100%
- ◆ **Neutrophil response (N)** (pretreatment ANC $< 1.0 \times 10^9/L$)
At least 100% increase and an absolute increase $> 0.5 \times 10^9/L$
- ◆ **Blast response (B)**
 $\geq 50\%$ reduction in peripheral blood or bone marrow blasts but still $> 5\%$

9 DISCONTINUATION OF TREATMENT:

9.1 Discontinuation Criteria for Individual Patients

9.1.1 Patient Withdrawal

Patients may voluntarily withdraw consent to participate in the clinical study at any time and without giving any reason. Their withdrawal will not jeopardize their relationship with their healthcare providers or affect their future care. Patients may also choose to withdraw from study treatment, but agree to remain in the study for follow-up procedures.

9.1.2 Investigator Discontinuation of Patient

The investigator may exercise medical judgment to discontinue study treatment if clinically significant changes in clinical status or laboratory values are noted.

9.1.3 Criteria for Protocol-Defined Required Discontinuation of Treatment

The protocol requires discontinuation of study treatment for the following reasons:

1. Patient requests discontinuation.
2. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy.
3. Clinically significant progressive disease.

4. Investigator discretion.

9.1.4 Follow-Up at Treatment Discontinuation or Early Withdrawal

Patients who discontinue treatment for any reason should complete end-of-treatment procedures when possible. End of treatment procedures will include a physical examination, CBC with differential and platelets and a limited chemistry profile (total bilirubin, serum creatinine, SGPT or SGOT). A bone marrow aspiration may be recommended only if non-response or progressive disease cannot be unequivocally diagnosed from peripheral blood. Although treatment will be discontinued at that time, all patients who do not withdraw consent for follow-up, die, or become lost to follow-up, will remain on study for follow-up evaluations. Subject will be followed for toxicity for at least 30 days after the last protocol treatment. The 30-day follow-up visit will be scheduled as a clinic visits for clinical evaluation and physical examinations. If the patient cannot make it to the MDACC clinic for this visit, the required follow up treatment procedures may be done with a local physician and the records forwarded to MDACC. The research nurse will contact the patient by telephone and get a verbal assessment of the patient's condition. The phone conversation will then be documented in the patient's charts.

9.2 Study Stopping Rules

The principal investigator and MDACC IND office have the right to terminate this clinical study at any time. The principal investigator and MDACC IND office, as appropriate, will be involved in any decisions regarding terminating the study, temporarily suspending enrollment, or stopping ongoing treatment with study treatment.

Reasons for terminating the clinical study or a study site's participation include, but are not limited to, the following:

- The incidence or severity of an adverse reaction related to treatment in this study or other studies indicates a potential health hazard to patients
- Data recording is significantly inaccurate or incomplete
- Study site personnel are noncompliant with study procedures
- Pattern of noncompliance is observed

9.3 Protocol Violations and Deviations

Protocol violations are defined as significant departures from protocol-required processes or procedures that affect patient safety or benefit potential, or confound assessments of safety or clinical activity. A protocol deviation is a departure from the protocol that does not meet the above criteria. Protocol violations or deviations may be grouped into the following classes:

- Enrollment criteria
- Study activities (missed evaluations or visits) except for those allowed per protocol
- Noncompliance with dose or schedule, including dose calculation, administration, interruption, reduction, or delay; or discontinuation criteria
- Investigational product handling, including storage and accountability
- Informed consent and ethical issues

10 ADVERSE EVENT REPORTING

- 10.1** 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 subjects enrolled on the trial.

- 10.2 Adverse Events (AEs) will be evaluated according to the latest CTC version 4 (Appendix C) and documented in medical record. Only unexpected AEs will be recorded in the Case Report Form (CRF). Expected events during leukemia therapy are:**

10.2.6 Myelosuppression related events (due to disease or leukemia therapy)

10.2.6.1 febrile or infection episodes not requiring management in the intensive care unit

10.2.6.2 epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage

10.2.6.3 anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia

10.2.7 Disease related events

10.2.7.1 symptoms associated with anemia

10.2.7.1.1 fatigue

10.2.7.1.2 weakness

10.2.7.1.3 shortness of breath

10.2.7.2 electrolyte abnormalities (sodium, potassium, bicarbonate, CO₂, magnesium)

10.2.7.3 chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)

10.2.7.4 coagulation abnormalities

10.2.7.5 disease specific therapy (induction, maintenance, salvage, or stem cell therapy)

10.2.7.6 alopecia

10.2.7.7 bone, joint, or muscle pain

10.2.7.8 liver function test abnormalities associated with infection or disease progression

10.2.7.9 disease progression

10.2.7.10 abnormal hematologic values

10.2.8 General therapy related events

10.2.8.1 catheter related events

10.2.8.2 renal failure related to tumor lysis syndrome or antibiotic/antifungal therapy

10.2.8.3 rash related to antibiotic use

10.2.9 Hospitalization for the management of any of the above expected events

10.3 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.

10.4 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).

- 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).
- **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.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy

10.5 Serious Adverse event Reporting to Bristol-Myers Squibb Inc.

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.
- **SAE Fax Number:** 609-818-3804

10.6 Data Safety Plan

The PI of this Clinical Protocol will be responsible for the management of the protocol and data safety. Confidentiality of personal health information (PHI) will be maintained throughout the study. The investigators do realize that a risk to patient PHI confidentiality exists whereby personal information could accidentally be released, however, all necessary precautions will be taken to prevent this from happening. Unique patient identifiers will be used to replace patient name and medical record number. Patient identifiers will be available only to the investigators for the study and will be kept in a password-protected database and locked file cabinet. Paper records (data forms, list of patient names and unique identifiers, etc.) will be kept in a locked file cabinet with access granted only to study investigators. No identifying personal health information will be used in any publication from this study. Collected information (including patient identifiers) will be destroyed within 5 years after publication. The protected health information used in this study will not be reused or disclosed to any person or entity outside of the investigators nor will it be used for other research.

11.0 STATISTICAL CONSIDERATIONS

This will be a single arm, single center, open label study of lirilumab in combination with 5-azacytidine in patients with refractory, relapsed or untreated AML.

11.1 Sample Size

Part a. Lead-in phase

The primary objective of the lead-in phase is to determine the safety of lirilumab in combination with 5-azacytidine in patients with refractory/ relapsed AML. Up to 24 patients will be accrued into lead-in part of the study.

Part b. Phase II

Up to 40 patients (including 6 patients treated at the MTD from the lead-in part) will be recruited for the Phase II part.

The primary objective of the phase II is to determine the efficacy of lirilumab in combination with 5-azacytidine in patients with refractory, relapsed or untreated AML. The efficacy of the combination will be measured by the overall response rate (ORR), defined as CR (complete remission) + CRp (complete remission with incomplete platelet recovery) + CRi (complete remission with incomplete count recovery) + PR (partial response) + marrow clearance of blasts + HI (Hematological improvement) within 3 months of treatment initiation among adult patients with refractory/ relapsed AML. ORR and toxicity will be monitored simultaneously using the Bayesian approach of Thall, Simon, Estey (1995, 1996) and the extension by Thall and Sung (1998).

Once safety of the MTD has been established, any patients still on study at a dose lower than MTD can be dose escalated up to MTD. Patients treated in the lead-in phase at MTD will be included in the phase II portion of the study.

11.2 Statistical Design

Part a. Lead-in phase

The MTD is defined as the highest dose level with ≤ 1 out of 6 patients experience a DLT during the first 28 days of treatment. DLT is defined in section 5.2.2. The dosing schema for the combination treatment during the lead in phase is shown in Table 1 in section 5.2.1.

Part b. Phase II

Historical data on similar patients shows an ORR of 10-15%. The target ORR with the experimental treatment is 30%. This regimen of the combination treatment will be considered worthy of further investigation if it elicits an increase in ORR to 30% with acceptable toxicity. A $>30\%$ drug-related grade 3/4 toxicity rate is considered unacceptable. Thus, interim monitoring rules, assuming the prior distributions above, were constructed that meet the following two conditions,

- 1) Stop if $\text{Prob}\{p(\text{ORR}, E) < p(\text{ORR}, H) + 0.15 \mid \text{data}\} > 0.975$, or
- 2) Stop if $\text{Prob}\{p(\text{TOX}, E) > 0.30 \mid \text{data}\} > 0.975$,

where $P(\text{ORR}, E)$ and $P(\text{TOX}, E)$ are the true ORR and toxicity rates for the combination treatment, and $p(\text{ORR}, H)$ is the true ORR rate of the standard treatment. The first rule provides for stopping the study if the data suggest that it is unlikely (i.e., probability $< 2.5\%$) that ORR rate of the combination treatment is greater than the ORR rate of standard treatment by 15.0%. The second condition will stop the study early if excessive therapy-related grade 3/4 toxicity ($>30\%$) is highly probable (i.e., probability $>97.5\%$) for the combination treatment. Monitoring for toxicity and futility will not begin until 5 patients have been evaluated, and cohort size for future evaluations is 5.

The monitoring rule for the toxicity rate, based on these assumptions and monitoring conditions above is found in Table 4. **For example, accrual will cease if 4 or more patients experience toxicities among the first 5 patients.**

Table 4. Stop accrual if the number of drug-related grade 3/4 toxicities is greater than or equal

to indicated (i.e., # patients with toxicities) among the number of patients evaluated								
# patients evaluated	5	10	15	20	25	30	35	40
# patients with toxicities	4-5	6-10	8-15	10-20	12-25	14-30	16-35	Always stop with this many patients

Monitoring the ORR rate, based on the above assumptions and monitoring conditions is found in Table 5. **For example, accrual will cease if less than 2 patients experience an overall response within 3 months of initiation of therapy in the first 10 patients treated.**

Table 5. Stop accrual if the number with overall response is less than or equal to indicated (i.e., # patients with overall response) among the number of patients evaluated					
# patients evaluated	5	10-15	20-25	30-35	40
# patients with overall response	Never stop with this many patients	0-1	0-2	0-3	Always stop with this many patients

Multic Lean Desktop (version 2.1.0) was used to generate the toxicity and futility stopping boundaries and the OC table (Table 6). In order to utilize the software for the design, a beta (0.3, 1.7) and beta (0.4, 1.6) priors were assumed for the standard treatment response distribution and experimental treatment response prior distribution, respectively. In addition, a 30% toxicity constant rate and beta (0.6, 1.4) priors were assumed for the standard treatment toxicity constant rate and experimental treatment toxicity prior distribution, respectively.

The probability of stopping the study early if the true ORR of the combination treatment was 30% and the true toxicity rate was 30% was 15.1%. Probabilities of stopping early for high true toxicity rates (i.e., 50%) were 84.0% when the true ORR was 30% and 83.6% when true ORR rate was 40%.

Table 6. Operating characteristics for simultaneous monitoring response and toxicity rates for patients treated with combination treatment		
True Toxicity Rate	True ORR	Prob(stop the trial early)
0.10	0.15	0.3001
	0.20	0.1479
	0.25	0.0703
	0.30	0.0328

Table 6. Operating characteristics for simultaneous monitoring response and toxicity rates for patients treated with combination treatment

True Toxicity Rate	True ORR	Prob(stop the trial early)
	0.35	0.0151
	0.40	0.0069
0.20	0.15	0.3101
	0.20	0.1601
	0.25	0.0836
	0.30	0.0466
	0.35	0.0292
	0.40	0.0211
0.30	0.15	0.3859
	0.20	0.2523
	0.25	0.1842
	0.30	0.1514
	0.35	0.1358
	0.40	0.1286
0.40	0.15	0.6194
	0.20	0.5367
	0.20	0.4945
	0.30	0.4741
	0.35	0.4645
	0.40	0.4600
0.50	0.15	0.8841
	0.20	0.8589
	0.25	0.8460
	0.30	0.8398
	0.35	0.8369
	0.40	0.8355

All patients who received any dose of the study agent will be included in the analysis for efficacy and safety. Demographic/clinical characteristics (including duration of response) and safety data of the patients will be summarized using descriptive statistics such as mean, standard deviation, median and range. For the primary efficacy analysis, we will estimate the ORR for the combination treatment, along with the 95% confidence interval. Patients who drop out of the study before completing all the cycles will be treated as “failures” for the primary analysis. ORR during the study period will also be presented with the 95% confidence interval. The association between ORR and patient’s clinical characteristics will be examined by Wilcoxon’s rank sum test or Fisher’s exact test, as appropriate. Toxicity type, severity and attribution will be summarized for each patient using frequency tables.

The distribution of time-to-event endpoints (DFS and OS) including overall survival and progression free survival will be estimated using the method of Kaplan and Meier. Comparisons of time-to-event endpoints by important subgroups will be made using the log-rank tests. Paired t-tests will be used to determine the immunological and molecular changes in the peripheral blood and bone marrow from baseline to the time of response, and to the time of disease progression. Correlation analysis (such as logistic regression analysis) will be conducted to determine the relationship between induction of hypomethylation / DNA damage and clinical response.

Statistical analysis of biomarker data: 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 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.

12.0 PROTOCOL ADMINISTRATION

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

Protocol amendments

Changes to the protocol will be made only when protocol amendments have been signed by the principal investigator and approved by the sponsor and the IRB of the study center.

Archival of data

All patient data (including source data) generated in connection with this study will be kept in the archives of the MDACC for at least 15 years after the study has been completed. All data will be available for inspection by company representatives of the Medical Department and by regulatory authorities.

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14.0 APPENDICES

Appendix A: Prioritization List – Priority List

Appendix B: Protocol Checklist

Appendix C: CTCAE version 4.0

Appendix D: Leukemia specific AE recording and reporting guidelines

Appendix E: Lirilumab BMS Investigator Brochure

Appendix F: Vidaza Drug Information

Appendix G: Management algorithms for immuno-oncology drug-related adverse events

Appendix H: Outside Physician Form

Appendix I: DOSING PROCEDURE MANUAL for Lirilumab and Nivolumab Version
2.0