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A Phase 1 Study of Venetoclax with Obinutuzumab and Magrolimab (VENOM) in Relapsed and Refractory Indolent B-cell Malignancies

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Drug Name:	Magrolimab	Venetoclax (Venclexta®)	Obinutuzumab (Gazyva®)
IND Number:	148205		
Sponsor:	Center for Cancer Research		
Manufacturer:	Gilead Sciences, Inc.	AbbVie	Genentech
Supplier:	Gilead Sciences, Inc.	Genentech	Genentech

PRÉCIS

Background:

- Indolent B-cell malignancies are associated with frequent disease relapse
- Standard frontline therapy includes a monoclonal anti-CD20 antibody with or without chemotherapy; novel targeted therapies have changed the treatment landscape and are preferred therapy for some patients with high-risk molecular features
- Targeted therapies given indefinitely add to drug resistance, treatment-emergent toxicities, and non-compliance
- CD47 is a rational target for indolent B-cell malignancies; CD47 expression is higher in tumor cells than normal B-cells, and blocking CD47 results in phagocytosis of tumor cells
- Magrolimab is an anti-CD47 monoclonal antibody with activity in refractory indolent lymphomas when combined with rituximab (a first generation anti-CD20 monoclonal antibody)
- Obinutuzumab is a novel anti-CD20 monoclonal antibody with enhanced binding to the Fc receptor that may improve antibody-dependent cell-mediated cytotoxicity (ADCC), and phagocytosis, when combined with magrolimab
- We aim to test the safety and efficacy of venetoclax when added to the backbone of magrolimab and obinutuzumab in patients with relapsed or refractory indolent B-cell malignancies
- Treatment duration will be response-adapted and time-limited in all patients

Objective:

- To determine the safety of the triplet combination of venetoclax, magrolimab and obinutuzumab in relapsed and refractory indolent B-cell malignancies

Eligibility:

- Follicular lymphoma (FL) (grades 1-2, or 3a), marginal zone lymphoma (MZL), mantle cell lymphoma (MCL) or chronic lymphocytic leukemia (CLL) with ≥2 prior therapies, with at least one of those therapies containing an anti-CD20 monoclonal antibody
- ECOG performance status 0-2
- Adequate bone marrow and organ function

Design:

- Phase 1 study with expansion cohorts of up to 76 patients with relapsed or refractory FL, MZL, MCL or CLL
- The safety profile of magrolimab, venetoclax, and obinutuzumab will first be determined in a dose-finding phase of up to 24 patients (6-12 patients with FL and 6-12 patients with MZL, MCL or CLL). Patients without dose-limiting toxicity (DLT) will receive an additional 5 cycles (total 6 cycles) of the triplet combination.
- After dose-finding is completed, expansion cohorts of each histology will first receive magrolimab and obinutuzumab for 2 cycles in a window for translational research. After the window, venetoclax will be added and patients will receive 6 cycles (total 8 cycles) of the triplet combination.

- Patients who achieve a complete response (CR) (after a total of 6 cycles of the triplet combination) will stop treatment and initiate active monitoring with radiologic imaging and assays for circulating tumor DNA (ctDNA); if these patients relapse, they can be retreated with an 6 additional cycles. Patients who achieve partial response (PR) after 6 cycles of the triplet will continue for an additional 6 cycles; then, will initiate active monitoring.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To determine the safety of the triplet combination of magrolimab, venetoclax, and obinutuzumab in relapsed and refractory indolent B-cell malignancies

1.1.2 Secondary Objectives

- To determine the best overall response rate (CR + PR) of triplet combination therapy with magrolimab, obinutuzumab, and venetoclax
- To determine the rate of complete molecular remission (MRD negativity) by flow cytometry or similar assays as they become available in patients after triplet combination therapy with magrolimab, obinutuzumab, and venetoclax (in CLL patients only)
- To determine the duration of response (DOR) of triplet combination therapy with magrolimab, obinutuzumab, and venetoclax
- To estimate progression-free survival (PFS), event-free survival (EFS), and overall survival (OS) of triplet combination therapy with magrolimab, obinutuzumab, and venetoclax

1.1.3 Exploratory Objectives

- To determine the best overall response rate (CR + PR) of 2 cycles of doublet combination therapy with magrolimab and obinutuzumab ('Window Treatment')
- To determine the rate of complete molecular remission (MRD negativity) by circulating tumor DNA (ctDNA) assay or similar assays as they become available after doublet-combination therapy with magrolimab and obinutuzumab and/or triplet combination therapy with magrolimab, obinutuzumab, and venetoclax
- To identify a mutational or gene-expression signature that predicts response to magrolimab and obinutuzumab

- To identify a mutational or gene-expression signature associated with intrinsic resistance to magrolimab and obinutuzumab
- To explore immunologic correlates of response and mechanisms of resistance to magrolimab and obinutuzumab
- To determine if ctDNA assays identify molecular relapse prior to clinical progression
- To test immunogenicity of magrolimab and to assess the effect of anti-drug antibodies (ADA) on the pharmacokinetics, pharmacodynamic markers, efficacy, and safety of magrolimab

1.2 BACKGROUND AND RATIONALE

1.2.1 Trial Design Summary

This study will evaluate the safety and efficacy of magrolimab added to venetoclax and obinutuzumab in patients with relapsed and/or refractory indolent B-cell malignancies. The first portion of the study will determine the dose of venetoclax to be used during expansion. The triplet combination will use a 5-week safety ramp-up of venetoclax in patients with mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and chronic lymphocytic leukemia (CLL). Patients with follicular lymphoma (FL) will have venetoclax started at the target dose without a ramp-up. Patients without DLT in the dose-finding portion will be treated with an additional 5 cycles of triplet combination therapy.

After the dose finding portion is complete and the dose of venetoclax is known, further expansion cohorts will test the efficacy of the triplet combination within individual histologies. In the expansion phase of the study, patients will first receive a "window" of two cycles of magrolimab and obinutuzumab in order to define the early indicators of efficacy of this combination in indolent B-cell malignancies. The primary translational endpoints will occur during this window, including the molecular and immunologic correlates of response and mechanisms of resistance. After the window, venetoclax will be added. Patients who achieve CR after 6 cycles of the triplet combination will stop therapy and initiate active surveillance with periodic standard imaging and research assays for ctDNA. Patients with PR after the initial 6 cycles of the triplet combination will continue for an additional 6 cycles before stopping therapy and initiating active surveillance. Patients who do not achieve at least PR after the initial 6 cycles of the triplet combination or those who discontinue treatment before 6 cycles will stop therapy and initiate active surveillance.

1.2.2 Indolent B-cell Lymphomas: Follicular Lymphoma and Marginal Zone Lymphoma

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma (NHL)(1), accounting for ~25% of cases with an estimated incidence of 74,680 new cases diagnosed in 2018. The clinical course of FL is highly variable; many patients have indolent disease that is slowly progressive and defined by a perpetually relapsing and remitting course, while other patients experience rapid growth of lymph nodes and aggressive clinical behavior that requires therapy shortly after diagnosis(2, 3). FL is generally not curable with standard frontline systemic chemotherapy, so most patients require multiple sequential treatment regimens throughout their disease course. Further, a subset of FL patients who relapse within 2 years from frontline therapy have a poor overall prognosis with standard treatment. A retrospective analysis of 588 patients with FL in the National LymphoCare database demonstrated that approximately 20% of patients experience progression of disease within 2 years of diagnosis (POD24) despite therapy with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone with (R-CHOP)(4).

The patients with POD24 had significantly worse overall survival including a hazard ratio for early death of 7.17 (95% CI, 4.83 to 10.65) compared with the reference group. 5-year survival of patients with POD24 was ~50%, compared with a 5-year survival rate of 90% for the remaining patients(4). Early disease progression after therapy was further validated as a surrogate marker of poor overall survival with a pooled analysis of 13 randomized studies in FL and >5,000 patients known as the Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) dataset(5). In the FLASH dataset, POD24 was confirmed to be associated with poor subsequent overall survival (OS) (hazard ratio (HR) = 5.24; (4.63 - 5.93); $p < .01$). Current research focuses on understanding the molecular biology of FL patients with POD24 after standard frontline chemotherapy, so these patients can be prioritized for treatment with novel combinations designed to overcome intrinsic chemotherapy resistance(6). FL patients who relapse beyond 2 years from initial chemotherapy may also benefit from novel combinations, particularly regimens that are not administered indefinitely. In particular, patients who have become refractory to rituximab-based regimens have limited treatment options and should be considered for novel treatment combinations. Most trials incorporating novel agents for FL have continued treatment until disease progression, death or unacceptable toxicity. Given that many FL patients have a long life expectancy, there is a need for time-limited treatment regimens that provide deep, durable responses, and avoid cumulative toxicities.

Marginal zone lymphoma (MZL) is an indolent B-cell lymphoma that includes three (3) subtypes: nodal marginal zone lymphoma (NMZL), extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), and splenic B-cell marginal zone lymphoma (SMZL). Together, these MZLs account for ~12% of cases of NHL(1). The average age at diagnosis is 60 years. Marginal zone lymphomas arise from a post-germinal center marginal zone B cell and may present in the lymph nodes, spleen, or extranodal tissues. The treatment approach to MZL is not standardized and ranges from watchful waiting, localized radiation, or systemic treatment with chemotherapy and/or anti-CD20 monoclonal antibodies(7, 8). Similar to FL, MZL is generally incurable with standard frontline systemic chemotherapy, and patients often require multiple sequential treatments throughout their disease course. Although many patients with MZL will have an indolent disease course, some cases of MZL are associated with resistance to chemotherapy and/or rituximab. Patients with MZL with short remission durations and those who are refractory to rituximab should be prioritized for novel treatment combinations.

Recently, the FDA granted accelerated approval for the use of ibrutinib monotherapy in patients with MZL who require systemic therapy and have received at least one prior anti-CD20-based therapy. This approval was based on a phase 2 study of ibrutinib in 63 patients with relapsed/refractory MZL(9). In this study, the overall response rate was 46% (95% CI: 33.4-59.1), but only 3% were complete responses. Efficacy was observed across all three MZL types. However, the treatment with ibrutinib was administered indefinitely. The treatment experience in CLL has demonstrated that many patients do not tolerate prolonged ibrutinib monotherapy, and treatment-emergent toxicities include hemorrhage, infections, cytopenias, and atrial fibrillation(10).

Recommendations for clinical trial development in FL and related indolent B-cell lymphomas emphasize the importance of effective treatment combinations with a good safety profile able to provide durable clinical benefit for patients(11). The ultimate therapeutic goal for indolent B-cell lymphomas is time-limited combination regimens of novel targeted agents that offer the potential for cure.

1.2.3 Indolent B-cell Leukemias: Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma

Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) (henceforth called CLL) and mantle cell lymphoma (MCL) are also incurable B-cell malignancies that are considered separately in this protocol because they are frequently associated with a leukemic component that manifests with high levels of circulating tumor cells. These patients may be more susceptible to specific toxicities such as tumor lysis syndrome (TLS), and hence, will receive a lower target dose of venetoclax on this protocol.

CLL is the most common B-cell malignancy in developed countries and is estimated to result in approximately 21,000 new cases in the United States in 2018. Similar to the other B-cell malignancies included in this protocol, CLL predominantly affects older patients with a median age at diagnosis of 72 years(12). Furthermore, treatment of CLL is generally not curative and patients with resistant disease or multiple disease relapses need novel combinations. The combination of chemotherapy with anti-CD20 monoclonal antibodies has been the mainstay of therapy for decades, but most patients will not have durable remissions with this approach beyond 3-4 years. Moreover, a subset of patients with CLL, such as those with *TP53* aberration, either because of deletion of chromosome 17p or *TP53* mutation, relapse very early after frontline chemoimmunotherapy(13). Another important consideration is that the toxicity associated with chemotherapy can be challenging in patients over the age of 65 years. For all of these reasons, the treatment landscape has changed dramatically over the last few years towards novel targeted small molecule inhibitors of BTK and Bcl-2(14). One significant advantage of these small molecule inhibitors is their activity in patients with high-risk features such as a *TP53* aberration(15, 16). As single agents, however, these targeted therapies do not achieve deep remissions, are not curative, and must be taken indefinitely. A recent 5-year follow-up study of ibrutinib monotherapy at the NIH in patients with both treatment-naïve and relapsed CLL demonstrated an overall 5-year PFS of 58.2% in patients with *TP53* aberrations(17). However, patients with relapsed/refractory CLL had a 5-year PFS of only 19.4% (95% CI, 6.3%-60%). Venetoclax is a small molecule inhibitor of Bcl-2 that has also shown significant single agent activity in patients with relapsed CLL. In a phase 1b study, the 15 month PFS of venetoclax in patients treated with the maximum dose was estimated at 69% and similar activity in patients with or without chromosome 17p deletions(18). Notably, venetoclax has demonstrated an overall response rate of 59% in patients who have progressed after ibrutinib(19).

Although the treatment of CLL has been improved with the use of small molecule inhibitors, new challenges have arisen due to the extended durations of treatment which lead to long-term toxicities, noncompliance, and a significant financial burden. A recent population-based study of 616 patients who started on ibrutinib monotherapy for CLL showed that after only 17 months, an estimated 41% of patients had discontinued ibrutinib with a median time of only 7 months on treatment prior to discontinuation(10). The most common reason for discontinuation was intolerance rather than disease progression. These data highlight the potential benefit of time-limited treatment strategies with adequate safety profiles. Another potential limitation of small molecule inhibitors as monotherapy is the infrequent achievement of complete response or achievement of minimal residual disease (MRD) negativity. For this reason, novel treatment combinations have been explored that are capable of clearing MRD. A recent study of venetoclax-rituximab in relapsed CLL demonstrated a superior PFS compared to bendamustine-rituximab and this benefit was observed across all clinical and biological subgroups(20). The improved PFS was

due to the ability of venetoclax-rituximab to attain deep remissions since the landmark analysis at 9 months showed 62.4% of patients were negative for MRD while only 13.3% of patients were MRD negative in the bendamustine-rituximab arm. These data support the notion that novel combinations are more likely to achieve deep remissions that translate to durable clinical benefit.

Mantle cell lymphoma (MCL) is a distinct B-cell lymphoma that represents about 6% of all B-cell NHLs. It is characterized by the t(11;14) translocation that results in aberrant expression of cyclin D1(21). Despite this unifying genetic event, MCL is biologically and clinically heterogeneous. A subset of patients with MCL have an indolent disease course and can safely have their initial therapy deferred without an impact on survival(22, 23). In contrast, other patients with MCL will have rapid disease progression and relapse quickly after frontline therapy despite the use of highly intensive immunochemotherapy and consolidation with autologous stem cell transplant (ASCT)(24, 25). Importantly, MCL is not curable with highly intensive chemotherapy and long-term follow-up has demonstrated a continuous incidence of disease relapse(26). MCL has worse prognosis than most indolent B-cell malignancies, partly because it occurs in older men. The median age at diagnosis of MCL is ~65 years which limits the broad use of highly intensive therapies such as ASCT. Hence, both those patients who have relapsed after intensive therapies as well as those who are not candidates for highly intensive treatments can potentially benefit from effective treatment combinations with a good safety profile.

Over the last decade, numerous targeted agents have been FDA-approved for use in patients with relapsed MCL including the proteasome inhibitor, bortezomib, the immunomodulatory agent, lenalidomide, and the inhibitors of Bruton's tyrosine kinase (BTK), ibrutinib and acalabrutinib(27-31). The use of these novel targeted agents with anti-CD20 antibodies and chemotherapy has led to improvements in overall survival for all ages of MCL patients according to a recent analysis of the SEER database(32). One particularly challenging clinical problem, however, is that patients who progress after ibrutinib often have a very aggressive disease course associated with poor outcomes. In an international, multicenter, retrospective cohort study involving 114 patients with a median of 3 prior treatments, the median OS following cessation of ibrutinib was 2.9 months (95% CI 1.6-4.9 months)(33). Patients with ibrutinib resistance or intolerance do not have good treatment choices and represent a population that needs effective novel combinations with an acceptable safety profile.

1.2.4 Magrolimab

1.2.4.1 Background and Pre-Clinical Studies

Magrolimab is a monoclonal antibody that targets CD47 and is being developed in combination with rituximab for the treatment of both indolent and aggressive B-cell malignancies(34). CD47 was discovered by Stanford researchers to play a key role in the ability of cancer cells to evade phagocytosis by the innate immune system(35). Cancer cells are able to overcome intrinsic phagocytic ("eat me") signals via the binding of CD47 to its ligand, signal regulatory protein alpha (SIRPα), that is expressed on phagocytic cells, including macrophages, monocytes, and dendritic cells (**Figure 1**). The binding of SIRPα on phagocytic cells to CD47 on lymphoma cells initiates recruitment of the src homology-2 domain containing protein tyrosine phosphatases SHP-1 and SHP-2 resulting in inhibition of phagocytosis. CD47 expression is higher in tumor cells than in normal peripheral blood and germinal center B cells across a variety of B-cell NHL subtypes including FL, CLL, and MCL, and is associated with a worse clinical prognosis(36). Blocking of the SIRPα-CD47 pathway ("don't eat me" signal) with magrolimab leads to phagocytosis of the

lymphoma cell. As tested in Raji cell lines, there was a positive correlation between CD47 expression and degree of anti-CD47 antibody-mediated phagocytosis with both mouse and human macrophage effector cells. Beyond the postulated effect on the innate immune system, magrolimab may also activate the adaptive immune system against the tumor. Phagocytosis of tumor cells by macrophages leads to cross-presentation of tumor antigens, and xenograft models have shown that blocking anti-CD47 primed CD8+ T-cells for cytotoxic effects producing sustained responses(37). Through these immunologic mechanisms, blocking CD47 with magrolimab is a promising immune checkpoint inhibitor therapy across a variety of malignancies(38, 39).

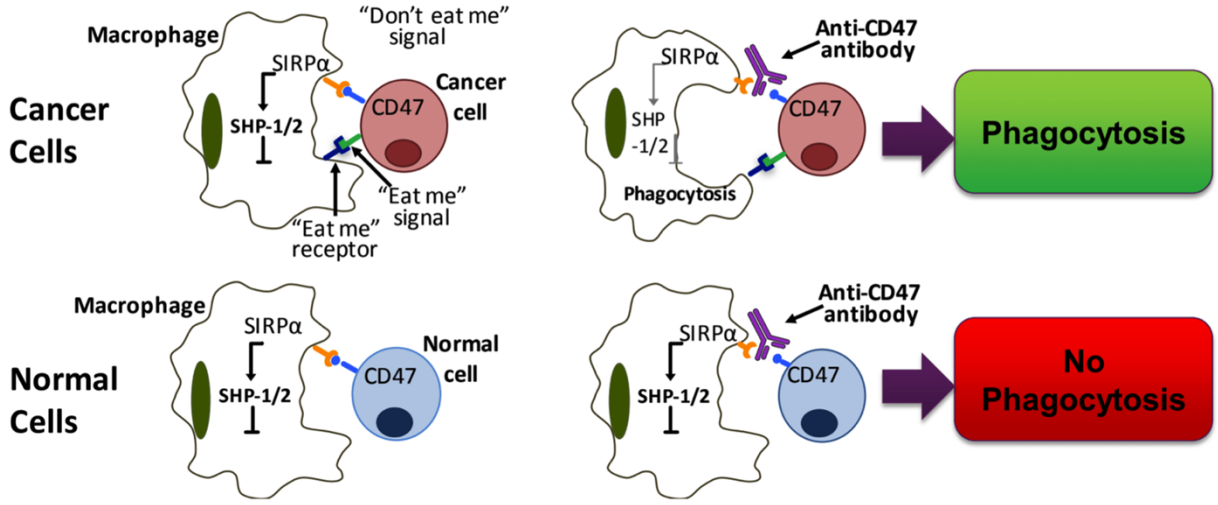


Figure 1: CD47 antibody (yellow) binds to its antigen on the cancer cell, preventing its interaction with SIRPα ("don't eat me signal") leading to phagocytosis of the cancer cell mediated through the intrinsic phagocytic ("eat me") signals.

In a pre-clinical study using cell lines, blocking anti-CD47 resulted in phagocytosis of tumor cells without an effect on normal peripheral blood cells(36). The selective targeting of tumor cells compared to normal cells was postulated to be due to the presence of pro-phagocytic ("eat me") signals that are not found on normal cell counterparts. One exception to this selectivity is aging red blood cells (RBCs) since CD47 expression protects them from elimination. As RBCs age, they accumulate prophagocytic changes in their cell membrane, which ultimately renders them susceptible to CD47 blockade. Thus, depletion of older CD47+ RBCs is an expected on-target clinical effect of magrolimab.

Magrolimab binding to RBCs may cause interference with cross-matching of units for transfusion. This observation is supported by multiple lines of data. First, pre-clinical and clinical studies have shown that the initial magrolimab priming dose leads to a pruning or cleaving of CD47 antigen off from RBCs, in which the remaining RBCs are found to be CD47 negative.(40) Given that RBCs are negative for CD47 after the initial magrolimab priming dose, RBC transfusion interference as well as on target RBC effects caused by magrolimab are significantly mitigated. Second, while crossmatch interference is occasionally observed with magrolimab, these events are less frequently observed after the initial several doses of magrolimab. Third,

patients have been able to successfully be typed and crossmatched and have had no significant adverse safety findings during RBC transfusions while on magrolimab therapy.

In-vitro phagocytosis assays have demonstrated a synergistic action between magrolimab and rituximab – a monoclonal anti-CD20 antibody(36). In primary NHL cells incubated with either anti-CD47 antibody or rituximab alone, or both in combination at half of the single agent dose, NHL cells exhibited a significant increase in phagocytosis when incubated with the combination compared to either antibody alone. No phagocytosis of normal peripheral blood cells was observed. When a similar experiment was performed in NSG mice deficient in T, B and NK cells, combination therapy eliminated disseminated lymphoma (Raji cells) in 60% of mice and localized lymphoma (Raji cells) in 86% of mice treated with combination treatment. All showed no evidence of tumor growth, remained relapsed free, and were alive at over 197 days after tumor engraftment. This is in comparison with mice treated with anti-CD47 antibody alone, which demonstrated a decrease in the rate of lymphoma growth but eventually had to be sacrificed due to enlarging tumors.

1.2.4.2 Magrolimab Clinical Efficacy

Our NCI lymphoma team has been participating in a multicenter phase 1b/2 study of magrolimab with rituximab in relapsed and refractory FL, MZL and diffuse large B-cell lymphoma (DLBCL) (NCT02953509). The interim results of the phase 1 component were published, and the updated results of phase 1b and phase 2 components were recently presented(41, 42). A total of 35 patients with relapsed or refractory FL (with 3 median prior therapies and 85% refractory to prior obinutuzumab-containing regimen) have been treated on this study. Results of all patients with indolent lymphomas (28 FL and 1 MZL evaluable patients) were presented together – ORR was 66% and CR rate was 24% as of February 2019. Survival data has been reported for Phase 1b FL patients (N=7). With median follow up of 18 months, the median duration of response had not been reached (range: 6.2 – 22.6+ months), including some durable CRs for > 20 months. Based on these results, magrolimab has achieved "Fast Track Designation" designation by the FDA for FL. These early clinical results of magrolimab with rituximab demonstrate a potentially highly effective immunotherapy for FL with a safety profile that is tolerable across all age groups. The achievement of CR with a novel immunotherapy platform is a promising sign that this could serve as the therapeutic backbone for a potentially curative regimen.

Further development of magrolimab-based combinations is justified, but important clinical and translational questions remain. First, use of magrolimab combinations should be broadened to related indolent B-cell malignancies included on this protocol: CLL, MCL, and MZL. In order to fully maximize the potential of this therapy, a nuanced understanding of the molecular and immunologic correlates of clinical response is critical. Equally important will be the identification of potential immune subsets that confer resistance to magrolimab-based therapy. Lastly, the favorable safety profile of magrolimab allows for the addition of other active agents such as venetoclax with non-overlapping toxicities in indolent B-cell malignancies.

1.2.4.3 Pharmacokinetics (PK) and toxicokinetics (TK)

1.2.4.3.1 Pharmacokinetics and product metabolism in humans

Data from a first-in-human Phase I study in 58 patients with advanced solid tumors and lymphomas was presented as a poster in ASCO 2018 (NCT02216409)(43). Multiple intravenous (IV) doses in the range 0.1 – 30 mg/kg were given at once or twice weekly frequencies. The PK parameters were

consistent with the presence of a CD47 antigen sink (receptor binding in the blood cells and normal tissues), which was saturated at doses ≥ 10 mg/kg. Above this dose level, increases in Cmax and AUC were dose proportional and the half-life of the antibody was ~14 days – typical of human IgG4. Similar parameters were observed in another ongoing study of magrolimab monotherapy or in combination with azacytidine in patients with hematological malignancies (NCT03248479). Simulations with the model from the solid tumor study predicted that a maintenance dosing regimen of 30 mg/kg every other week from cycle 2 onwards would result in serum concentrations ≥200 µg/mL, a level where full CD47 receptor occupancy on blood cells was observed in this study and where preclinical efficacy has also been previously reported. Based on these PK results, every other week dosing of 30 mg/kg will provide adequate drug exposure for maintenance(44).

1.2.4.4 Toxicity

Safety data in relapsed and refractory NHL is available from an ongoing Phase 1b/2 study of magrolimab and rituximab (NCT02953509). Toxicity data for 22 patients were published(41); and updated safety data in 115 patients were recently presented at European Hematology Association (EHA) annual meeting (**Figure 2**)(42). Overall, the treatment has been well-tolerated.

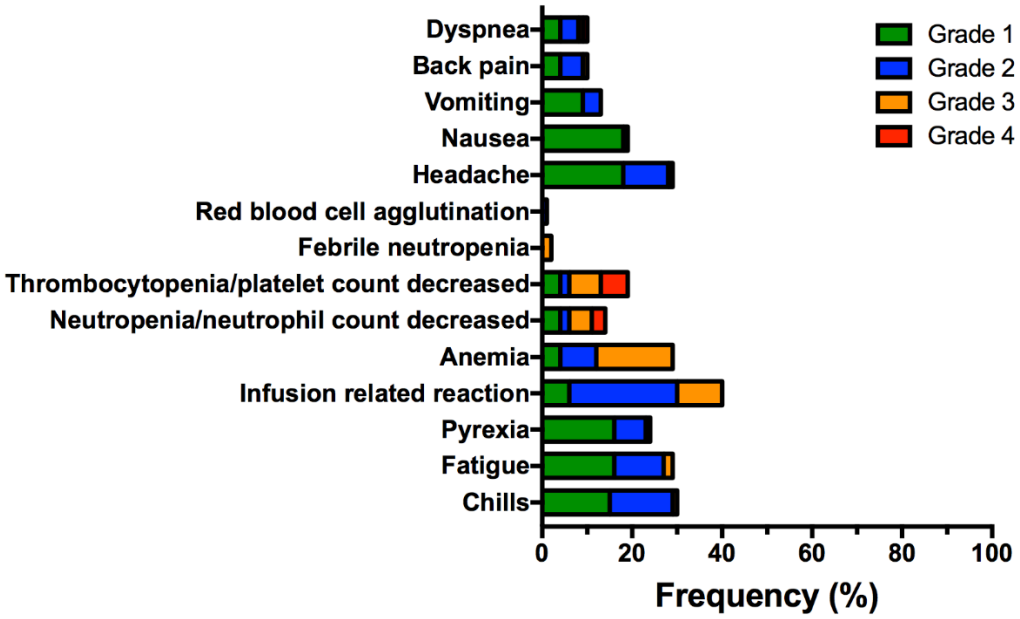


Figure 2: Treatment-related adverse events >10% for patients treated with magrolimab

In the phase 1b portion of the study, no maximum tolerated dose was reached. Three (3) DLTs were observed across 10, 20 and 30 mg/kg dose levels – neutropenia (1), immune thrombocytopenic purpura (1), and pulmonary embolism (1). The pulmonary embolism occurred after infusion of rituximab and during infusion of magrolimab on treatment Day 8. The patient was found to have a deep venous thrombosis (DVT) in a lower extremity in the setting of lymphoma disease at this site. No evidence of hemagglutination was observed. The patient was restarted on treatment with a 50% dose reduction in magrolimab and did not experience further thrombotic events.

Across 115 patients on the study, magrolimab was well-tolerated with the most common treatment-related AEs were infusion-related reactions, headache, anemia, and nausea. Drug-related toxicities occur mostly during the first infusion, with anemia improving despite repeated infusions.

Pharmacokinetic and pharmacodynamic studies show that a priming dose of 1mg/kg is effective at preventing on target anemia and limits the effect of hemolysis during the first cycle of infusion. Reduction in hemoglobin levels observed was mild (average hemoglobin drop 0.8 g/dL), transient and reversible despite continuation of therapy at higher doses (30 or 45 mg/kg). The incidence of other ≥G3 toxicities was 7%. Treatment discontinuation due to AE occurred in only 8/115 (7%) of patients. No autoimmune toxicities were observed.

1.2.5 Venetoclax

1.2.5.1 Background and Clinical Studies

The Bcl-2 family of proteins are key regulatory mediators of the intrinsic mitochondrial apoptotic pathway. The specific protein, Bcl-2, is an antiapoptotic protein that promotes cell survival. The B-cell malignancies included on this protocol frequently overexpress Bcl-2 through a variety of mechanisms including a translocation involving *BCL2* to the immunoglobulin heavy chain promoter [t(14;18)], chromosome 18q21 amplification, and from loss of the endogenous microRNAs, miR-15 and miR-16, that act as negative regulators of Bcl-2(45-48). Overexpression of Bcl-2 has been demonstrated in all of the included indolent B-cell malignancies and has been implicated as a resistance factor for certain therapeutic agents(49).

Venetoclax is a selective, orally bioavailable, small-molecule Bcl-2 family protein inhibitor being developed by AbbVie and Roche/Genentech(50). Venetoclax helps restore the process of apoptosis in NHL cells by binding directly to the Bcl-2 protein, displacing pro-apoptotic proteins like BIM, and triggering mitochondrial outer membrane permeabilization and the activation of caspases resulting in apoptosis via intrinsic pathway, without measurable binding to other Bcl-2 proteins, such as MCL-1. As monotherapy, venetoclax has demonstrated clinical activity in all of the indolent B-cell malignancies included on this protocol(18, 51). In a phase I dose-escalation study of venetoclax in relapsed/refractory CLL, 116 patients (56 in dose-escalation and 60 in safety expansion cohort) were treated. Patients received a median of 3 prior therapies, including 86% patients who received previous therapy with fludarabine. 92/116 (79%) patients had an objective response including a 20% complete response rate (5% without MRD on flow cytometry)(18). Responses occurred at every dose level, the toxicity profile was manageable and a maximum tolerated dose (MTD) was not identified. The most notable adverse events included upper respiratory tract infection (48%), nausea (47%), and grade 3 or 4 neutropenia (41%). An important toxicity associated with venetoclax was TLS which occurred in 10/56 (18%) patients in dose-escalation cohort. The first three patients had laboratory evidence of TLS that necessitated an extended intrapatient ramp-up schedule to mitigate the risk of TLS. TLS, either laboratory (7/56) or clinical (3/56), occurred either after the administration of the first dose or immediately after ramping-up of the dose. Of the 3 patients with clinical tumor lysis syndrome, 2 had severe sequelae: acute renal failure requiring dialysis and hospitalization in one patient and sudden death in another patient. The third patient had a transient elevation in serum creatinine, which resolved within 2 days. After resolution of the tumor lysis syndrome, 9 of 10 patients resumed taking venetoclax. Of these patients, 8 had no recurrence of TLS at subsequent doses. Additional toxic effects reported in all 116 patients are reported in **Table 1** below**.**

Table 1: Adverse events in >20% patients or any grade 3/4 adverse events in 116 CLL patients receiving venetoclax monotherapy(18)

Event	Any Grade N (%)	Grade 3 or 4 N (%)
Adverse event		
Diarrhea	60 (52)	2 (2)
Upper respiratory tract infection	56 (48)	1 (1)
Nausea	55 (47)	2 (2)
Neutropenia	52 (45)	48 (41)
Fatigue	46 (40)	4 (3)
Anemia	29 (25)	14 (12)
Thrombocytopenia	24 (21)	14 (12)
Serious adverse events		
Any	**52 (45)**	
Febrile neutropenia	7 (6)	
Pneumonia	5 (4)	
Upper respiratory tract infection	4 (3)	
Immune thrombocytopenia	3 (3)	
TLS	3 (3)	
Diarrhea	2 (2)	
Fluid overload	2 (2)	
Hyperglycemia	2 (2)	
Prostate cancer	2 (2)	
Pyrexia	2 (2)	

Venetoclax monotherapy has also been studied in patients with relapsed or refractory MCL, FL, and MZL. In a phase 1 study, 106 patients with relapsed and refractory NHL were treated with escalating doses of venetoclax(51). The study population included 28 MCL, 29 FL and 3 MZL patients. Risk of TLS was managed mostly as outpatients with hydration, allopurinol and occasional rasburicase. All patients were given escalating doses of venetoclax in a ramp-up fashion to minimize the risk of TLS. Laboratory monitoring of TLS was performed at 8 and 24 hours on day 1 and higher doses were administered with no evidence of TLS. Doses were further escalated once per week until target dosing was attained.

No MTD of venetoclax was defined and the mean duration of treatment was 5.3 months (range, 0.2-46). Two DLTs occurred, both in the 600-mg dose-escalation cohort: one grade 4 neutropenia and one grade 3 febrile neutropenia that both resolved after dose delay and growth factor support. Grade 3 and 4 adverse events occurred in 59 (56%) patients and across all doses of venetoclax. Most common grade 3/4 AEs were anemia (15%), neutropenia (11%), fatigue (7%), and diarrhea (3%). No cumulative toxicity was apparent with prolonged dosing. Fifteen patients required dose reductions, including nine of the 51 patients treated at 1,200 mg dose (five for nausea, four for diarrhea); clinical TLS was not observed. Three patients with bulky disease (maximal lymph node diameter > 10 cm) had laboratory changes meeting Cairo-Bishop criteria for laboratory TLS within

24 hours of initial dosing. All three patients received TLS treatment and continued venetoclax as scheduled without dose interruption.

ORR of 44% was observed with responses in all subgroups with 21/28 (75%) MCL, 11/29 (38%) FL and 2/3 (66.7%) MZL patients having an overall response. Complete responses were achieved in 6/28 (21%) MCL, 4/29 (14%) FL and 0/3 (0%) MZL patients. Patients with MCL or FL who achieved CRs had more durable responses than those who achieved PRs as best response. For MCL, responses were seen even at doses ≤800 mg (ORR, 76%, including CR rate of 24%) and not at a higher rate at doses higher than this. In FL, objective responses were more frequent at doses higher than 600 mg. A summary of adverse events in ≥20% patients is presented in **Table 2**.

Table 2: Adverse events reported in 106 NHL patients treated with venetoclax

Adverse Event	**Any Grade N (%)**	**Grade 3/4 N (%)**
Any event	103 (97)	59 (56)
Nausea	51 (48)	0 (0)
Diarrhea	48 (45)	3 (3)
Fatigue	44 (42)	7 (7)
Decreased appetite	23 (22)	1 (1)
Vomiting	23 (22)	0 (0)
Constipation	22 (21)	2 (2)
Serious adverse events		
Any	**27 (25)**	
Hyponatremia	3 (3)	
Influenza	3 (3)	
Lower RTI	3 (3)	
Dehydration	2 (2)	
Diarrhea	2 (2)	
Febrile neutropenia	2 (2)	
Hypotension	2 (2)	
Pleural effusion	2 (2)	
Viral infection	2 (2)	
Viral RTI	2 (2)	

Venetoclax has also been studied in combination with an anti-CD20 agent, rituximab, in recurrent FL. In a phase II study of 164 patients, this combination was safely administered at a target dose of 800 mg with most common grade 3-4 toxicities being hematologic with 27% neutropenia and 8% thrombocytopenia, and only 1 patient experiencing grade 3 tumor lysis syndrome. Further, 17 (33%) patients achieved an overall response, with 14 % CR.(52)

1.2.5.2 Venetoclax Approvals

Venetoclax is currently approved for the treatment of adult patients with relapsed/refractory (R/R) CLL either as monotherapy or in combination with rituximab. In 2019, venetoclax was also approved by the FDA for the treatment of previously untreated CLL or SLL patients in combination with obinutuzumab. In addition, it is approved in combination with azacytidine or

decitabine or low-dose cytarabine (LDAC) for the treatment of newly diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

A summary of Serious Adverse Drug Reactions (ADRs) Considered Expected in Adult Subjects for Safety Reporting Purposes for Venetoclax (Safety Analysis Set – Adult Subjects [≥ 18 Years of Age]) is presented in **Table 3**.

Table 3: Serious Adverse Reactions From Multiple Clinical Trials

ADVERSE REACTIONS	All SARs N = 4858		
	n (%)	Fatal	Life Threatening
Blood and lymphatic system disorders	46 (0.95%)		
Anaemia		NA	NA
Febrile neutropenia	354 (7.29%)	NA	NA
Neutropenia	68 (1.40%)	NA	NA
Infections and infestations			
Bacteraemia	14 (0.29%)	NA	NA
Pneumonia	187 (3.85%)	NA	NA
Sepsis	46 (0.95%)		
Septic shock	10 (0.21%)		
Upper respiratory tract infection	21 (0.43%)	NA	NA
Urinary tract infection	12 (0.25%)	NA	NA
Investigations			
Blood potassium increased	8 (0.16%)	NA	NA
Neutrophil count decreased	6 (0.12%)	NA	NA
Metabolism and nutrition disorders			
Hyperkalaemia	15 (0.31%)	NA	NA
Hyperphosphataemia	20 (0.41%)	NA	NA
Tumor lysis syndrome	42 (0.86%)	NA	NA

1.2.6 Obinutuzumab

CD20 receptor is universally expressed by normal B cells in all stages of development, from the pre-B cell up to the mature plasma cell. It is also widely expressed on cell surface by most B-cell malignancies(53). Rituximab is a type I CD20 mAb which was first approved by the FDA in 1997 for the treatment of relapsed and refractory non-Hodgkin lymphoma(54). It has now demonstrated impressive clinical activity across the majority of B-cell neoplasms and is routinely used in all phases of NHL treatment, including first-line therapy, maintenance, and salvage therapy.

However, the effectiveness of rituximab is ultimately limited in part by the development of treatment resistance. Obinutuzumab is a novel type II, humanized, CD20 monoclonal Ab (mAb) that was developed in an attempt to overcome several postulated mechanisms of rituximab-resistance. Obinutuzumab has been glycoengineered to reduce core fucosylation, conferring enhanced affinity for the human FcGamma receptor 3A (FCGRIIIa) on effector cells and, hence, enhanced antibody-dependent cell-mediated cytotoxicity (ADCC)(55, 56). Compared to type I mAbs (i.e., rituximab and ofatumumab), obinutuzumab has lower capacity to relocalize CD20 into

lipid rafts upon binding compared with type I antibodies and is a less potent in inducing complement-dependent cytotoxicity (CDC), but more potent in mediating homotypic cell adhesion and direct cell death (DCD), primarily by caspase-independent mechanisms(57). Enhancing DCD by mechanisms independent of caspase activation was thought to be desirable, as certain B-cell malignancies upregulate anti-apoptotic proteins that inhibit caspase-dependent suicidal pathway(54).

1.2.6.1 Summary of Pharmacokinetics and Product Metabolism in Humans

The clinical pharmacology properties of obinutuzumab have been characterized in a number of clinical studies, in patients with CLL and indolent NHL, including FL and non-FL, and aggressive NHL (DLBCL).

Important observations in both NHL and CLL patients were as follows:

- Increased doses of obinutuzumab led to increases in serum obinutuzumab concentrations, Cmax and AUC parameters for 50-200 mg doses of obinutuzumab were less than dose proportional.
- For 400-2000 mg doses of obinutuzumab, there was a trend towards dose proportionality. However, due to low patient numbers and disease heterogeneity no meaningful conclusions could be made regarding dose proportionality.
- At low doses of obinutuzumab (50-200 mg), administered once every three weeks over 8 cycles, little or no accumulation in serum concentrations (Cmax and Ctrough) or exposure were observed over the treatment cycles. Therefore, Cmax and Ctrough values were similar in Cycle 8 to Cycle 1. In contrast, when doses of 400-2000 mg were administered there were increases in serum concentration (Cmax and Ctrough) and exposure over the treatment cycles such that Cycle 8 values were higher than Cycle 1 values(58).
- In order to provide a robust description of the PK of obinutuzumab, pooled PK data from 1454 patients (343 CLL, 961 iNHL [814 with FL and 119 with MZL], 130 DLBCL and 20 MCL) were analyzed together. The differences in steady-state exposure due to differences in body weight and gender were limited (<30%) and therefore do not warrant any dose adjustment for the recommended dose and regimen for obinutuzumab of 1000 mg based on body weight and gender. Please refer to investigator's brochure for more details.
- Regimens with different loading and maintenance doses (from 50*2000 mg) have been compared to fixed-dose regimen using 1000 mg (D1, D8 and D15, C1; D1, C2 onwards)(58). Fixed dose 1000 mg regimen resulted in similar serum concentrations to loading dose of 1600 mg on D1, D8 and D15 of C1 followed by maintenance 800 mg (1600/800 regimen) on D1, C2 onwards.

1.2.6.2 Clinical Safety and Toxicity

Safety data is available for obinutuzumab as monotherapy in CLL and indolent NHLs; and in combination with venetoclax in CLL. Overall the safety profile across indications is similar with the following exceptions:

- A higher incidence of Grade 3-5 infections was observed in patients with indolent NHL, particularly MZL
- A higher incidence of infusion-related reactions was observed in CLL

- A higher incidence of TLS was observed in CLL

1.2.6.2.1 Monotherapy Studies

1.2.6.2.1.1 Obinutuzumab monotherapy in relapsed/refractory CLL

The safety of obinutuzumab monotherapy has been established in patients with relapsed and refractory CLL. In a phase 1-2 study of 33 patients with relapsed and refractory CLL, 13 patients received obinutuzumab 400 to 1200 mg (days 1 and 8 of cycle 1; day 1 of cycles 2-8) during the phase 1 part, and 20 patients received a fixed dose of 1000 mg (days 1, 8, and 15 of cycle 1; day 1 of cycles 2-8) during the phase 2 expansion(59). During phase 1, all patients experienced infusion-related reactions (IRRs) and 10/13 (77%) patients experienced ≥ grade 3 AEs. Seven (54%) patients had at least 1 episode of grade ≥ 3 neutropenia with a median duration of 10 days (range, 7-62 days). No patient required dose reduction, no toxicities led to withdrawal, and no deaths. In phase 2, IRRs were reported in 19/20 (95%) patients and ≥ grade 3 neutropenia was reported in 4/20 (20%) patients.

Table 4: Summary of AEs occurring in ≥10%, and grade 3/4 AEs in CLL patients receiving obinutuzumab monotherapy(59, 60)

	Salles, et al Phase 1 (N=13)	**Salles, et al Phase 2 (N=20)**	**Leblond, et al (N=126)**
All grades	13 (100)	20 (100)	123 (97.6)
IRR	13 (100)	19 (95)	Not reported
Neutropenia	7 (54)	4 (20)	50 (39.7)
Thrombocytopenia	4 (31)	3 (15)	28 (22.2)
Pyrexia	3 (23)	4 (20)	29 (23)
Anemia	1 (8)	5 (25)	20 (15.9)
Febrile neutropenia	1 (8)	2 (10)	8 (6.3)
Grade 3 or higher AEs	8 (62)	13 (65)	95 (75.4)
IRR	2 (15)	5 (25)	31 (24.6)
Neutropenia	7 (54)	4 (20)	42 (33.3)
Febrile neutropenia	1(8)	1(5)	8 (6.3)
Thrombocytopenia	2 (15)	3 (15)	15 (11.9)
Anemia	0 (0)	2 (10)	7 (5.6)

1.2.6.2.1.2 Obinutuzumab monotherapy in indolent NHL

Safety data will be discussed from two phase 2 studies in relapsed/refractory indolent NHL. In the phase 2 part of a Phase 1/2 study, indolent NHL patients (34 FL, 3 MZL, 2 LPL, 1 Waldenstrom's macroglobulinemia) were randomly assigned 1:1 to receive eight cycles of obinutuzumab as a flat dose of 400/400 mg or 1,600/800 mg. Obinutuzumab was given on days 1 and 8 of cycle 1, and day 1 of subsequent cycles (every 21 days) for a total of nine infusions(61). The most common AEs were IRRs, which were experienced by 13 /18 (72%) of patients in the 400/400-mg arm and 16/22 (73%) in the 1,600/800-mg arm. The majority of IRRs were grade 1 or 2 and were associated with the first infusion. Only 2 patients experienced grade 3 or 4 IRRs, both in the

1,600/800mg arm. No IRRs were considered SAEs, and no patient withdrew. Other grade 3 to 4 AEs occurring in more than one patient were infection (1 in the 400/400-mg arm, grade 4; 1 infection in three patients in the 1,600/800-mg arm, all grade 3), lymphopenia (1 in the 400/400-mg arm; 2 in the 1,600/800-mg arm), and neutropenia (3 in the 1,600/800-mg arm). Twelve SAEs occurred during treatment: three (17%) in the 400/400-mg arm and six (27%) in the 1,600/ 800-mg arm.

In another phase 2 study, FL patients received obinutuzumab – four (4) once-per-week IV infusions of 1000 mg during cycle 1, followed by once every 2 months for up to 2 years. Safety analysis included 87 patients (**Table 5**)(62). Sixty-four (74%) patients experienced IRR with 10 (11%) grade 3 or 4 events. Twelve (14%) SAEs were reported, and treatment was discontinued because of AEs in 8% of patients in the obinutuzumab group.

Table 5: Summary of AEs Occurring in ≥10%, and Grade 3/4 AEs in Indolent NHL Patients Receiving Obinutuzumab Monotherapy

	Salles, et al 400/400 mg Cohort (N=18)	**Salles, et al 1600/800 mg Cohort (N=22)**	**Sehn, et al 1000 mg (N=87)**
IRR	13 (72)	16 (72)	64 (74)
Neutropenia	0 (0)	3 (14)	3 (3)
Infection	6 (33)	11 (50)	--
Pyrexia	1 (6)	3 (14)	6 (7)
Fatigue	5 (28)	8 (36)	23 (26)
≥ grade 3 AEs	4 (22)	9 (41)	
IRR	0 (0)	2 (9)	10 (11)
Neutropenia	0 (0)	3 (14)	3 (3)
Febrile neutropenia	0 90)	1 (5)	0 (0)
Thrombocytopenia	0 (0)	1 (5)	0 (0)

Recent data suggests that patients with MZL may be more susceptible to infections from obinutuzumab combinations than combinations including rituximab(63). In a recent Phase 3 study, obinutuzumab was evaluated in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone); bendamustine; or cyclophosphamide (C), vincristine (V), and prednisone (P) in patients with previously untreated advanced FL and chemo-naïve advanced MZL.(64) The MZL cohort included a higher percentage of patients in the G-chemo arm, compared with the R-chemo arm who experienced fatal AEs, Grade 3-5 AEs, SAEs and AEs leading to dose interruption and that the higher rate was due to a higher incidence of AEs with fatal outcome in the G-chemo MZL population (11.9%, compared with 4.0% for the FL population). The higher number of AEs primarily reflected significantly higher rate of infections. It is currently unknown if obinutuzumab is associated with a higher rate of infections, including opportunistic infections, in chemotherapy-free combinations. However, to maximize safety monitoring, all MZL patients will receive prophylaxis to prevent *pneumocystis jiroveci* pneumonia and will include early stopping rules for this cohort (see **Section 10.4)**.

1.2.6.3 Clinical Efficacy of Obinutuzumab

A Phase 1 study of obinutuzumab in dose-escalating fashion (range 50/100-1200/2000 mg) in patients with relapsed/refractory NHL demonstrated an ORR of 43%. Lymphoma subtypes were FL (n = 13), MCL (n = 4), and SLL/CLL (n = 1). No DLTs were observed. Responses were observed in patients who underwent prior ASCT and also in patients who were rituximab refractory(65). Another phase 1 study testing obinutuzumab induction and maintenance in relapsed/refractory NHL showed similar results (23% ORR at the end of induction and 32% ORR at during maintenance therapy including 1 CR) in this group of heavily pretreated patients(66).

Phase II enrolled 40 patients, including 34 FL patients and 1 MZL. Median number of prior therapies was 3 and 55% (22/40) patients were rituximab refractory. Two doses were tested – 400/400 and 1600/800. ORR was 55% in 1600/800 mg group with 9% complete responses. However, the response rate and duration of response appeared lower at lower doses of obinutuzumab. At a median follow-up of 33.7 months, the median PFS was 11.9 months in the 1600/800 mg group (1.8-33.9+ months) and 6.0 months in the 400/400 mg group (1.0-33.9+ months). Median response duration in 9 previously rituximab refractory who responded to therapy was 8.8 months (0.7-30.8+), with three responses lasting more than 18 months(61). In 15 MCL patients enrolled, 4 received 1600/800 mg dose and 11 received 400/400 mg dose. ORR was 27% (2/4 patients in the 1600/800 mg dose group and 2/11 in 400/400 mg dose group) with 2 CRs in the 400/400 mg group. One (1) of 7 rituximab-refractory patients had a response at end-of-treatment. Overall median PFS for MCL patients was 2.7 months (0.3-36.1) in the 1600/800 mg group and 2.6 months (0.2-32.7) in the 400/400 mg group. One patient with MCL had an ongoing response for 30.5+ months. The remaining three patients with MCL whose disease showed response had response durations of 29.8, 11.2 and 5.5 months(67).

As tested in comparison to rituximab, obinutuzumab showed trend towards a higher ORR (44.6% [33/74] vs 33.3% [25/75], P=0.08) than rituximab in 149 patients with relapsed indolent NHL. A blinded independent review panel measured a significantly higher ORR for obinutuzumab (44.6% [33/74] vs 26.7% [20/75], P=0.01) with an overall similar safety profile(68).

1.2.7 Combination Studies

1.2.7.1 Obinutuzumab and Venetoclax in Patients with CLL

Venetoclax has been tested in combination with obinutuzumab in patients with previously untreated CLL and coexisting conditions(69). Obinutuzumab was administered for 6 cycles starting with 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on day 8 and 1000 mg on day 15 of cycle 1, and subsequently 1000 mg on day 1 of cycles 2 through 6. The daily oral venetoclax regimen was initiated on day 22 of cycle 1, starting with a 5-week dose ramp-up from 20 mg to 400 mg, thereafter continuing at 400 mg daily until completion of cycle 12(69). At least one adverse event of any grade occurred in 200/212 (94%) of patients. Adverse events leading to drug discontinuation occurred in 34/212 (16%) of the patients. The most common grade 3 or 4 adverse event was neutropenia. Grade 3 or 4 febrile neutropenia and grade 3 or 4 infections were reported in 11/212 (5.2%) and 35/212 (17.5%) of patients, respectively. Tumor lysis syndrome was reported in 3 patients (all cases occurred during treatment with obinutuzumab and before treatment with venetoclax); while 5 patients had fatal AEs during treatment with infection being the cause of death in 4 patients, and MDS in 1 patient.

Table 6: Summary of AEs Occurring in ≥10%, and Grade 3/4 AEs in 212 CLL Patients Receiving Venetoclax and Obinutuzumab(69)

	All Grades N (%)	Grade 3/4 N (%)
Any	200 (94)	167 (78)
Neutropenia	122 (58)	112 (53)
Thrombocytopenia	51 (24)	29 (14)
Anemia	35 (17)	17 (8)
IRR	95 (45)	19 (9)
Diarrhea	59 (28)	9 (4.2)
Nausea	40 (19)	0 (0)
Infections	Not reported	10 (4.7)
Fatigue	48 (23)	0 (0)
Serious adverse events	**104 (49)**	
Pneumonia	10 (5)	
Sepsis	6 (3)	
IRR	9 (4)	
Febrile neutropenia	11 (5)	
Cardiac failure	3 (1)	
Tumor lysis	1 (0.5)	

In terms of efficacy, venetoclax-obinutuzumab group had longer 24-month PFS, when compared to chlorambucil-obinutuzumab group (88.2% [83.7-92.6] vs 64.1[57.4-70.8]) with consistent advantage in patients with *TP53* deletion, mutation, or both, and in patients with unmutated immunoglobulin heavy-chain genes(69). The percentages of patients with both a complete response and minimal residual disease negativity in peripheral blood or bone marrow were significantly higher with venetoclax–obinutuzumab than with chlorambucil-obinutuzumab (peripheral blood, 42.1% vs. 14.4% [P<0.001]; bone marrow, 33.8% vs. 10.6% [P<0.001]). Another recent study utilized venetoclax-obinutuzumab combination for 6 cycles, followed by venetoclax monotherapy for fixed 1-year treatment in relapsed/refractory CLL patients.(70) Combination achieved responses in 95% (41/43) patients with 37% (16/43) CR/CRi. 64% (27/42) patients had undetectable MRD on peripheral blood ≥3 months after last obinutuzumab dose with sustained MRD negativity (63% [25/40]) at 12 months from the last obinutuzumab dose.

1.2.7.2 Venetoclax and Obinutuzumab with Other Novel Agents

Venetoclax has been safely combined with obinutuzumab and other novel agents in relapsed or refractory NHL patients. A Phase 1 study tested three dose levels of venetoclax (200mg, 400mg and 800mg) in MCL patients with median 2 prior lines of therapy(71). No DLT was reported at any dose levels. During the first 3 months of therapy, there were no clinically relevant Grade 3-4 non-hematological AEs. 7 patients had 29 Grade 3-4 hematological AEs including 1 febrile neutropenia, 4 neutropenia and 4 thrombocytopenia. Among 9 evaluable patients after 6 cycles, 5 were in CR.

Another Phase 1 trial of 22 patients with relapsed or refractory NHL treated with venetoclax, lenalidomide and obinutuzumab included 5 patients with FL and 1 with MZL(72). The study

incorporated 4 dose-levels with different combinations of lenalidomide and venetoclax doses. Three doses of venetoclax were evaluated (400mg, 600mg and 800mg). Patients commenced venetoclax at full target dose without a safety ramp-up. No clinically relevant TLS was observed. One patient had a DLT - neutropenic fever at DL1 (venetoclax 400mg, lenalidomide 15mg), but with expansion of DL1 and from DL2-4, no further DLTs were seen. Hematologic Grade 3-4 AEs included neutropenia in 20 (91%), thrombocytopenia in 5 (23%) and anemia in 3 (14%) patients. DL4 (venetoclax 800mg, lenalidomide 20mg) was determined to be the maximum tolerated dose. 4 of 5 patients with FL achieved responses (2 CR and 2PR) and the 1 MZL patient went into CR.

An ongoing Phase 1 study in our branch utilizes a combination of venetoclax and obinutuzumab with ibrutinib, prednisone and lenalidomide in relapsed or refractory NHL and early results were been presented at American Society of Hematology annual meeting in 2019(73). A total of 31 patients were enrolled with 11 FL and 2 MZL. Median number of prior therapies was 3 (range, 1-8) and 19 (70%) pts were refractory to last therapy. 1 DLT was reported – Grade 3 intracranial hemorrhage at DL1 of venetoclax (200mg). Patient was receiving comcomitant enoxaparin and aspirin. ≥G3 neutropenia, thrombocytopenia and anemia were reported in 16 (52%), 11 (35)% and 6 (19%) patients. Recommended Phase 2 dose of venetoclax was 800mg. In 13 total evaluable patients with FL and MZL, responses were observed in 12 (92%) patients, with CR in 7 (54%). Phase 2 testing in FL and Phase 1 testing in MCL is currently ongoing.

1.2.8 Scientific Rationale

1.2.8.1 Triplet Combination of Magrolimab, Obinutuzumab and Venetoclax

The primary purpose of our study is to test the safety and efficacy of the triplet combination of magrolimab, obinutuzumab, and venetoclax. The safety profile of venetoclax with obinutuzumab has already been established, and we will determine if adding magrolimab to this combination is safe and can further deepen clinical responses(69). The safety profile of magrolimab with rituximab has already been established, but no studies with obinutuzumab and magrolimab have been conducted(41). Both agents have a risk of infusional reactions, and the risk of neutropenia is higher with obinutuzumab than rituximab(74). These potential safety concerns, however, are likely manageable and direct comparisons of obinutuzumab with rituximab in both CLL and FL have suggested that it is more effective(74, 75). Further, we anticipate that the majority of patients with relapsed or refractory non Hodgkin Lymphoma would have already received rituximab as part of frontline therapy, and obinutuzumab has demonstrated clinical activity in patients who have relapsed after rituximab(76, 77).

A unifying biologic feature of the indolent B-cell malignancies included in this protocol is the frequent overexpression of Bcl-2 through a variety of mechanisms. Up to 85% of cases of FL will be associated with a balanced translocation involving *BCL2* to the immunoglobulin heavy chain promoter [t(14;18)]. It is widely appreciated that Bcl-2 overexpression occurs in the majority of CLL from loss of endogenous microRNAs, miR-15 and miR-16, that act as negative regulators of Bcl-2(45, 46). Many cases of MCL overexpress Bcl-2 with a major mechanism being the amplification of chromosome 18q21(47). Although the mechanism is unknown, Bcl-2 is also frequently overexpressed in most cases of MZL(49).

As a Bcl-2 mimetic, venetoclax has established itself as an agent that can induce deep remissions when given in combination with other targeted agents or anti-CD20 agent as discussed in earlier sections(20, 78). Synergy may exist between anti-CD47 antibodies and venetoclax. Mateo et al. published initial report of caspase-independent cell death in CLL cells using immobilized

monoclonal antibody against CD47(79). After 18 hours of CD47 ligation by the antibody, features typical of apoptosis were seen including cell shrinkage and loss in mitochondria membrane potential. Valentin et al. reported that in primary CLL cells, ex vivo treatment with SRF231 (anti-CD47 antibody) in combination with rituximab not only induced phagocytosis, but also induced cell death of non-phagocytosed target tumor cells via a mechanism that is partially mediated by phospholipase C(80). Based on these studies, combination of these two agents can induce cell-death via two independent pathways. Moreover, venetoclax as an anti-apoptotic inhibitor has the potential to induce prophagocytic signals on tumor cells, leading to potential enhanced activity when combined with magrolimab and obinutuzumab. In a xenograft mouse model of B-cell lymphoma, SRF231 displayed profound antitumor activity and led to complete and durable tumor regression in combination with venetoclax.

Magrolimab with rituximab has already demonstrated clinical activity in relapsed/refractory FL with minimal toxicity. Moreover, venetoclax with rituximab has been effective in producing deep responses in both CLL and FL(20, 52). Obinutuzumab is a newer anti-CD20 antibody, and was derived by humanization of the parental B Ly1 mouse antibody and subsequent glycoengineering. It has the following characteristics, compared to type I monoclonal antibodies such as rituximab: high-affinity binding to the CD20 antigen, lower complement-dependent cytotoxicity activity, higher direct cell death induction, higher antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis(55, 81, 82). In head-to-head comparison studies, it has shown a higher response rate than rituximab in relapsed indolent NHL patients(62). Additionally, its combination with venetoclax has been well-tolerated and effective in relapsed or refractory MCL, MZL, FL and CLL(70-73). Increased direct cell death induction and antibody dependent phagocytosis makes it the most rational anti-CD20 agent to combine with venetoclax and magrolimab.

An important objective of this trial is to define the complete molecular remission rate after combination therapy with magrolimab, obinutuzumab, and venetoclax. Based on the ability of venetoclax to achieve MRD negativity when used in combination with other targeted agents, and the above discussed data on potential synergy between Bcl-2 inhibitor, anti-CD47 antibody and type II anti-CD20 antibody; we believe the next logical step is to combine these active agents. We hypothesize that the novel-novel triplet combination in this study will leverage the efficacy of these targeted agents in indolent B-cell malignancies and produce deep and durable remissions without the need for indefinite therapy. This combination will have additive, if not synergistic, effects and the anticipated toxicities will be manageable.

1.2.8.2 Rationale for Dose Selection

We will be using fixed doses of magrolimab and obinutuzumab throughout this study as no significant dose-dependent increase in toxicity has been demonstrated with both of these agents. Magrolimab at 10, 20 and 30mg/kg dose was tested in combination with rituximab 375mg/m^2 in relapsed and refractory NHL and had minimal toxicity. A priming dose of 1mg with maintenance doses of 30mg/kg showed ~100% CD47-receptor occupancy – this was the recommended phase 2 dose and will be used in this study. Although rituximab was used in this study with magrolimab, both rituximab 375mg/m^2 and obinutuzumab 1000mg have largely similar toxicity profiles as compared head-to-head in a Phase 2 study, with the exception of grade 3 or 4 infusion-related reactions (IRR) which were seen in 11% patients receiving obinutuzumab and 5% patients receiving rituximab(62). IRRs are most common and most severe with first infusion, and hence

we will separate out the first doses of infusional medications on this study. All patients will receive the first dose of obinutuzumab on Day 1, and first dose of magrolimab on Day 2 of the first cycle.

In indolent NHL, an apparent improvement in ORR has been observed for the higher doses versus lower doses of obinutuzumab. For patients receiving a loading dose of 1600 mg on Day 1, Day 8 and Day 15 of Cycle 1 followed by maintenance doses of 800mg (1600/800mg regimen) on Day 1, Cycle 2 and onwards, ORR was 55% (95%CI: 32-76) and 2 patients (9%) had a CR; whereas, for the 400/400mg regimen, ORR was 17% (95%CI: 4-41) and no patient had a CR(58). A simpler fixed-dose regimen of 1000mg (D1, D8 and D15, C1; D1, C2 onwards) results in similar serum concentrations when compared with the 1600/800mg regimen, and will be used in this study(58).

As described in Section **1.2.7.2**, venetoclax 800mg was the recommended phase 2 dose in combination with other targeted agents for indolent NHL patients. This will be DL1 for eligible FL patients on this study(71, 73). When used in combination with other agents, there is a trend towards higher incidence of neutropenia with higher dose levels of venetoclax(73). Therefore, a DL-1 of 600mg venetoclax will be available.

In patients with relapsed or refractory CLL, venetoclax is approved at a dose of 400mg, and the same dose has been used in combination studies with obinutuzumab for CLL and MCL with a tolerable safety profile as discussed in Sections **1.2.7.1** and **1.2.5.1** (69-73). The dose of 400mg once daily will be used as dose level 1 (DL1) for CLL and MCL patients on this protocol, with an available DL-1 of 200mg should DLT occur. Even though the 800mg dose has been utilized in prior studies with MZL, very few MZL patients were enrolled on these trials(71, 73). Considering limited safety data is available (see Section **1.2.7.2**), DL1 will be 400mg and DL-1 200mg for MZL patients enrolled on this protocol.

1.2.8.3 Rationale for Use of MRD to Guide Duration of Therapy in CLL

Eradication of MRD usually results in improved clinical outcomes in CLL independent of the choice of therapy. (83-85) Specifically, with venetoclax monotherapy, a comprehensive MRD analysis of the two large phase II trials in relapsed/refractory CLL patients showed peripheral blood MRD $<10^{-4}$ by flow cytometry in 26% of the 174 patients. (86) Among MRD-positive patients, 23% showed intermediate ($\geq 10^{-4}$ to $<10^{-2}$) MRD levels and 51% had high MRD ($\geq 10^{-2}$). 24-month PFS rates were 92.8%, 84.3%, and 63.2% for MRD $<10^{-4}$, intermediate MRD, and high MRD patients ($p<0.0001$).

The rates of undetectable MRD (uMRD) increase substantially when venetoclax is combined with obinutuzumab. In a study, an optional debulking with bendamustine was followed by an induction and MRD-guided maintenance treatment of venetoclax and obinutuzumab in patients with treatment-naïve or relapsed/refractory CLL. (87) After induction, 87% patients had uMRD, with the majority of patients completing maintenance treatment at the earliest possible time point due to confirmed uMRD. In the phase III CLL14 trial, a higher rate of undetectable MRD in peripheral blood (via ASO-PCR) less than 10^{-4}, was observed in patients given venetoclax plus obinutuzumab than in patients given chlorambucil plus obinutuzumab (76% vs 35%, $p<0{\cdot}0001$). In a landmark analysis from last treatment exposure (ie, after 12 cycles) patients with undetectable MRD after the end of either treatment regimen had longer PFS compared with patients with low MRD or high MRD (HR 0·10, 95% CI 0·06–0·15, $p<0.0001$). In a post-hoc analysis, OS was also longer in patients who had undetectable MRD at the end of treatment ($p<0.0001$). (69, 88) Another phase II study used the same combination with a different treatment scheme: after 2 months of obinutuzumab, induction with 6 months of combined venetoclax and obinutuzumab followed by

6 additional months of venetoclax.(89) After that, patients who were at least in partial remission were randomly assigned to receive either maintenance treatment with 12 additional cycles of venetoclax irrespective of MRD, or MRD-guided (by flow cytometry) venetoclax maintenance. 26/28 (92.9%) patients had uMRD after induction. Follow-up is ongoing for patients randomized to the two maintenance groups. Of note, there was 92.3% concordance between bone marrow and peripheral blood MRD results at end of induction.

Based on these and other prospective studies, the 2018 iwCLL guidelines recommend that clinical trials aimed at maximizing the depth of remissions should include at least 1 test to assess for MRD - six-color flow cytometry, ASO PCR, or high-throughput sequencing using the ClonoSEQ assay. (90) Six-color peripheral blood flow cytometry (i.e., CD19, CD20, CD5, CD43, CD79b, and CD81) is reliably sensitive down to a level of <1 CLL cell in 10000 leukocytes. (91) Given $>10^{-4}$ sensitivity, real time availability at our institution and high concordance between peripheral blood and bone marrow MRD, we will be utilizing peripheral blood flow cytometry in this study as a marker of MRD assessment at the end of first 6 cycles of triplet combination therapy to guide further duration of treatment. (88, 92, 93) See Section **3.1.1**.

1.2.8.4 Molecular and Immunologic Profiling of Tumors

A critical translational component of this trial will be the comprehensive assessment of molecular and immunologic correlates that predict response to magrolimab in tissue and peripheral blood. Accurate identification of patients most likely to respond to treatment will be paramount for the success of our precision medicine trial. Similarly, the identification of both intrinsic and acquired resistance mechanisms to magrolimab will enhance further drug development. To reach these goals, we aim to study the molecular and immunologic correlates of response with a comprehensive molecular analysis of baseline biopsies. Further, the study design will utilize a "window of opportunity" in which patients will receive magrolimab and obinutuzumab for 2 cycles prior to the triplet combination. This study design will allow us to characterize predictive biomarkers from on-treatment tissue biopsies taken during the window and at disease progression. We will assess changes in RNA expression, clonal evolution and mechanisms of resistance.

The National Cancer Institute's (NCI) Center for Cancer Research (CCR) is uniquely positioned to execute the strong translational emphasis of this proposal. The Staudt lab will perform comprehensive molecular characterization of the tumors at baseline on FFPE blocks, including whole-exome sequencing, transcriptome profiling, AffySNP6.0 and arrays for copy number abnormalities, and will explore emerging technologies such as single cell RNA sequencing. Given the influence of cells in the tumor microenvironment (TME) to tumor behavior, we aim to study the molecular evolution of both the tumor and the TME during therapy(94). Recent advances in genomic technologies enable the gene expression profiling at the single cell level, a distinct advantage over conventional GEP which cannot always distinguish tumor vs. non-tumor gene expression(95, 96). Single-cell approaches allow identification of the evolution of rare populations of tumor cells, prone to distant spread or therapy resistance, as well as identification of TME cells that may be critical for the survival of the tumor and/or those immune populations that can be harnessed to attack the malignancy. The NCI-CCR operates a single cell analysis core facility with expert staff headed by Dr. Michael Kelly within the CCR Genomics Core. This facility can take purified viably frozen cells banked from patient biopsies and prepare them, using well-validated 10X Genomics technology, for single-cell RNA sequencing. This core is directly integrated with the NCI Sequencing core facility to provide high-quality, deep-sequencing of the single cell RNA-SEQ samples, as well as 'first-pass' data processing and analysis. Data can then

be transferred to scientists and bio-informaticians in the Staudt lab for further analysis of gene expression patterns and cellular population dynamics.

The TME within indolent lymphomas influences both response and resistance to targeted therapy. FL is a proliferation of malignant germinal center B-cells admixed with a varying proportion of nonmalignant immune cells such as T-cells, follicular dendritic cells and stromal cells. FL tumor cells in nodes retain a substantial dependence with the nonmalignant cells and other stromal elements from the TME in a pattern described as "re-education"(97). Interactions of FL cells with dendritic cells and macrophages allow them to survive in the germinal center environment even in the absence of an attached antigen(98, 99). Moreover, in some models of carcinogenesis, progression is associated with a macrophage phenotype switch with low IL-12 expression, high IL-10 expression, and low tumoricidal activity and promotion of tissue remodeling and angiogenesis(100). Increased number of lymphoma-associated macrophages has been associated with worsened OS in patients treated with chemotherapy, but in patients receiving rituximab with chemotherapy, it was associated with improved survival(101, 102). Other studies have found no association of tumor-associated macrophages on prognosis(103). Neoplastic follicles also contain T cells, primarily CD4+, with a higher CD4:CD8 ratio in low-grade (Grade 1-2) than in Grade 3 FL(104). Multiple studies have associated Treg and T_{FH} cells with clinical outcomes, but the results are inconsistent with some studies finding high Treg or high CD8+ cell numbers to be associated with favorable prognosis, and others non-significant(105-107).

These studies involved different patient populations and treatment regimens, and that may have contributed to discordant results. Moreover, most of these studies utilized immunohistochemistry for detecting the types of cells and the results are subject to difference between pathologists in interpreting the results. The cell types initially believed to represent a single lineage are actually many distinct subsets with distinct functions. Optical tissue imaging has revealed specialized localization of a few of these cellular subsets in FL such as lack of naïve B cells (mantle zone), presence of follicular dendritic cells in extranodal sites and absence of FDCs in diffuse areas of FL; and high prevalence of Tregs in follicular areas and absence in areas transformed to DLBCL(98, 104, 108). The spatial arrangement of the TME in FL varies across patients and depends on the genetic aberrations within the tumor cells as well as dependence on external stimuli for survival, proliferation, and immune escape. Conventional microscopy provides spatial information, but typically identifies cells by one or a very few markers. Hence, visualization and quantification of cellular subsets defined by complex phenotypic marker combinations is challenging. In contrast, flow cytometry provides more robust phenotypic data, but no information about spatial distribution of the various cell subsets. A combination of both these modalities would be ideal to study tumor microenvironment in indolent lymphomas.

In collaboration with Dr. Ronald N. Germain, in the Center for Advanced Tissue Imaging (CAT-I), we have developed a lymphoma-specific antigen panel that can be assessed by a tissue imaging method called "histo-cytometry." This strategy combines multiparameter 3D confocal imaging, spillover and deconvolution correction, identification and 3D reconstruction of specific cells of interest, and graphical data display. Histo-cytometry allows visualization, quantification, and positional analysis of diverse cell populations characterized by multiple markers directly in tissue sections. In initial studies, the histo-cytometry based cell positioning was consistent with normal biological localization of cell types in murine lymph nodes(109). When tissue quantitative cells subset discrimination by this method was compared with flow-cytometry based quantitation of contralateral lymph nodes in the animals, the correspondence was close to 1:1. Moreover, histo-

cytometry reliably tracked the phenotypic changes associated with T-cell activation and proliferation and was able to identify intranodal spatial distribution of all conventional dendritic cell subsets. This novel imaging technology will enable highly multiplexed, quantitative image analysis of lymph node samples and can be performed serially. We plan to explore the three-dimensional relationship of immune cells and stromal cells of interest in all indolent lymphomas using this technique. This is of particular interest to our study, as the mechanism of action of magrolimab depends on activation of innate immune system by enabling macrophage induced phagocytosis of NHL cells, and also activation of adaptive immunity by dendritic cell mediated priming of CD8+ T-cells(36, 37). Patients will have tumor biopsies at baseline (if required, based on inadequate existing tissue), during the "window" treatment period with magrolimab and obinutuzumab, and at the time of progression. Dense phenotypic and spatial data made available by histo-cytometry at these timepoints will enable us to better understand immunological correlates of response, and resistance to treatment with anti-CD47 antibody and obinutuzumab. The diverse mechanism of action of immune checkpoint inhibitors (including magrolimab) in modulating the tumor microenvironment requires a careful assessment of the end points, such as while using functional imaging (^{18}FDG-PET). Because the TME is responsible for a significant amount of ^{18}FDG uptake, agents causing immune activation may also cause an initial increase in PET activity, similarly to effects of anti-PD1/anti-CTLA4 antibodies observed in solid tumors(110). Histo-cytometry will also provide additional information to distinguish immune reaction from tumor progression.

1.2.8.5 Use of Circulating Tumor DNA

Measurement of minimal residual disease (MRD) is not part of the standardized criteria for disease response or disease monitoring in indolent lymphomas, but many research applications are currently being developed. Multiple methods have been tested for detecting MRD in B-cell malignancies with limitations. Multiparameter flow cytometry (MFC) can easily be performed on peripheral blood or bone marrow as a marker of MRD, but this method may not be sensitive enough in diseases that do not routinely circulate(111). Even in CLL, where MFC reliably quantitates CLL cells to the level of 10^{-5}, NGS-based approaches appear to have a lower limit of detection and can assess clonal evolution(112).

The tumor-specific component of cell-free DNA, known as circulating tumor DNA (ctDNA), is a highly sensitive and specific marker of all B-cell malignancies and is an emerging technology designed to overcome the fundamental limitations of response assessment based on imaging scans. A secondary objective of this trial is to utilize ctDNA as a marker of MRD and compare the results to the standard assessment of disease response and monitoring for disease recurrence after therapy stops. Many patients who achieve a CR based on conventional criteria will have the persistence of MRD below the detection limit of imaging scans highlighting the need for more sensitive measures(113, 114). As a measure of the depth of response, we will define the complete molecular remission rate after triplet combination therapy. Further, we will analyze the predictive ability of ctDNA for predicting disease relapse when measured at pre-planned timepoints after therapy stops.

Various technologies exist for the detection and analysis of ctDNA. Malignant B cells possess a unique DNA sequence that encodes its rearranged immunoglobulin variable, diversity, and joining (VDJ) genes. Using universal primers in combination with next-generation sequencing (NGS), this unique VDJ sequence can be utilized as a quantitative biomarker of disease(114). This technique requires identification of rearrangements in tumor tissue (a clonotype), which can then be followed in peripheral blood. In a study comparing NGS-based method with RQ-PCR in MCL,

49 out of 55 (89%) patients had a clonotype detected by NGS compared to 45 out of 55 (82%) by RQ-PCR(115). Clonotypes identified by both techniques were identical in 96% of the cases. NGS demonstrated at least the same level of sensitivity as RQ-PCR, without the need for patient-specific reagents. Technologies have since evolved, and in a more recent study, tumor clonotypes were successfully detected at baseline and followed serially in 96% of patients with MCL(116). Of note, in all patients who had baseline formalin-fixed paraffin embedded (FFPE) tissue available, one or more clonotypes were detected. A linear association was demonstrated between baseline quantitative ctDNA levels and tumor burden as measured by total metabolic tumor volume (TMTV). More importantly, ctDNA was able to provide an early readout of sensitivity to therapy as decrease in levels as early as after 1 cycle of treatment with chemotherapy and targeted agents (EPOCH-R plus bortezomib) was shown to associated with improved PFS. The utility of this assay has also been preliminarily tested in FL(117). In a randomized study of FL patients, a subset of patients had tumor and plasma samples available for analysis for VDJ sequences. At least one tumor clonotype could be detected in 29 patients (85%) in the diagnostic tumor sample. ctDNA corresponding to the clonotypes were detected in 25/29 (86%) of the matched plasma samples.

We will use a modern ctDNA platform that combines universal PCR primers for the variable-diversity-joining (VDJ) region of the immunoglobulin receptor with next-generation sequencing (NGS) technologies (i.e., clonoSEQ®)(118). This ctDNA assay is highly tumor-specific and can be used as a method for disease detection at the molecular level in a variety of B-cell malignancies(115, 117, 119). Since the clinical utility of achieving complete molecular remission is unknown, this will be an exploratory endpoint. Lastly, we aim to study the utility in using ctDNA as an active surveillance tool after therapy has been completed to determine the kinetic relationship between ctDNA reappearance and clinical relapse. These data could inform future studies that initiate intervention on the basis of molecular relapse. Altogether, ctDNA will be used in this study as a non-invasive method to monitor tumor response kinetics during therapy, define the depth of response, and as a surveillance tool for early disease detection after therapy cessation.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have a confirmed histologic diagnosis of an indolent CD20 positive B-cell lymphoma according to the criteria established by the 2016 version of the World Health Organization (WHO) classification system. Lymphomas with any prior CD20 expression (by immunohistochemistry or flow cytometry) will be considered eligible. Diagnosis must be confirmed by Laboratory of Pathology, NCI and the following indolent B-cell lymphomas are included:

- Follicular lymphoma (FL): must be grade 1-2 or 3a
- Marginal zone lymphoma (MZL)
- Mantle cell lymphoma (MCL)
- Chronic lymphocytic leukemia (CLL)

2.1.1.2 Participant must have relapsed and/or refractory disease, as defined below:

- FL: relapsed after and/or refractory to at least two (2) prior lines of therapy with at least one of those therapies containing an anti-CD20 monoclonal antibody.

  NOTE: Participants with FL may be eligible after one (1) prior line of therapy if they have either:

  - Follicular lymphoma international prognostic index (FLIPI) ≥2 (120)
  - Disease progression within 24 months of the end of last therapy (POD24)
- MZL: relapsed after and/or refractory to at least two (2) prior lines of therapy, with at least one containing an anti-CD20 monoclonal antibody.
- MCL: relapsed after and/or refractory to at least two (2) prior lines of therapy, with at least one containing an anti-CD20 monoclonal antibody.

  NOTE: Participants with MCL may be eligible after one (1) prior line of therapy if they have either:

  - Blastoid or pleomorphic histology
  - 17p deletion
  - *TP53* mutation or deletion
  - Ki67 ≥30%
  - Received a BTK inhibitor as first line therapy
- CLL: relapsed after and/or refractory to at least two (2) prior lines of therapy. Participants with CLL are not required to have had therapy containing anti-CD20.

  NOTE: Participants with CLL may be eligible after one (1) prior line of therapy if they have either:

  - 17p deletion
  - *TP53* mutation or deletion
  - Received both a Bruton's Tyrosine Kinase (BTK) inhibitor AND a B-cell

lymphoma 2 (BCL2) inhibitor as first line therapy

NOTE: Participants must not have received prior treatment with a CD47 or SIRPα targeting agent.

2.1.1.3 Adequate tissue from diagnostic biopsy (archival or fresh) must be available for performance of correlative studies

NOTE: Tumor tissue may be from any previously collected tissue and adequacy is at the discretion of the Principal Investigator. If prior tissue is not available, patient must be willing to undergo baseline tissue biopsy (for patients with known or suspected bone marrow involvement, bone marrow may be acceptable tissue per discretion of the investigator).

2.1.1.4 Patients must have at least evaluable disease as assessed by clinical exam (i.e., palpable lymphadenopathy, measurable skin lesions, etc.), laboratory assessment (i.e., lymphoma involvement of bone marrow or peripheral blood by morphology, cytology or flow cytometry), and/or imaging (measurable lymph nodes or masses on CT or MRI and/or evaluable FDG-avid lesions on PET). Patients may also have measurable disease.

NOTE: Patients with known active CNS lymphoma are not eligible.

2.1.1.5 Age ≥18 years

NOTE: Because no dosing or adverse event data are currently available on the use of magrolimab in patients <18 years of age, children are excluded from this study

2.1.1.6 ECOG performance status ≤ 2 (see **Appendix A**)

2.1.1.7 Adequate organ function as evidenced by the following laboratory parameters:

Absolute neutrophil count (ANC)	≥ 1,000 /mm^3
Platelets	≥ 50,000 / mcL (transfusions permitted)
Hemoglobin	≥ 9 g/dL (transfusions permitted). **NOTE:** Patients must have required fewer than 2 units of RBC transfusion in the 4 weeks prior to screening. Additional transfusions after screening and prior to enrollment are acceptable.
Renal function	Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m2 as estimated by the Modification of Diet in Renal Disease (MDRD) abbreviated formula. If not on target, a 24-hour urine creatinine clearance can be used to directly measure.
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	≤ 3.0 x the upper ULN **NOTE:** Patients with liver involvement with lymphoma ≤ 5.0 x ULN
Bilirubin	≤ 1.5 × ULN **NOTE:** Patients with Gilbert's syndrome may have a bilirubin level > 1.5 × ULN, per discretion of the investigator

2.1.1.8 The effects of the study drugs on the developing human fetus are unknown. For this

reason, women of childbearing potential (WOCBP) and men must agree to use effective contraception when sexually active. This applies for the time period between signing of the informed consent form and for the following time frames after the last dose of drug, whichever is later: 90 days after the last dose of magrolimab, 30 days after the last dose of venetoclax, and 18 months after the last dose of obinutuzumab for women and 6 months after the last dose of obinutuzumab for men. Men should refrain also from donating sperm for these same timeframes, and women must also refrain from donating eggs.

NOTE: WOCBP is defined as any female who has experienced menarche and who has not undergone successful surgical sterilization or who is not postmenopausal (i.e., amenorrheic for >12 months without alternative medical cause; post-menopausal status in females under 55 years of age should be confirmed with a serum follicle-stimulating hormone [FSH] level within applicable local laboratory reference range for postmenopausal women). Permanent sterilization methods include but are not limited to hysterectomy, bilateral salpingectomy and bilateral oophorectomy. The investigator or a designated associate is requested to advise the patient how to achieve highly effective birth control (failure rate of less than 1%), e.g., intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner and sexual abstinence. The use of condoms by male patients is required unless the female partner is permanently sterile. See **Appendix B** for complete details of acceptable contraceptive methods.

2.1.1.9 Ability of patient to understand and the willingness to sign a written informed consent document

2.1.1.10 Patients with prior autologous or allogeneic stem cell transplantation are potentially eligible if transplanted > 6 months ago, and no active graft-vs-host disease requiring immunosuppressants.

2.1.2 Exclusion Criteria

2.1.2.1 Concomitant use of any investigational anti-lymphoma treatment

2.1.2.2 Known primary or acquired immunodeficiency syndrome (e.g., HIV) or known infection with human T-cell leukemia virus 1 (HTLV1). **NOTE:** HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with the study drugs. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. In the future, appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

2.1.2.3 History of hemolytic anemia or autoimmune thrombocytopenia in the 3 months prior to enrollment. Patients with positive Direct Agglutination Test (DAT) but no evidence of clinically active hemolysis are eligible.

2.1.2.4 Hepatitis B surface antigen or hepatitis B DNA PCR positive. **NOTE:** Subjects who are hepatitis B core antibody positive will need to have a negative HBV DNA PCR result before enrollment. Those with a positive PCR for hepatitis B are excluded.

2.1.2.5 Pregnant or breastfeeding patients. **NOTE:** Pregnant women are excluded in this study because of the potential for teratogenic or abortifacient effects. Because there is an

unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with the study drugs, breastfeeding should be discontinued.

2.1.2.6 Requirement to continue on any of the medications that have significant potential for drug-drug interactions with the study regimen, as indicated in Section **4.2** For example, the following:

- Use of strong CYP3A inhibitors 7 days prior to or at initiation of venetoclax, and during ramp-up phase is contraindicated in patients with MZL, CLL and MCL (see Sections **4.2.1**, **4.2.1.2**, and **Appendix C**, also see Section **4**). For FL patients, use of strong CYP3A inhibitors is contraindicated 7 days prior to and during the first two weeks of venetoclax treatment.
- Consumption of one or more of the following within 3 days prior to the first dose of any study drug:
    - Grapefruit or grapefruit products
    - Seville oranges including marmalade containing Seville oranges
    - Star fruit

2.1.2.7 Uncontrolled intercurrent illness including, but not limited to the following that may limit interpretation of results or that could increase risk to the patient at the discretion of the investigator:

- Active hepatitis C infection. **NOTE:** Subjects who are hepatitis C antibody positive will need to have a negative HCV PCR result before enrollment. Those with a positive PCR for hepatitis C are excluded.
- Any second malignancy that requires active systemic therapy
- Known mental or physical illness that would interfere with cooperation with the requirements of the trial or confound the results or interpretation of the results of the trial and, in the opinion of the treating investigator, would make the patient inappropriate for entry into the study
- Known active infection, or any major infection requiring treatment with IV antibiotics or hospitalization within 4 weeks prior to commencement of the study treatment.

2.1.2.8 Vaccination with a live vaccine ≤28 days prior to commencement of the study treatment.

2.1.2.9 Inability or unwillingness to swallow a large number of tablets.

2.1.2.10 Known hypersensitivity to any of the study medications or their excipients.

2.1.2.11 History of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis).

2.1.2.12 History of malabsorption syndrome felt to be significant enough to interfere with enteral absorption at the discretion of the investigator.

2.1.3 Recruitment Strategies

Study participants will be recruited from the population of patients screened in the lymphoid malignancies' clinic of the National Institutes of Health. Our research team currently has an active protocol to study the clonal evolution in FL that enrolls patients with untreated FL who are

appropriate for observation as well as those who require immediate treatment. In addition, we participate in a locoregional consortium of eight academic institutions within the Mid-Atlantic region (Mid-Atlantic Lymphoma Research Consortium) that shares information regarding active clinical protocols and aims to enhance patient recruitment across the region. Our patients for this study will therefore consist of those from the FL clonal evolution study, referrals from outside physicians, and patient self-referrals.

This protocol may also be abstracted into a plain language announcement posted on NIH websites (ccr.cancer.gov/ Lymphoid-Malignancies-Branch, ClinicalTrials.gov) and on NIH social media platforms.

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the study consent OR the consent for study 01C0129 (provided the procedure is permitted on that study), on which screening activities will be performed. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent, unless otherwise noted.

NOTE: Assessments and procedures to confirm study eligibility should be completed within 28 days prior to the start of treatment (unless otherwise noted). See also the Study Calendar (**Appendix G**).

2.2.3 Clinical Evaluations

- Disease history, including: diagnosis, prior chemotherapy and/or radiation treatment (if applicable), and significant prior/ongoing side effects and symptoms
- Complete medical history, including: all active conditions considered to be clinically significant by the treating investigator
- Physical examination, including: height (screening only), weight, vital signs (i.e., temperature, pulse, respiratory rate, and blood pressure); review of concomitant medications and symptoms/side effects; and, assessment of performance status using the ECOG scale

2.2.4 Laboratory Evaluations

NOTE: Results from outside NIH are accepted.

- CBC with differential
- Chemistry panels (as noted) or specific analyte required for eligibility, including: Creatinine (i.e., or Acute Care Panel/Basic Metabolic Panel); ALT, AST, total and direct (if required) bilirubin (i.e., or Hepatic Panel/Liver Function Panel); and 24-hour urine creatinine clearance (if needed to measure CrCl)
- Coagulation panel: PT/INR and aPTT
- LDH
- Urinalysis
- Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody, Hepatitis C antibody (HCV) [qualitative]) (within 3 months allowed)
- HIV antibody (within 3 months allowed)
- Urine and/or serum HCG in women of childbearing potential (within 7 days prior to initiation of study therapy)
- Direct Anti-Globulin Test (DAT)
- Assessment of 17p deletion by karyotyping of blood, bone marrow, or tissue sample (results from outside of NIH and/or prior to the 28-day screening window are accepted)

2.2.5 Imaging Studies

NOTE: Results from NIH only.

- CT chest, abdomen and pelvis or MRI

2.2.6 Other Procedures to be performed/samples to be collected

- Pathologic review/confirmation of diagnosis by Laboratory of Pathology, NCI (no time limit). A tissue sample is required for this evaluation; if archival sample is not available, a fresh tumor or bone marrow biopsy will be obtained.
- Bone marrow aspiration with flow cytometry and biopsy within 12 months prior to starting treatment, unless repeat at screening/baseline felt to be clinically indicated in the opinion of the investigator (results from outside NIH are accepted; flow cytometry not required in these cases).
- Flow cytometry will be performed on peripheral blood for both diagnostic and staging purposes (only NIH results accepted; NCI Laboratory of Pathology)

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at:

https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.3.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

2.3.2 Treatment Assignment Procedures

NOTE: For NCI CCR registration purposes only.

2.3.2.1 Cohorts

Number	Name	Description
1	Dose-finding: Relapsed/refractory FL	Patients with relapsed or refractory FL (a minimum of 6 patients; up to 12 patients)
2	Dose-finding: Relapsed/refractory MZL, MCL, and CLL	Patients with relapsed or refractory MZL, MCL and CLL (a minimum of 6 patients; up to 12 patients)
3	Dose-expansion: Relapsed/refractory FL	Patients with relapsed or refractory FL (up to 18 patients)
4	Dose-expansion: Relapsed/refractory MZL	Patients with relapsed or refractory MZL (up to 6 patients)
5	Dose-expansion: Relapsed/refractory MCL	Patients with relapsed or refractory MCL (up to 12 patients)
6	Dose-expansion: Relapsed/refractory CLL	Patients with relapsed or refractory CLL (up to 6 patients)

2.3.2.2 Arms

Number	Name	Description
1	Experimental treatment: FL Dose-finding	Magrolimab IV with a 1 mg/kg priming dose followed by 30mg/kg loading and maintenance doses + obinutuzumab IV 1000mg + venetoclax 800mg PO combination administered to 6 patients for six (6) cycles (28-days each, Cycles 1-6); further treatment with additional cycles will be response-adapted. Note: DLT assessment of the magrolimab + obinutuzumab + venetoclax triplet will take place during Cycle 1. If ≥2 patients experience DLT, an additional 6 patients will be enrolled at DL(-1) of venetoclax 600mg with magrolimab and obinutuzumab.
2	Experimental treatment: MZL, MCL, and CLL Dose-finding	Magrolimab IV with a 1 mg/kg priming dose followed by 30mg/kg loading and maintenance doses + obinutuzumab IV 1000mg + venetoclax ramp-up to target dose of 400mg over 5 weeks (35 days, Cycle 1) administered to 6 patients. Triplet combination of magrolimab + obinutuzumab + venetoclax (target dose, no ramp-up) will continue for five (5) additional cycles (28-days each, Cycles 2-6); further treatment with additional cycles will be response-adapted. Note: DLT assessment of the magrolimab + obinutuzumab + venetoclax triplet will take place during Cycle 1. If ≥2 patients experience DLT, an additional 6 patients will be enrolled at DL(-1) of venetoclax 200mg with magrolimab and obinutuzumab.

Number	Name	Description
3	Experimental treatment: FL Dose expansion	Window of magrolimab IV with a 1 mg/kg priming dose followed by 30mg/kg loading and maintenance doses + obinutuzumab IV 1000mg combination for two (2) cycles (28-days each, Cycles -2 and -1), then venetoclax will be added at target dose (dose determined from Arm 1). Triplet combination treatment with magrolimab + obinutuzumab + venetoclax will be 6 cycles (28-days each, Cycles 1-6); further treatment will be response-adapted.
4	Experimental treatment: MZL, MCL, CLL Dose expansion	Window of magrolimab IV with a 1 mg/kg priming dose followed by 30mg/kg loading and maintenance doses + obinutuzumab IV 1000mg combination for two (2) cycles (28-day cycles, Cycles -2 and -1), then venetoclax safety ramp-up to target dose (dose determined from Arm 2) over 5 weeks (35-days, Cycle 1). Triplet combination treatment with magrolimab + obinutuzumab + venetoclax (target dose, no ramp-up) will continue for 5 additional cycles (28-days each, Cycles 2-6); further treatment will be response-adapted.

2.3.2.3 Arm Assignment

This is a four arm, non-randomized study. All patients will receive experimental treatment. During the dose-finding portion, patients in Cohort 1 will be assigned to Arm 1; patients in Cohort 2 will be assigned to Arm 2.

During the dose-expansion portion, patients in Cohort 3 will be assigned to Arm 3; Cohorts 4, 5 and 6 will be assigned to Arm 4.

2.4 BASELINE EVALUATION

The baseline evaluations should be performed within 28 days prior to the first dose of magrolimab, unless otherwise noted; tests performed as part of screening do not need to be repeated if they were performed within the specified window. See the Study Calendar (**Appendix G**) for details.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a non-randomized, open-label, four arm, single institution phase 1 study of magrolimab, obinutuzumab, and venetoclax for patients with relapsed/refractory indolent B-cell malignancies. The study involves a novel design that includes a treatment window with a doublet in order to maximize the potential for translational research as well as a safety period to assess the safety of the triplet combination of venetoclax added to magrolimab with obinutuzumab in different disease sub-types.

Research biopsies of lymph nodes and/or bone marrow will be collected at baseline, during the window period treatment with magrolimab + obinutuzumab, and at the time of disease progression.

3.1.1 Dose-Finding Phase

The dose-finding phase will assess the safety of venetoclax when added to obinutuzumab and magrolimab. Up to 6 FL patients in Arm 1 will be treated and undergo DLT assessment during the first 4 weeks (Cycle 1) of triplet combination therapy with magrolimab, obinutuzumab and venetoclax. Venetoclax will be administered at DL1 without a safety ramp-up (**Figure 3**). If ≥2

patients experience DLT at DL1, up to 6 additional patients will be enrolled (Cohort 1, Arm 1) and treated at DL(-1) of venetoclax. Dose-finding will follow the rules mentioned in **Table 8**.

Up to 6 MZL, MCL or CLL patients treated in Arm 2 will undergo DLT assessment during the first 5 weeks of triplet combination therapy (Cycle 1). Venetoclax will be administered with a safety ramp-up to target dose (dose level 1) (**Table 10**, **Figure 4**). If ≥2 patients experience a DLT at DL1, up to 6 additional patients will be enrolled (Cohort 2, Arm 2) and treated at DL (-1) of venetoclax (**Figure 3**). Dose-finding will follow the rules mentioned in **Table 8**.

No more than 2 patients can be in a DLT assessment period at any given time. If a DLT has occurred, only 1 patient can be in the respective DLT assessment period at a given time. Patients who withdraw before completing DLT assessment for reasons other than a DLT, will not be evaluable for assessment of DLT for dose review decisions, and will be replaced.

After completion of the DLT evaluation as above, all patients will be treated with an additional 5, 4-week cycles of triplet combination therapy (magrolimab and obinutuzumab and venetoclax). Final duration of therapy will be based on response to the first 6 cycles of triplet combination therapy. FL, MZL and MCL patients who achieve a CR and CLL patients who achieve a CR with undetectable peripheral blood MRD by flow cytometry after 6 cycles of triplet combination therapy will stop treatment but remain potentially eligible for an additional 6 cycles upon disease relapse provided that they still meet re-treatment criteria and the duration of CR is ≥ 6 months. Disease relapse is defined by conventional criteria for clinical relapse that is associated with radiographic progression. Additionally, for CLL patients, positive flow cytometry during follow-up will be considered relapsed for re-treatment. Reappearance of ctDNA is not considered disease relapse on this protocol. Patients who achieve a PR after 6 cycles of triplet combination therapy will be eligible for an immediate additional 6 cycles, and then will stop treatment.

Table 7: Venetoclax Dose Levels

Cohort	Dose Level	Target Dose of Venetoclax*
Arm 1, Cohort 1 (FL)	Level 1	800 mg by mouth daily
	Level (-1)	600 mg by mouth daily
Arm 2, Cohort 2 (MZL, MCL and CLL)	Level 1	400 mg by mouth daily
	Level (-1)	200 mg by mouth daily

*Stated dose of venetoclax is the target (maximum) dose.

Table 8:Venetoclax dose-finding rules for Arms 1 and 2

Number of Patients with DLT at a Given Dose Level	Dose-Finding/Dose Decision Rules
<2 out of 6	This target dose will be used in expansion phase
≥2 out of 6 at DL1	Six (6) patients will be entered at dose level (-1).
≥2 out of 6 at DL (-1)	Further enrollment will be stopped, and a safety analysis will be performed to determine further course of action.

3.1.2 Dose-Expansion Phase

Once safety is confirmed, expansion cohorts (Cohorts 3 and 4 and Arms 3 and 4) will be enrolled to collect additional safety information as well as disease response (**Figure 5**). During the dose expansion portion of the study, all patients will receive magrolimab with obinutuzumab for 2 cycles during the "window" period (i.e., Cycle -2 and Cycle -1) designed to assess for early clinical activity and correlates of response to magrolimab and obinutuzumab. The purpose of the window is to study the molecular and immunologic correlates of response to magrolimab-based therapy. It is not intended to provide complete information regarding the clinical activity of this doublet.

After completing the window, venetoclax will be added with the dose determined from the dose-finding cohorts as described above. Patients must fulfill the clinical and laboratory criteria mentioned in **Table 9** below prior to addition of venetoclax**.** Patients with unequivocal PD during the treatment window who are tolerating therapy will be allowed to be moved immediately to the next phase (i.e., addition of venetoclax). After completion of Cycle 1, all patients will be treated with an additional five (5), 4-week cycles of triplet combination therapy (magrolimab and obinutuzumab and venetoclax). Final duration of therapy will be based on response to the first 6 cycles of triplet combination therapy. FL, MZL and MCL patients who achieve a CR and CLL patients who achieve a CR with undetectable peripheral blood MRD by flow cytometry after 6 cycles of triplet therapy will stop treatment but remain potentially eligible for an additional 6 cycles upon disease relapse provided that they still meet re-treatment criteria and the duration of CR is ≥ 6 months. Disease relapse is defined by conventional criteria for clinical relapse that is associated with radiographic progression. Additionally, for CLL patients, positive flow cytometry during follow-up will be considered relapsed for re-treatment. Reappearance of ctDNA is not considered disease relapse on this protocol. Patients who achieve a PR after 6 cycles of triplet combination therapy will be eligible to receive an additional 6 cycles and then will stop treatment.

Table 9: Criteria for commencing treatment with triplet combination therapy

Parameter	Value
• ECOG PS	0-2
• Absolute neutrophil count (ANC)	≥ 1,000 /mm^3
• Platelets	≥ 50,000 / mcL (transfusions permitted)
• Hemoglobin	≥ 9.0 g/dL (transfusions permitted)
• Renal function	Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m2 as estimated by the Modification of Diet in Renal Disease (MDRD) abbreviated formula. If not on target, a 24 hour urine creatinine clearance can be used to directly measure.
• Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	Patients without liver involvement with lymphoma ≤ 3.0 x the upper limit of normal (ULN) Patients with liver involvement with lymphoma ≤ 5.0 x the upper limit of normal (ULN)

3.1.3 Study Schemas

Figure 3: Arm 1: FL Dose-finding

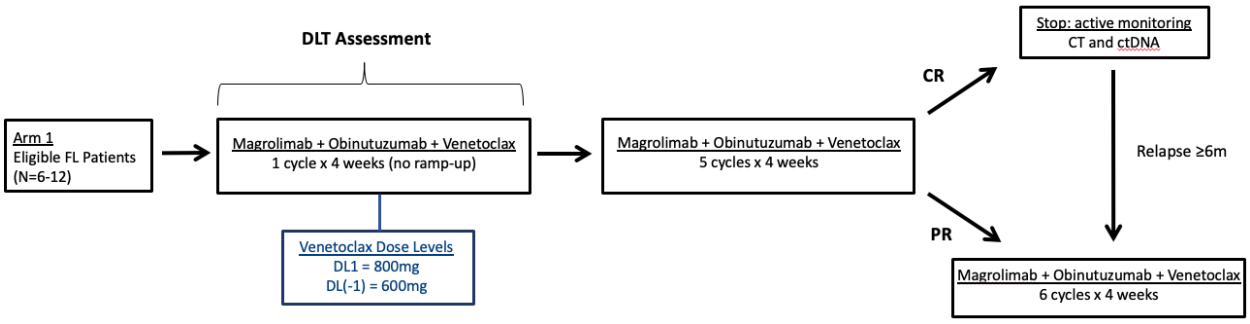


Figure 4: Arm 2: MZL, MCL and CLL Dose-finding

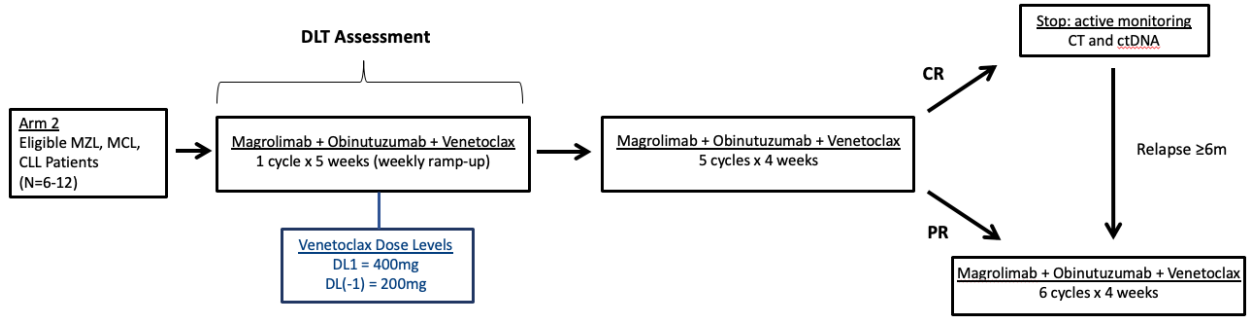
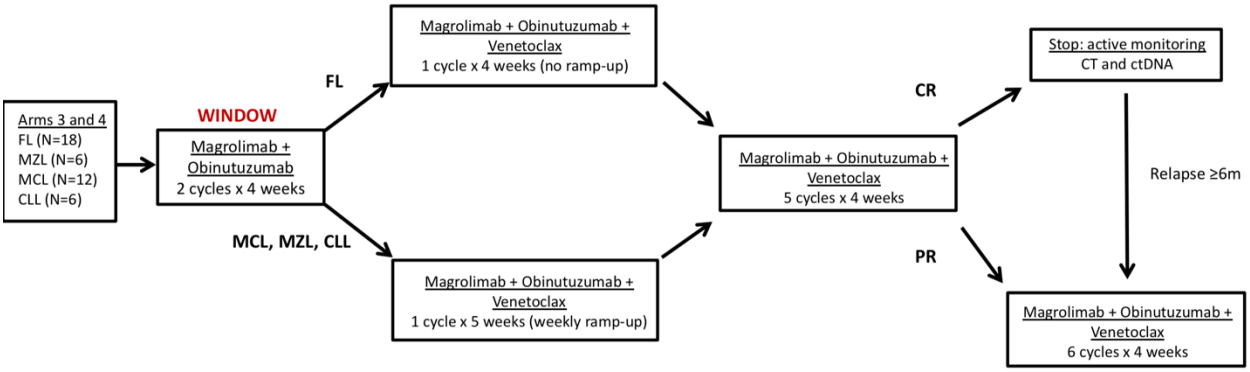


Figure 5: Arms 3 and 4 – Dose Expansion



3.1.4 Dose-Limiting Toxicity

Dose limiting toxicities (DLTs) will be assessed during the venetoclax dose-finding for Arms 1 and 2 as follows:

- the first 4 weeks of triplet combination therapy for patients enrolled in Arm 1, Cohort 1 (C1D1 to C1D28)

- the first 5 weeks after starting venetoclax in Arm 2, Cohort 2 (C1D1 to C1D35).

Dose reductions of magrolimab and obinutuzumab are not permitted during DLT assessment period.

A DLT for this study is defined as any grade 3 or higher adverse event that is clinically relevant and deemed probably or definitely related to any of the study drugs or to the combination therapy, in the opinion of the Principal Investigator and occurs during the venetoclax dose-finding period with the exception of following:

3.1.4.1 Non-hematologic AEs

- Grade 3 nausea, vomiting, or diarrhea that persist ≤ 7 days with supportive care
- Grade 3 fatigue with improvement to ≤ grade 2 within 7 days
- Grade 3 infection that improves to ≤ grade 2 after initiation of antimicrobials
- Grade 3 electrolyte disturbances that improve to ≤ grade 2 within 72 hours with appropriate medical management and are not associated with other clinically significant consequences.
- Grade 3 magrolimab- or obinutuzumab-infusion reactions that resolve to ≤ grade 1 within 24 hours. **NOTE:** In a patient, if it is not clear if the AE is an infusion-related reaction (IRR), the patient may be replaced.
- Other grade 3 laboratory abnormality that is asymptomatic and deemed by the investigator to be not clinically significant

3.1.4.2 Hematologic AEs

- Grade 3 neutropenia not associated with clinical sequelae
- Grade 3 thrombocytopenia not associated with ≥ grade 2 bleeding
- Grade 3 anemia that lasts less than 3 days and responds to blood transfusion. **NOTE:** Grade 3 hemolytic anemia that requires hospitalization or prolongation of existing hospitalization, is disabling, or limits self-care activities of daily life (ADLs) will be considered a DLT.
- Grade 3 or 4 lymphopenia

3.1.5 Safety Ramp-Up of Venetoclax

Patients with FL (Arms 1 and 3; Cohorts 1 and 3) will start venetoclax at target dose for that particular dose level.

Intra-patient dose escalation of venetoclax will be performed with fixed doses of magrolimab and obinutuzumab for patients with MZL, MCL and CLL (Arms 2 and 4; Cohorts 2, 4, 5 and 6) during Cycle 1 (**Table 10**). If tolerated, venetoclax will be administered at the target dose level once daily for all subsequent cycles.

NOTE: During safety ramp-up, an individual patient who experiences a DLT or toxicity that meets DLT criteria during dose expansion (serious toxicity) can have venetoclax dose reduced to the dose of venetoclax that was tolerated and continue treatment (**Table 10**), if felt to be in the best interests of the patient. Once DLT assessment is complete, all dose modifications during safety ramp-up will be conducted per Sections **3.3.2** and **3.3.3**. DLT rules apply to all arms.

Table 10: Intrapatient ramped-up dose-escalation schedule for venetoclax in MZL, MCL and CLL patients

Week of safety ramp-up period	Patients with MZL, MCL and CLL (Arms 2 and 4)	
	DL(-1): 200 mg	**DL1: 400 mg**
1	20 mg	20 mg
2	50 mg	50 mg
3	100 mg	100 mg
4	200 mg	200 mg
5	200 mg	400 mg

3.2 DRUG ADMINISTRATION

Treatment schedule from Cycles 1 to 12 is provided below (**Table 11** and **Table 12** for dose-finding and dose-expansion respectively). A flexibility window between cycles of -3/+7 days is allowed due to scheduling or other administrative reasons; additional delays may apply based on toxicities.

Magrolimab doses will be calculated based on actual body weight measured at the most recent clinical assessment prior to administration. Patients will be encouraged to complete and return an optional drug diary as a memory aid to help document the date and time of all self-administered study drugs (**Appendix D**). This drug diary as well as study drug containers and any unused study drug should be returned to the research team at the end of each cycle of therapy.

Table 11: Drug administration schedule for study medications for dose-finding cohorts

Arm	Drug[a,b,c]	**Cycle 1** Arm 1: 28 days Arm 2: 35 days	**Cycles 2-12** Arms 1 and 2: 28 days
1	**Magrolimab**	**D2:** 1mg/kg **D8,15,22:** 30mg/kg	**D1,15:** 30mg/kg
	Obinutuzumab	**D1:** 100mg **D2:** 900mg **D8,15:** 1000mg	**D1:** 1000mg
	Venetoclax	**D1-28:** DL1: 800mg DL(-1): 600mg	**D1-28:** DL1 800mg DL(-1) 600mg
2	**Magrolimab**	**D2:** 1mg/kg **D8,15,22:** 30mg/kg	**D1,15:** 30mg/kg
	Obinutuzumab	**D1:** 100mg **D2:** 900mg **D8,15:** 1000mg	**D1:** 1000mg
	Venetoclax	**DL1:** **D1-7:** 20mg **D8-14:** 50mg **D15-21:** 100mg **D22-28:** 200mg **D29-35:** 400mg **DL(-1):** **D1-7:** 20mg **D8-14:** 50mg **D15-21:** 100mg **D22-28:** 200mg **D29-35:** 200mg	**D1-28:** DL1 400mg DL (-1) 200mg

[a] When both magrolimab and obinutuzumab are given on the same visit day, obinutuzumab will be administered at least 1 hour after the completion of magrolimab administration.

[b] Premedication with acetaminophen 650 mg and diphenhydramine 25-50mg (or comparable regimen) will be administered 30-60 minutes prior to all obinutuzumab doses. Similar premedication will also be given prior to priming dose and first loading dose of magrolimab. Additional premedication with dexamethasone 4 to 20 mg or comparable regimen will be given before the priming dose and first loading dose of magrolimab. Premedication is not required for subsequent doses of magrolimab.

[c] Obinutuzumab and magrolimab are administered as intravenous infusions.

Table 12: Drug administration schedule for study medications for expansion cohorts

Cohort	Drug[a,b,c]	Window		Triplet Combination	
		Cycle-2 Cohorts 3, 4, 5, and 6: 28 days [a,b,c]	**Cycle-1** Cohorts 3, 4, 5, and 6: 28 days [a,b,c]	**Cycle 1** Cohort 3: 28 days Cohort 4/5/6: 35 days [a,b,c]	**Cycles 2-12** Cohorts 3, 4, 5, and 6: 28 days [a,b,c]
3	Magrolimab	**D2:** 1mg/kg priming dose **D8,15,22:** 30mg/kg	**D1,15:** 30mg/kg	**D1,15:** 30mg/kg	**D1,15:** 30mg/kg
	Obinutuzumab	**D1:** 100mg **D2:** 900mg **D8,15:** 1000mg	**D1:** 1000mg	**D1:** 1000mg	**D1:** 1000mg
	Venetoclax	**N/A**	**N/A**	**D1-28:** at target dose (dose established from dose-finding cohorts)	**D1-28:** at target dose (dose established from dose-finding cohorts)
4, 5,6	Magrolimab	**D2:** 1mg/kg priming dose **D8,15,22:** 30mg/kg	**D1,15:** 30mg/kg	**D1,15:** 30mg/kg	**D1,15:** 30mg/kg
	Obinutuzumab	**D1:** 100mg **D2:** 900mg **D8,15:** 1000mg	**D1:** 1000mg	**D1:** 1000mg	**D1:** 1000mg
	Venetoclax	**N/A**	**N/A**	**D1-35:** ramp-up to target dose (dose determined from dose-finding cohorts)	**D1-28:** at target dose (dose established from dose-finding cohorts)

[a] When both magrolimab and obinutuzumab are given on the same visit day, obinutuzumab will be administered at least 1 hour after the completion of magrolimab administration.
[b] Premedication with acetaminophen 650 mg and diphenhydramine 25-50mg (or comparable regimen) will be administered 30-60 minutes prior to all obinutuzumab doses. Similar premedication will also be given prior to priming dose and first loading dose of magrolimab. Additional premedication with dexamethasone 4 to 20 mg, or comparable regimen will be given before the priming dose and first loading dose of magrolimab. Premedication is not required for subsequent doses of magrolimab.
[c] Obinutuzumab and magrolimab are administered as intravenous infusions.

3.2.1 Magrolimab Administration

All patients will receive a magrolimab priming dose of 1 mg/kg on Day 2 of the first cycle of treatment. The duration of infusion of the priming dose will be 3 hours (±30 minutes). Use of an inline filter is required. All subsequent loading or maintenance doses of magrolimab will be infused over a duration of 2 hours (±10 minutes). When both obinutuzumab and magrolimab are given on the same visit day, obinutuzumab will be administered at least 1 hour after the completion of

magrolimab administration. All patients should be monitored for 1 hour post-infusion for all doses during Cycle -2. Post-infusion monitoring should begin after the last study drug is given. Post-infusion monitoring is not required for doses after Cycle 1, Day 22 for Arms 1 and 2 (dose-finding arms), and Cycle -2, Day 22 for Arms 3 and 4 (dose expansion arms). Patients who experience any treatment-related AEs during the observation period should be further monitored, as clinically appropriate.

Complete Blood Count with Differential will be performed prior to each dose, and 3-6 hours after the first and second doses of magrolimab - Cycle 1, Days 2 and 8 for dose-finding arms (Arms 1 and 2), and Cycle -2, Days 2 and 8 for dose-escalation arms (Arms 3 and 4). Complete Blood Count with Differential will also be performed twice weekly for the first cycle (Cycle 1 for dose-finding arms [Arms 1 and 2], and Cycle -2 for dose-escalation arms [Arms 3 and 4]).

3.2.1.1 Premedication for magrolimab

The optimal pretreatment regimen is defined as acetaminophen 650 mg (or a comparable non-steroidal anti-inflammatory agent) and oral or IV diphenhydramine 25 to 50 mg (or comparable regimen) for the priming dose and the first loading dose. Additional premedication with dexamethasone 4 to 20 mg will be given before the priming dose and first loading dose of magrolimab. Premedication is required before administration of the first 2 doses of magrolimab. Premedication is not required for subsequent doses unless the patient has experienced a prior grade 3 infusion reaction; however, premedication for subsequent magrolimab treatments may be continued based on the treating physician's clinical judgement and the presence/severity of prior infusion reactions. Intravenous corticosteroid (e.g., 100mg prednisone/prednisolone or 4 to 20mg dexamethasone or 80mg methylprednisolone) may be administered if a patient has experienced a prior grade 3 infusion reaction, or at investigator's discretion.

3.2.2 Obinutuzumab Administration

Table 13: Dose and infusion rate of obinutuzumab for all patients

Day of treatment cycle		Dose of obinutuzumab	Rate of infusion
Cycle 1 (Dose-finding, Arms 1 and 2) Cycle -2 (Dose expansion, Arms 3 and 4)	Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	If no IRR occurred during the previous infusion, administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr. If the patient experienced an IRR during the previous infusion, start administration at 25 mg/hr. The rate of infusion can be escalated in increments of up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	1000 mg	If no IRR occurred during the previous infusion where the final infusion rate was ≥100 mg/hr,
	Day 15		

Day of treatment cycle		Dose of obinutuzumab	Rate of infusion
Cycle 1 (Dose-finding, Arms 1 and 2) Cycle -2 (Dose expansion, Arms 3 and 4)	Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	If no IRR occurred during the previous infusion, administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr. If the patient experienced an IRR during the previous infusion, start administration at 25 mg/hr. The rate of infusion can be escalated in increments of up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	1000 mg	If no IRR occurred during the previous infusion infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If the patient experienced an IRR during the previous infusion administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
All subsequent cycles (all arms)	Day 1	1000 mg	

3.2.2.1 Premedication for Obinutuzumab

Detailed guidance for the optimal pretreatment regimen is provided below (**Table 14**).

Table 14:Premedication recommendations for obinutuzumab

Day of treatment cycle	Patients requiring premedication	Premedication	Administration
Cycle 1, Days 1 and 2 (Dose-finding, Arms 1 and 2) Cycle -2, Days 1 and 2 (Dose expansion, Arms 3 and 4)	All patients	Intravenous corticosteroid[1]	Administered 30-60 minutes before obinutuzumab infusion
		Acetaminophen 650 mg or equivalent NSAID	
		Anti-histaminic[2]	
All subsequent infusions[3]	All patients	Acetaminophen 650 mg or equivalent NSAID	Administered 30-60 minutes before obinutuzumab infusion
		Anti-histaminic[2]	

[1] 100 mg prednisone/prednisolone or 20mg dexamethasone or 80mg methylprednisolone. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.

[2] For example: 25 or 50 mg diphenhydramine or equivalent

[3] Additional premedications may be given based on PI discretion and nature of previous infusion reactions

3.2.3 Venetoclax administration

Venetoclax should be taken with a meal. If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another dose may be given. Otherwise, no replacement dose is to be given. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible and ensure that the minimal interval between the current dose and the next dose is at least 16 hours in order to avoid excessive drug accumulation after the next dose.

Venetoclax will be dispensed to patients in bottles. All doses of venetoclax taken in the clinic or day hospital should be taken from the bottle dispensed to the subject. Unused venetoclax tablets dispensed during previous visits must be returned. Returned tablets must not be re-dispensed to anyone.

Patients will be encouraged to complete and return an optional drug diary as a memory aid to help document the date and time of all self-administered study drugs (**Appendix D**).

3.3 DOSE MODIFICATIONS

The following sections detail dose modifications/delay guidelines for each individual drug of the window or triplet combination regimen based on documented toxicity. It is the responsibility of the investigator to determine the most likely agent responsible for the observed toxicity and follow dose modification/delay guidelines in the appropriate section listed below. Dose reductions or delay for multiple study agents based on the same toxicity is not necessary and dosing should be modified or delayed only for the most likely offending agent identified by the investigator.

Dose adjustments are to be made according to the system showing the greatest toxicity. If a patient experiences several toxicities and there are conflicting recommendations, the recommended dose adjustment that reduces the dose to the lowest level will be used.

Dose modifications of magrolimab and obinutuzumab are not allowed throughout the study treatment, only dose delays can be considered per investigator's discretion. If AEs occur that are related to either of these infusional agents, then dose delays of up to 2 weeks during the window period, and up to 4 weeks during the triplet therapy, are permitted until the investigator feels it is safe to resume. If, after the delay the investigator does not feel it is safe to re-initiate therapy with magrolimab or obinutuzumab, then the patient should be taken off study treatment.

3.3.1 Exceptions to Dose Modifications/Delays during DLT Evaluation Windows

3.3.1.1 During venetoclax dose-finding (addition of venetoclax to magrolimab and obinutuzumab)

Dose delays of magrolimab and obinutuzumab should be avoided during the DLT assessment (i.e., Cycle 1 of triplet combination therapy in Arms 1 and 2) to allow for identification of toxicities. If a patient experiences a DLT to triplet combination therapy, then all study therapy should be held for up to 2 weeks per the investigator. If DLT resolves and it is deemed safe to re-initiate therapy, then magrolimab and obinutuzumab should be re-started at the prior dose, and venetoclax should be re-started at one dose level lower. Dose levels for venetoclax dose modifications are mentioned in the table below (**Table 15**).

Table 15: Venetoclax dose levels for dose-modifications

Dose level	Cohorts 1,3 (FL)	Cohorts 2, 4, 5, 6 (MZL, MCL, CLL)
DL-3	200 mg	50 mg
DL-2	400 mg	100 mg
DL-1	600 mg	200 mg
DL1	800 mg	400 mg

3.3.2 Modifications for Hematologic Toxicity

Dose modifications for hematologic toxicities must be done according to the guidelines below (**Table 16**). The investigator may judge a more conservative dose modification if appropriate. Therefore, if these guidelines are not followed, the rationale for other measures is to be documented in detail in the patient's medical record. Use of growth factors (filgrastim, pegfilgrastim, etc.) and transfusion support is permitted per investigator's discretion.

Table 16: Dose modifications for hematologic toxicity

Event(s)	Dose Delay or Modification
CTCAE Grade 3 or 4 neutropenia, without infection or fever CTCAE Grade 3 or 4 thrombocytopenia Febrile neutropenia[a] CTCAE Grade 3 or 4 anemia	**During window period** Delay next magrolimab and obinutuzumab infusion until toxicity recovers to ≤ Grade 2. Upon recovery to ≤ Grade 2, resume previous doses of magrolimab and obinutuzumab. Dose delays of longer than 2 weeks are not permitted. **During triplet therapy after DLT assessment (Cycle 1, Arms 1 and 2)** Hold venetoclax and delay next magrolimab and obinutuzumab infusions until toxicity recovers to ≤ Grade 2. If toxicity recovers to ≤ Grade 2, patient may be treated at one venetoclax dose level lower.[b] Dose delays of longer than 4 weeks are not permitted.

CTCAE = Common Terminology Criteria of Adverse Events;

a. These patients should recover from neutropenia, without fever
b. If subsequent treatment with venetoclax at lower dose levels does not result in recurrent Grade 3 or higher hematologic toxicity, the dose of venetoclax can be increased to the original dose level during later cycles.

3.3.3 Modifications for Non-hematologic Toxicity (for all toxicities except as specified below)

Dose modifications for non-hematologic toxicities are outlined below (**Table 17**). The investigator may judge a more conservative dose modification appropriate; therefore, if these guidelines are not followed, the rationale for other measures is to be documented in detail in the patient's medical record.

Table 17: Dose modifications for non-hematologic toxicity

Event(s)	Dose Delay or Modification
Grade 1-2[a]	No dose reduction or delay is necessary. Symptomatic management per investigator's discretion.
Grade 3[a]	**During window period** Delay next magrolimab and/or obinutuzumab infusion for a maximum of 2 weeks. If improvement to Grade ≤ 2 or baseline, resume previous doses of magrolimab and obinutuzumab. Dose delays of longer than 2 weeks are not permitted. **During triplet therapy after DLT assessment (Cycle 1, Arms 1 and 2)** Per investigator's discretion, venetoclax, magrolimab and obinutuzumab can be delayed for a maximum of 4 weeks. First episode: If improvement to Grade ≤ 2 or baseline, resume previous doses of venetoclax, magrolimab and/or obinutuzumab. For subsequent episodes: If improvement to Grade ≤ 2 or baseline, venetoclax can be restarted at one dose level lower.[b] ≥3 episodes: Consider permanent discontinuation of the offending agent. Permanent discontinuation of all study treatment may be considered per investigator's discretion.
Grade 4[a]	Permanently discontinue all study treatment
Toxicity requiring delay for >4 weeks	Permanently discontinue all study treatment

a. Appropriate supportive care may be provided per investigator's judgement.
b. If subsequent treatment with venetoclax at lower dose levels does not result in recurrent Grade 3 or higher hematologic toxicity, the dose of venetoclax can be increased to the original dose level during later cycles.

3.3.4 Infusion Reactions to Magrolimab

Infusion-related reactions are defined by the NCI CTCAE Version 5.0 under "Injury, poisoning and procedural complications" as follows: "a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances." The time frame for infusion reaction assessment is the 24-hour period beginning from the start of the magrolimab infusion. Re-challenge of patients has not resulted in worsening of any adverse reaction and patients who continue on therapy following an initial infusion reaction have tolerated subsequent treatments without incident. There have been no late hypersensitivity reactions.

3.3.4.1 Grade 1

For Grade 1 symptoms (mild transient reaction; infusion interruption not indicated; intervention not indicated):

- Monitor patient until recovery from symptoms.

- Patients who experience IRRs with the first 2 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the Principal Investigator's discretion.

3.3.4.2 Grade 2

For Grade 2 IRR, described as requiring symptomatic treatment and prophylactic medications (e.g. antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids) for ≤ 24 hours, infusion interruption is indicated:

- Stop the magrolimab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or 500 to 750 mg oral paracetamol/acetaminophen.
- Monitor patient until resolution of symptoms.
- Corticosteroid therapy may also be administered.
- If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate when symptoms resolve.
- If no further complications ensue after 60 minutes, the rate may be increased to 100% of the original infusion rate. Monitor the patient closely.
- If symptoms recur, then stop infusion and disconnect the patient from the infusion apparatus; no further magrolimab will be administered at that visit.
- Patients who experience IRR with the first 2 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the Principal Investigator's discretion.
- Patients who experience an infusion reaction of Grade 2 during the 4-hour post-infusion observation period that does not resolve during that time should be observed for 24 hours or until the adverse event resolves, with vital sign measurements every 4 hours and additional evaluations as medically indicated for the management of the adverse event.

3.3.4.3 Grade 3 or 4

For Grade 3 IRR described as prolonged reactions or recurrence of symptoms following initial improvement, or where hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates), or Grade 4 IRR described as having life-threatening consequences, where urgent intervention is indicated:

- Immediately discontinue infusion of magrolimab.
- Begin an IV infusion of normal saline. Systemic steroids, bronchodilators and/or epinephrine may be used as per institutional guidelines.
- The patient should be monitored until the investigator is comfortable that the symptoms will not recur.
- Patients who have Grade 3 infusion reactions with the first dose can be offered the opportunity to stay on study and must be given premedication prior to subsequent doses. In this setting, premedication with acetaminophen (650 mg PO), diphenhydramine (25-50 mg PO or IV) and dexamethasone (4-20 mg IV), or a comparable regimen, is recommended for the subsequent 2 doses. Long-term premedication can be discontinued if clinically indicated, for example if the patient does not demonstrate further infusion reactions after multiple doses.

- In patients who receive premedication and still experience a recurrent Grade 3 infusion reaction, or patients who experience a Grade 4 IRR at any time should be permanently discontinued from the study treatment.
- All patients with Grade 3 or greater infusion related reactions will be observed for an additional 24 hours or longer until the adverse event resolves, with vital sign measurements every 4 hours and additional evaluations as medically indicated for the management of the AE.
- In the case of late-occurring hypersensitivity symptoms (e.g., appearance of localized or generalized pruritus after Day 1 but within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

3.3.5 Infusion Reactions to Obinutuzumab

The most frequently observed adverse drug reactions (ADRs) in patients receiving obinutuzumab were IRRs which occurred predominantly during infusion of the first 1000 mg. In patients with CLL who received the combined measures for prevention of IRRs (adequate corticosteroid, oral analgesic/anti-histamine, omission of antihypertensive medication), a decreased incidence of IRRs of all grades was observed. The rates of Grade 3-4 IRRs (which were based on a relatively small number of patients) were similar before and after mitigation measures were implemented. The incidence and severity of infusion-related symptoms decreased substantially after the first 1000 mg was infused, with most patients having no IRRs during subsequent administrations of obinutuzumab.

In the majority of patients, irrespective of indication, IRRs were mild to moderate and could be managed by the slowing or temporary halting of the first infusion, but severe and life-threatening IRRs requiring symptomatic treatment have also been reported. IRRs may be clinically indistinguishable from IgE-mediated allergic reactions (e.g., anaphylaxis). Patients with a high tumor burden and/or high circulating lymphocyte count in CLL [> 25 x 10^9/L] may be at increased risk of severe IRR. Rate modifications depending on the severity of IRRs are provided in the table below (**Table 18**).

Table 18: Obinutuzumab infusion rate modifications for infusion-related reactions

Grade	Intervention
Grade 1-2 (mild and moderate)	Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion. If patient does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see **Table 13** and **Table 14**). For CLL patients receiving the Cycle -2, Day 1 dose split over 2 days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.
Grade 3 (severe)	Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred). If patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see **Table 13** and **Table 14**:). For CLL patients receiving the Cycle -2, Day 1 dose split over 2 days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further. If the patient experiences a second occurrence of a Grade 3 IRR, stop infusion and permanently discontinue therapy.
Grade 4 (life-threatening)	Stop infusion and permanently discontinue therapy.

3.4 Safety Management Guidelines for Other Common Toxicities

Guidelines for management of other common anticipated toxicities from study medications will be discussed in this section. It is emphasized that these are general guidelines and may or may not be followed depending on the patient's clinical situation and investigator's judgement. Other supportive measures which the investigator deems appropriate for the clinical situation, may be utilized. Therefore, if other measures are used, it must be documented appropriately.

3.4.1 Tumor Lysis Syndrome (Venetoclax and Obinutuzumab)

See Section **4.1.2**

3.4.2 Magrolimab

3.4.2.1 Anemia

Treatment with a priming dose of 1 mg/kg followed by higher weekly maintenance dosing is associated with an early, transient, acute decline in hemoglobin levels of about 2 g/dL, with nadirs occurring in most patients within the first 2 weeks of starting therapy. In most patients with adequate bone marrow reserve, hemoglobin levels gradually recovery to baseline by Week 4 or later, despite continued treatment with magrolimab. Based on these data, all patients must have a documented hemoglobin ≥ 9 g/dL within 24 hours prior to each of the first 2 doses of magrolimab infusion during initial treatment. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet ≥ 9 g/dL prior to each of the first 2 doses of magrolimab. For patients after exposure to magrolimab, hemoglobin will be monitored frequently for response

and/or toxicity prior to each dose, and 3 to 6 hours after the initiation of the first and second doses of magrolimab. The patient should be transfused as clinically appropriate.

Magrolimab binds to RBCs and may cause transient interference with cross-matching of units for transfusion. During the screening period, red blood cell typing per NIH CC guidelines will be performed for each patient. For all elective red cell transfusions, leukocyte-reduced units matched for the phenotype of the patients will be used. Where exact matching for all the specified blood groups proves impractical (e.g., for MNS blood group), local sites will decide on the best matched donor units to be used. Cytomegalovirus (CMV) matching (i.e., CMV-seronegative units for CMV-seronegative patients) will not be required for this study because it will limit the inventory for antigen matching.

If the crossmatch is incompatible, the RBC units that are Coombs crossmatch-incompatible will be selected (e.g., phenotype-matched or least incompatible) for issue at the discretion of the local site's Transfusion Service Medical Director or equivalent person, where available. For emergency transfusions, the transfusion laboratory may consider using emergency Group O Rhesus negative units if phenotyped units are not available. Blood plasma therapy will be blood-type specific. Platelets will be blood type compatible whenever possible, and if not, will have been tested and found not to have high titer anti-A or anti-B.

3.4.2.2 Pneumonitis

Pneumonitis has been infrequently observed in patients receiving magrolimab. Generally, immune-related AEs have not been observed in clinical use with magrolimab. In contrast to T-cell checkpoint inhibitors, magrolimab primarily exerts its antitumor efficacy through macrophage-mediated phagocytosis of tumor cells. Nonspecific T-cell or other host immune responses that are seen with T-cell checkpoint inhibitors have not been observed with magrolimab in nonclinical studies. Additionally, no events of macrophage activation syndrome or hemophagocytic lymphohistiocytosis have been reported in clinical studies. In instances of suspected pneumonitis, first rule out noninflammatory causes (e.g. infections). If a noninflammatory cause is identified, treat accordingly and continue therapy per protocol. Evaluate with imaging (e.g. chest x-ray or CT) and pulmonary consultation. Management of potential pneumonitis follows ASCO guidelines for immune-related AEs. Patients who experience Grade 3 to 4 pneumonitis will be permanently discontinued from study treatment.

3.4.2.3 Thromboembolic Events

Thromboembolic events, including deep vein thromboses and pulmonary embolisms, have been reported in some patients receiving magrolimab, sometimes early in therapy. Available data for magrolimab do not support a clear or consistent relationship between clinical thromboembolic events and magrolimab use. Patients should be closely monitored for the symptoms of thromboembolic events and treated accordingly.

3.4.2.4 Severe Neutropenia Prophylaxis

Severe neutropenia and febrile neutropenia were reported in patients treated with magrolimab in combination with chemotherapy. Close monitoring of hematologic parameters including neutrophils is required for all patients treated with
magrolimab. For patients with high risk of developing Grade 4 neutropenia and febrile neutropenia, primary and secondary prophylaxis with G-CSF is highly recommended. Prophylactic use of antimicrobials may be considered at the discretion of the treating physician. Management of neutropenia and dose modifications will be per Section **3.3.2**.

3.4.2.5 Serious Infections

Patients (with or without neutropenia) should be regularly monitored for signs and symptoms of infection. For patients with prolonged neutropenia or patients at risk, consider infection prophylaxis including antibiotics (eg. fluoroquinolone) or antifungal agents (eg. oral triazoles or parenteral echinocandin) in accordance with current guidelines.

- For patients being treated for serious infections, hold the next dose of magrolimab until the infection has resolved clinically.
- For serious infections that remain active for ≥ 14 days, consider discontinuation of magrolimab.

3.4.3 Obinutuzumab

3.4.3.1 Hypersensitivity Reactions

Hypersensitivity reactions with immediate (e.g., anaphylaxis) and delayed onset (e.g., serum sickness), have been reported in patients treated with obinutuzumab. If a hypersensitivity reaction is suspected during or after an infusion (e.g., symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion should be stopped, and treatment permanently discontinued. Patients with known hypersensitivity to obinutuzumab must not be treated. Hypersensitivity may be clinically difficult to distinguish from infusion related reactions.

3.4.3.2 Worsening of Pre-existing Cardiac Conditions

In patients with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with obinutuzumab. These events may occur as part of an IRR and can be fatal. Therefore, patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution in order to prevent a potential fluid overload.

3.4.3.3 Hepatitis B Reactivation

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with anti-CD20 antibodies including obinutuzumab. HBV screening should be performed in all patients before initiation of treatment with obinutuzumab. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active Hepatitis B disease should not be treated with obinutuzumab. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis reactivation.

3.4.3.4 Progressive Multifocal Leukoencephalopathy (PML)

PML has been reported in patients treated with obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset or changes to preexisting neurologic manifestations. The symptoms of PML are nonspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g., muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as “cortical” (e.g., aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for JCV DNA). Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently

discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the evaluation and treatment of PML.

3.5 ON STUDY EVALUATIONS

Upon successful enrollment, and following completion of the Screening/Baseline visits, patients will begin treatment as outlined in Section **3.1**. The results from all procedures/tests must be reviewed prior to initiation of each cycle of treatment for consideration of dose modifications.

Treatment with magrolimab, obinutuzumab, and venetoclax will continue until discontinuation per study protocol (Section **3.1**), disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section **3.9**. Refer to the Study Calendar (**Appendix G**) for additional information for all tests and procedures to be performed prior to each visit and in follow-up.

3.6 TREATMENT CONSIDERATIONS/EXCEPTIONS

3.6.1 Treatment Beyond Progression ("Pseudo-progression")

A minority of patients treated with immunotherapy such a magrolimab may derive clinical benefit despite initial evidence of progressive (PD). Patients suspected to have PD by response criteria will be permitted to continue study treatment beyond confirmed PD as measured by the appropriate evaluation criteria as long as they meet all of the following criteria as determined by the investigator:

- Investigator assessed clinical benefit such as improvement in disease-related symptoms
- Subject is tolerating therapy
- Stable performance status
- Absence of other signs and symptoms indicating disease progression
- Absence of evidence to suggest that other or alternative medical intervention or treatment is needed to treat the disease

Patients that meet the above criteria should have repeat radiographic evaluation within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD.

3.7 POST-TREATMENT/FOLLOW-UP EVALUATIONS

Please see the Study Calendar (**Appendix G**) for all applicable windows and complete information.

3.7.1 30-Day Safety Follow-Up visit

The mandatory Safety Follow-Up visit should be performed approximately 30 days following the last dose of study drug or before the first dose of new anti-cancer therapy, whichever comes first. Refer to the Study Calendar (**Appendix G**) for all tests and procedures to be conducted upon discontinuation of treatment and during follow-up. All AEs that occur prior to the safety follow-up visit should be recorded. See section **6.1.1** for documentation of AEs after study treatment has ended. The investigator or qualified designee will collect information about the new anti-neoplastic therapy initiated after the last dose of trial treatment. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

3.7.2 Follow-Up Visits – Prior to Disease Progression

Patients who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed approximately as follows: every 3 months for two years after completion of study therapy, every 6 months for years 3-5, and then annually thereafter at the discretion of the investigator. Any other evaluations and tests should be performed as clinically indicated. After 5 years of monitoring without disease progression the decision to continue further surveillance imaging, including any assessments and procedures, will be left to the discretion of the investigator.

3.7.3 Follow-Up Evaluations – Survival/Post Disease Progression

Upon disease progression or initiation of other anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted about every 3 to 6 months for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first; unless otherwise clinically indicated.

3.8 STUDY CALENDAR

See **Appendix G**.

3.9 COST AND COMPENSATION

3.9.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by their insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.9.2 Compensation

No compensation will be provided to patients for participating in this study.

3.9.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.10 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

A safety visit will occur 30 days post last dose of study drug. Prior to removal from study, effort must be made to have all patients complete an additional safety visit 18 months after the last dose of obinutuzumab as obinutuzumab has the longest half-life out of the experimental drugs for this study. Details of additional safety visits and follow-up will continue as per Section **3.7**.

3.10.1 Criteria for Removal from Protocol Therapy

- Disease progression
  - A patient may be granted an exception to continue on study treatment with initial radiographic progression if they meet the criteria outlined in Section **3.6**
  - Patient who progresses prior to initiation of venetoclax will not be removed from the protocol, but will move on immediately to the triplet therapy or safety ramp-up phase
- Completion of protocol therapy
- Intercurrent illness that prevents further administration of treatment
- Requirement for use of prohibited therapies as listed in Section **4.2**
- Pregnancy
- Patient requests to be withdrawn from protocol therapy
- Noncompliance with trial treatment or procedure requirements in the opinion of the investigator; such a decision/rationale will be clearly noted in the medical record
- Investigator's decision to withdraw the patient if felt to be in the best interest of the patient; such a decision/rationale will be clearly noted in the medical record

- Unacceptable adverse event(s) (see Section **3.3**), unless it is felt by the Principal Investigator to be in the patient's best interests to remain on study in exceptional circumstances (e.g., discontinue offending study agents while continuing others).

All subjects, regardless of reason for discontinuation of study treatment (with the exception of withdrawal of consent; unless consent to follow-up activities is documented) will be followed for progression and survival.

3.10.2 Off-Study Criteria

Patients who meet the following criteria should be discontinued from the study:

- Screen failure
- Subject requests to be withdrawn from study
- Subject is lost to follow-up
- Death
- Study is cancelled for any reason
- Permanent loss of capacity to consent

3.10.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 3 consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as is possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 PERMITTED THERAPY

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. Palliative and supportive care for the other disease-related symptoms and for toxicity associated with treatment will be offered to all patients in this trial. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

4.1.1 Growth factors

The use of hematopoietic growth factors filgrastim and pegfilgrastim are allowed.

4.1.2 Tumor Lysis Syndrome (TLS)

4.1.2.1 TLS and Venetoclax

TLS is a risk for patients with NHL who are treated with high cell-killing agents, including venetoclax. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Risk is highest for those with bulky disease, elevated leukocyte count, elevated pretreatment LDH levels, compromised renal function, and dehydration. We will perform tumor burden assessments, including radiographic evaluation (e.g., CT scan), assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing abnormalities prior to initiation of treatment with venetoclax.

Patients with MCL and CLL are at higher risk of TLS than FL. The risk is highest during the first 5 weeks of ramp-up. A low starting dose followed by gradual dose ramp-up allows for the tumor size to be gradually reduced and has been effective in reducing the risk of TLS. Hence, in our study, patients with MCL and CLL will undergo venetoclax dose ramped-up over 5 weeks, and the target dose will be lower than patients with FL. Limited data is available in patients with MZL and hence, as a safety measure, patients with MZL will also have venetoclax dose ramped-up over 5 weeks. Also, we believe that use of magrolimab+obinutuzumab in the window period in our study may decrease bulk of disease in most of the patients resulting in reduced risk of TLS when venetoclax is commenced.

The Cairo-Bishop Definition of TLS (clinical and laboratory) will be used in this study. See **Appendix E** for details. We will assess the risk for TLS based on clinical and radiological assessment (e.g., CT scan) prior to initiation of venetoclax treatment. For subjects at risk of TLS:

- Guidelines for monitoring of clinical chemistries and administration of prophylaxis for the safety ramp-up period or period of risk are delineated in **Table 19.**
- Investigator may modify the management as s/he deems appropriate for patient's clinical condition.

Table 19: Recommended TLS prophylaxis and monitoring during Cycle 1 of venetoclax

Tumor Burden	Prophylaxis	Blood Chemistry Monitoring Setting and Frequency of Assessments
Low: All LN <5 cm **AND** ALC <25 x10^9/L	Hydration: Oral (1.5-2 L) Anti-hyperuricemics: Allopurinol[a]	CLL, MZL and MCL: • Pre-dose, 6 to 8 hours, and 24 hours after the first dose of the first two weeks of safety ramp-up during C1 • Pre-dose at subsequent ramp-up doses FL: • Pre-dose, and 24 hours after the first dose of the first week venetoclax treatment • Pre-dose, on C1D8
Medium: Any LN 5 cm to <10 cm **OR** ALC ≥25 x10^9/L	Hydration: Oral (1.5-2 L) and consider additional intravenous fluids as tolerated Anti-hyperuricemics: Allopurinol	CLL, MZL and MCL: • Pre-dose, 6 to 8 hours, 24 hours after the first dose of the first two weeks of safety ramp-up during C1 • Pre-dose at subsequent ramp-up doses • Consider hospitalization for patients with CrCl <80ml/min at first two ramp-up doses; see below for monitoring in hospital FL: • Pre-dose, and 24 hours after the first dose of venetoclax treatment • Pre-dose, on C1D8 and C1D15
High: Any LN ≥10 cm **OR** ALC ≥25 x10^9/L **AND** any LN ≥5 cm	Hydration: Oral (1.5-2 L) or intravenous (150-200 mL/hr as tolerated)[c] Anti-hyperuricemics: Allopurinol; consider rasburicase[b] if baseline uric acid is elevated	CLL, MZL and MCL: **In hospital** at first dose of the first two weeks of safety ramp-up during C1. • Pre-dose, 4, 8, 12 and 24 hours Subsequent ramp-up doses • Pre-dose, 6-8 hours, and 24 hours FL: • Pre-dose, 6 to 8 hours, 24 hours at the first dose of venetoclax treatment • Pre-dose, weekly on D1 of each subsequent week during Cycle 1 * Hospitalization for high risk FL and MZL patients per investigator's discretion.

a. Allopurinol 600 mg 24 hours prior to first dose of venetoclax, followed by 200 mg/m2 (maximum daily dose of 600 mg) in divided doses daily for a minimum of first 28 days of therapy.
b. Rasburicase 0.2 mg/kg IV 24 hours prior to the first venetoclax dose. The dose may be repeated based on laboratory or clinical abnormalities, or per discretion of the investigator.
c. Intravenous fluids should be initiated at a rate of at least 1 mL/kg/hr (target 150-200 cc/hr; not <). Modification of fluid rate should also be considered for individuals with specific medical needs.

4.1.2.2 Recommendations for Initial Management and TLS Prevention

4.1.2.2.1 First Dose of Venetoclax or Dose Escalation

Within the first 24 hours after either the first dose or dose escalation, if laboratory criteria for TLS (**Table 21**) are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution.

- Availability of emergency dialysis should be ensured

- Intravenous (IV) fluids should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150-200 mL/hr; < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.

The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multidisciplinary management will be as per institutional protocols.

4.1.2.3 For any occurrence of laboratory TLS:

- Withhold the next day's venetoclax dose. If resolved within 24 to 48 hours of last dose, resume at the same dose.
- For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose.
- For any events of clinical TLS, resume at a reduced dose following resolution

In addition to the above, additional recommendations for patients with chronic lymphocytic leukemia/ small lymphocytic lymphoma receiving first dose of venetoclax:

- For potassium increase ≥ 0.5 mmol/L from baseline, AND > 5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium, and creatinine and follow guidelines per Section **4.1.2.2.1**
- For phosphorus increase of > 0.5 mg/dL AND > 4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium, and creatinine.

4.1.2.4 Tumor Lysis Syndrome from Obinutuzumab (Precautions During Cycle -2 of Dose-Expansion)

TLS, including fatal TLS, has been reported with obinutuzumab. Patients with CLL or MCL who are treated with the combination of obinutuzumab and magrolimab are considered at risk of TLS if they have lymph nodes ≥ 5 cm or ALC ≥ 25 × 10^9/L, splenomegaly, renal dysfunction (Cr. Cl. < 70 mL/min) or baseline clinical chemistry abnormalities consistent with TLS as per **Table 21**. Patients during dose-finding portion of the study will commence obinutuzumab in combination with venetoclax, and the guidelines outlined in Section **4.1.2** must be followed. During dose-expansion phase, however, patients will commence obinutuzumab in combination with magrolimab during Cycle -2 of the window period. CLL and MCL patients considered at risk of TLS when treated with obinutuzumab in combination with magrolimab must be treated and monitored as follows:

- Patients should receive IV or oral hydration (approximately 3 L per day recommended) starting 1 day before the first dose of obinutuzumab and should continue until and including D8 (approximately 3 L per day recommended).
- Patients should be treated with uricostatics (such as allopurinol) or urate oxidase (such as rasburicase) as per label or local guidance.
- Patients should undergo laboratory assessments for TLS (uric acid, calcium, phosphate, potassium, and creatinine) and the results must be known on the same day the sample was taken.
    - D1 of Cycle -2
    - D2 of Cycle -2
    - D3 of Cycle -2

- D8 of Cycle -2

4.1.3 Infectious prophylaxis for Pneumocystis Jiroveci

As mentioned in Section **1.2.6.2.1.2**, patients with MZL who received obinutuzumab based therapy had a higher rate of Grade 3-5 AEs compared to patients with FL, including a higher rate of infections. All adult subjects with MZL will receive prophylaxis for Pneumocystis Jiroveci during study therapy administration. Trimethoprim/sulfamethoxazole 1 DS tablet by mouth on Monday, Wednesday, and Friday is the preferred schedule. Subjects allergic to either component may receive inhaled pentamidine 300 mg once a month or other standard treatments.

Prophylaxis will begin with initiation of treatment (Cycle 1, Day 1 of dose-finding or Cycle -2, Day 1 of dose expansion) and will be stopped upon completion of therapy unless continued administration beyond this point is deemed necessary based on inadequate immune reconstitution. The use of antibiotics and/or anti-viral prophylaxis according to institutional guidelines is also allowed.

4.2 PROHIBITED FOOD AND MEDICATIONS

Patients are prohibited from receiving the following therapies during treatment on this trial:

- Any therapies intended for the treatment of lymphoma/leukemia whether FDA approved or experimental (outside of this study)
- Immunosuppressive therapy
- Radiation therapy. **NOTE:** Radiation therapy to a symptomatic solitary lesion may be allowed at the investigator's discretion.
- Steroid treatment with doses higher than 20 mg of prednisone or equivalent for prolonged duration is not allowed. Short term treatment with high dose steroids for non-neoplastic intent (e.g., COPD) is allowed. If a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose after the patient has signed the IC. Patients may be using topical or inhaled corticosteroids.
- Strong CYP3A4 inhibitors around initiation of venetoclax as mentioned below in Section **4.2.1.1**.
- Strong CYP3A inducers with venetoclax (Section **4.2.1.2**)
- Prohibited food: Use of the following foods is prohibited for at least 3 days prior to initiation of venetoclax treatment and throughout venetoclax administration. Constituents of these foods have been shown to inhibit CYP3A4, the major enzyme responsible for the metabolism of venetoclax. Consumption of these foods could lead to increased venetoclax exposure:
    - Grapefruit
    - Grapefruit products
    - Seville oranges (included marmalade containing Seville oranges)
    - Star fruit

It is not possible to produce an exhaustive list of medications that fall into these categories, so if in question, refer to the appropriate product label.

4.2.1 Venetoclax and CYP3A and P-gp Inhibitors/Inducers

4.2.1.1 Venetoclax Use with CYP3A and P-gp Inhibitors

Concomitant use of venetoclax with moderate to strong CYP3A inhibitors during the ramp-up phase in MZL, MCL and CLL patients is contraindicated. Concomitant use of venetoclax with CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during ramp-up phase. For FL patients, moderate to strong CYP3A inhibitors are contraindicated for up to 2 weeks after initiation of venetoclax. At stable doses of venetoclax, attempts must be made to avoid concomitant use of strong or moderate CYP3A or P-gp inhibitors. However, the inhibitor may be used if needed per investigator discretion, with dose modifications as outlined in **Table 20**:.

Table 20: Management of potential venetoclax interactions with CYP3A and P-gp inhibitors

Inhibitors	Ramp-Up Phase	Patients Receiving Stable Dose of Venetoclax
Strong CYP3A inhibitor	Contraindicated	Avoid inhibitor use or reduce the venetoclax dose by at least 75%
Moderate CYP3A inhibitor	Contraindicated	Avoid inhibitor use or reduce the venetoclax dose by at least 50%
P-gp inhibitor		

NOTE: Common CYP3A and P-gp inhibitors are mentioned in **Appendix C**.

4.2.1.2 Venetoclax Use with CYP3A Inducers

Avoid concomitant use of venetoclax with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort). Moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) may be used per investigator's discretion. Consider alternative treatments with less CYP3A induction.

5 CORRELATIVE STUDIES FOR RESARCH

5.1 BIOSPECIMEN COLLECTION

SUMMARY

One of the important exploratory aims of this study is to utilize multiplatform genomic analyses of tumor biopsies to identify biomarkers that predict response and/or resistance to magrolimab, both individually and in combination with venetoclax. To achieve this goal, tumor biopsies will be collected in all patients prior to therapy and optional biopsies will be obtained on patients with accessible sites of lymphoma involvement during the window period and at progression of disease. The Staudt lab will perform comprehensive molecular characterization of the tumors at baseline on FFPE blocks, and this evaluation will include whole-exome sequencing, transcriptome profiling, AffySNP6.0 arrays for copy number abnormalities, and emerging technologies such as single cell RNA sequencing. Single cell RNA sequencing will be repeated on tumor biopsies obtained during the window period, and upon progression. We also plan to analyze the tumor biopsies obtained at baseline, during window period, and upon progression with histo-cytometry in Dr. Germain's lab.

Blood and bone marrow samples will be collected for exploratory objectives to evaluate biomarkers of sensitivity or resistance. In blood, circulating tumor DNA (ctDNA) response and

correlation with molecular tumor analysis, is planned. We will use a modern ctDNA platform that combines universal PCR primers for the variable-dense-joining (VDJ) region of the immunoglobulin receptor with next-generation sequencing (NGS) technologies (i.e., clonoSEQ®)(118).

Research Samples Calendar – Bloods:

Sample	Collection Details*	Time Points#										Supervising Laboratory/ Investigator
		Baseline	Window†				Triplet Combination Therapy			Post-Treatment	PD	
			Cycle -2 D1	Cycle -2 D8	Cycle -2 D15	Post-Cycle -2	Post-Cycle -1	D1 of Cycles 1, 3, 7 & 11Δ	D1 of Cycles 1, 3, 5 & 9; Post-Cycle 12∂	Post-Cycles 3, 6, 9 & 12	Years 1-2= q3mos; Years 2-5= q6mos	
cfDNA/ctDNA, Mutational panels (liquid biopsy), Plasma banking	1 x 10 mL Streck tubes	X		X	X	X	X			X	X	X	Figg
Immune subsets, Protein, Immune Markers	2 x 8-10 mL CPTs (sodium citrate)	X		X	X	X	X			X	X	X	
Cytokine analysis, Serum banking	1 x 10 mL in SST tube	X		X	X	X	X			X	X	X	
Flow cytometry	Peripheral blood per SOC	X		X	X	X	X			X	X	X	NCI LP
Magrolimab pharmacokinetics	1 x 3.5mL in red SST		X					X	X				Figg/ PPD Richmond
Magrolimab ADA	1 x 3.5mL in red SST		X					X	X				Figg/ PPD Richmond

***** Tubes/media may be adjusted at the time of collection based upon materials available or to ensure the best samples are collected for planned analyses.
# All timeframes may be adjusted to similar windows as the Study Calendar (**Appendix G**).
† Samples from the window period will be available only for patients enrolled in dose-expansion cohorts (Cohorts 3, 4, 5 and 6).
Δ For patients in dose-expansion cohorts (Cohorts 3, 4, 5 and 6).
∂ For patients in dose-finding cohorts (Cohorts 1 and 2).

NOTE:

- All blood samples/tubes should remain at ambient temperature after collection and processed on the day of collection; do not place samples on ice unless otherwise instructed.
- Subjects who discontinue treatment for a reason other than disease progression and who do not start new treatment should continue to have samples collected at the scheduled time points.

Research Samples Calendar – Tissue/Other:

Sample	Collection Details*	Time Points	Supervising Laboratory/ Investigator
Tissue Samples			
Archival and/or Fresh Tissue Biopsy	• FFPE (block or slides); biopsy is required if archival is not adequate or unavailable • Excision (single or multiple nodes) or core (6 passes); placed in formalin/FFPE and media, as appropriate	• Baseline; if required for adequate tissue • During 1st cycle (Cycle -2; preferably day 8) of doublet therapy with magrolimab + obinutuzumab in window period (optional)† • At disease progression/end of treatment	Staudt, Germain, NCI LP
Tissue/Imaging Analyses	No additional tissues or imaging will be performed for these analyses, only use of already collected samples and/or imaging, as described in Section **5.3.6**		Ahlman
Other Samples			
Germline DNA	• Blood, Buccal swab, or Saliva (preferred)	• Baseline	Figg
Bone marrow aspirate (± flow cytometry) and biopsy	• Aspirate (± flow cytometry) (SOC; heparinized tubes or EDTA/sodium heparin or formalin, as appropriate) • Biopsy (SOC; formalin or no media, as appropriate)	• Baseline • During 1st cycle of doublet therapy with magrolimab + obinutuzumab (Cycle -2; preferably day 8) in window period (optional)† • At disease progression or suspicion of CR • After Cycle 6 of triplet therapy (magrolimab + obinutuzumab + venetoclax) in patients with involvement at baseline. For patients with no baseline bone marrow involvement, biopsy may be performed per investigator's discretion.	Figg, NCI LP\

*Tubes/media may be adjusted at the time of collection based upon materials available or to ensure the best samples are collected for planned analyses.
†Samples from the window period will be available only for patients enrolled in dose-expansion cohorts (Cohorts 3, 4, 5 and 6)

NOTE:

- All samples/tubes should remain at ambient temperature after collection and processed on the day of collection; do not place samples on ice unless otherwise instructed.
- Subjects who discontinue treatment for a reason other than disease progression and who do not start new treatment should continue to have samples collected at the scheduled time points.

5.2 SAMPLE COLLECTION AND PROCESSING

5.2.1 Summary

The planned analyses described below may be done on leftover and/or shared sample portions from the respective laboratories, as needed. In addition to the prospectively collected samples below, leftover portions of samples sent for routine laboratory testing (e.g., plasma from CBC/other hematology labs) may also be retrieved for research tests prior to being discarded. The planned prospective analyses are identified below; laboratories may share resources or collaborate on analyses, if appropriate (e.g., isolation/analysis of DNA not prospectively planned by one lab may be incorporated if needed during the planned analyses).

Portions of all samples may be banked for future research analyses; prospective consent will be obtained during the informed consent process.

5.2.2 Blood Samples – Figg Lab

For questions, please contact Dr. Figg's Clinical Pharmacology Program (CPP) at 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number). Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred). For sample pickup, page 102-11964. For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov. The samples will be processed, barcoded, and stored in Dr. Figg's lab until requested by the investigator.

5.2.2.1 Cell-free DNA (cfDNA)/Circulating Tumor DNA (ctDNA), Mutational Panels, and Plasma Banking

- Collect blood in cell-free DNA (e.g., Streck BCT/collection tubes); gently invert the tubes 8-10 times immediately after collection.
- Plasma will be isolated and frozen at -80ºC until analysis (e.g., centrifuged at 1800 x g for 10 minutes at room temperature; plasma transferred/frozen in aliquots of 1.5-2mL each).

5.2.2.2 Immune Subsets/Markers and Peripheral Blood Mononuclear Cells (PBMCs)

- Collect blood in Cell Preparation Tubes with sodium citrate (e.g., blue/black speckled top); gently invert tubes 8-10 times immediately after collection.
- PBMCs will be isolated per routine laboratory techniques

5.2.2.3 Cytokines and Serum Banking

- Collect blood in Serum Separator Tubes (e.g., red/gray or red/yellow top); gently invert the tubes 8-10 times immediately after collection and allow the blood to clot at room temperature for approximately 30 minutes.
- Serum will be isolated and frozen at -80ºC until analysis (e.g., centrifuged at 1200 xg for 5 minutes at 4ºC; serum transferred/frozen in aliquots of 1.5-2 mL each).

5.2.2.4 Magrolimab Pharmacokinetics (PK) and Anti-Drug Antibody (ADA) Samples

See **Appendix F** for additional details.

- Fill Red Top Serum Separator Tubes COMPLETELY, as far as the vacuum will allow.
- Mix immediately by gently inverting the tube 5 times.
- Allow blood to clot undisturbed for 30 minutes (max. 60 minutes), tube standing upright.

- Centrifuge tube within 1 hour of collection for 10-15 minutes at 1800 g until clot and serum are separated by a well –formed polymer barrier. If serum and cells have not completely separated, re-centrifuge the specimen for an additional 6-8 minutes.
- Transfer serum, using a transfer pipette, into the Transport Tube (s).
- Allow enough space between serum and tube caps to account for expansion during freezing. Do not overfill.
- Record the subject ID number on the specimen label.
- Wrap a small piece of parafilm around the cap of the transport tube. See parafilm instructions below.
- Store serum samples for a minimum of 8 hours at -80°C until shipment to PPD Richmond.

5.2.3 Blood Samples – NCI Laboratory of Pathology

The blood samples for flow cytometry should be sent to the NCI Laboratory of Pathology; please contact NCI Laboratory of Pathology (LP) for questions and for notification of samples.

5.2.3.1 Flow cytometry

- Collect blood, bone marrow, and/or lymph node samples in appropriate tubes (e.g., NaHep/sodium heparin, EDTA, etc.) tubes; gently invert the tubes 8-10 times immediately after collection.
- Send samples to the NCI LP for specialized flow cytometry processing and analysis.
- Studies to be performed on these samples include multi-parameter flow cytometry to determine the percentage of aberrant lymphoma cells. Reagents to be used include but are not limited to characteristic B-cell markers including: CD10, CD19, CD20, CD21, CD22, CD23, Bcl-2, Bcl-6, CD79B, kappa and lambda light chain as well as various T-cell markers including: CD3, CD5, CD4 and CD8.

5.2.4 Tissue Samples

5.2.4.1 Archival tissue

Archival block(s) or slides (i.e., at least 15 unstained slides, 5-microns) is required at baseline; these may also be required in follow-up in case of future routine procedures or in case additional tissue is needed even in the event of optional tumor biopsy.

5.2.4.2 Lymph node excision or core needle biopsy

Lymph node excision or core needle biopsy will be performed per routine standard of care, by Surgery Consultants or Interventional Radiology, as appropriate. A procedure-specific consent form will be signed by the patient prior to the procedure. Every attempt will be made to perform excisional lymph node biopsies to obtain the best quality tissue for translational investigation. Consideration of alternative biopsy methods (e.g., core needle biopsy) will only be made if follow-up excisional biopsy is not possible/safe or patient is unwilling to undergo repeat excisional lymph node biopsy.

In the event that a surgical biopsy procedure is performed, more than one lymph node and at more than one anatomic site may be collected, provided the additional procedures are not unacceptable risk to the patient. In the event of core needle biopsy, these are obtained typically by using a 16-18G needle at the discretion of the provider performing the procedure. Conscious sedation may be used, if warranted, and the use and risks are acceptable to the patient. General anesthesia will

not be performed to obtain biopsies for research purposes. The type of procedure to be done and manner in which it will proceed (e.g., excision/core, single vs. multiple sites of biopsy) will be discussed with the patient prior to the biopsy procedure; if CT guidance will be used for a research biopsy procedure, research radiation exposure will be discussed with the patient. Similar procedure may be followed for extranodal disease/masses. The patient will be reminded that all sampling for research is voluntary.

5.2.4.3 Sample handling/processing

When performed, excisions or core biopsies will be placed in sterile collection/core cylinder tubes (e.g., formalin); gently invert/inspect tubes with media 8-10 times immediately after collection to ensure the core(s) is completed immersed in the media.

Tissue samples will be handled/processed as below prior to planned analyses, as appropriate:

- Any required routine review for histopathologic confirmation of diagnosis and/or grade will occur per standard of care (e.g., H&E, immunohistochemistry), if required.
- Formalin samples will be fixed and paraffin-embedded per routine techniques.

5.2.5 Other Samples

5.2.5.1 Germline DNA

Germline DNA will be collected by blood, buccal swab, and/or saliva samples (preferred). These will ideally be collected at baseline; however, may be collected at any point on study based on supplies. Standardized, commercial collection kits or tubes will be used (e.g., 1, 5-10 mL K_2EDTA tube for blood; Isohelix SK-1 for buccal swabs; Salviette/Oragene® for saliva). In the case of buccal swabs, two (2) samples may be collected in order to ensure adequate DNA collection.

The samples will be processed and DNA extracted/isolated per kit instructions and established techniques. These will be handled by Dr. Figg's lab (see Section **5.2.2** for contact information).

5.2.5.2 Bone marrow aspiration (± flow cytometry) and core biopsy

Bone marrow collection will be performed per routine standard of care. A procedure-specific consent form will be signed by the patient prior to the procedure. Attempt will be made to collect both bone marrow aspirate and core biopsy. If required, the procedure may be performed under conscious sedation per the discretion of the investigator.

- Bone marrow aspirate and flow cytometry samples will be placed in sterile collection tubes (e.g., heparinized tubes or containing EDTA/sodium heparin or formalin, as appropriate); gently invert tubes 8-10 times immediately after collection.
- Core biopsies will be placed in sterile collection/core cylinder tubes (e.g., formalin or no media); gently invert/inspect tubes with media 8-10 times immediately after collection to ensure the core(s) is completely immersed in the media.
- Studies to be performed on these samples include cell analysis and histological (e.g., H&E), immunohistochemical (IHC)/fluorescence in situ hybridization (FISH) review/testing, and other analyses per established techniques (e.g., PD-1/PD-L1, BCL2, MUM1, Ki67, etc.).

5.3 BIOMARKER AND RESEARCH METHODS

The technology platforms that are able to interrogate genomic structure and function are constantly in flux; therefore, the exact nature of the methodologies that will be employed will be assessed at the time that the samples are collected and ready for analysis.

The following are technologies that are currently in use for each planned analysis:

5.3.1 Tumor Profiling

Immunohistochemical (IHC) analyses, including FISH for BCL2 will be performed on every FL sample. For all patients with MCL, IGH-CCND1 will be performed. D6Z1/MYB, D12Z3/MDM2, D11Z1/ATM, D13S319/LAMP1 and TP53/D17Z1 will be done on every patient's baseline CLL tumor biopsy, if available. The routine IHC panel for diagnosis of indolent lymphomas will be performed on tumor tissue samples, including but not necessarily limited to CD3, CD5, CD10, CD20, CD21, CD23, BCL2, BCL6, MUM1 and MIB-1.

5.3.2 Microenvironment Tissue Profiling

Immunohistochemical (IHC) analyses will take to assess for contribution of the tumor microenvironment. IHC that will be performed may include, but are not necessarily limited to: CD3, CD4, CD8, CD20, CD45RO, CD57, CD68, FOXP3, Granzyme B, LAG3, PD-1/PD-L1 (H-score), SIRPα CD14, CD33, CD47, CD163 and/or CD206.

5.3.3 Immune Subset Analysis

Peripheral blood mononuclear cells (PBMC) will be assessed using multiparameter flow cytometry for immune subsets including but not necessarily limited to CD8+ T-cells, CD4+Foxp3- T-cells, Tregs, T_{ex}, Th1, Th2 and Th17+ CD4+ T-cells, monocyte subsets, macrophage subsets, and MDSC subsets. Assessment may include functional markers, i.e., PD-1, Tim-3, CTLA-4, PD-L1, HLA-DR, Ki67, CD47, SIRPα and/or CD40.

5.3.4 Histo-cytometry/Multiplex Staining Technologies

Tissues samples will be provided to the laboratory of Dr. Ronald Germain (NIAID/NIH) for recently developed multiplex staining technologies in 2D and 3D. Dr. Germain's laboratory (NIAID/NIH) will return confocal images and quantitative analyses of these images in figure format for interpretation and analysis. Dr. Germain's group (NIAID/NIH) will not have direct access to the key that links sample identifiers with personally-identifiable information.

5.3.5 DNA/RNA Sequencing

Genomic DNA and total RNA will be extracted from tumor samples using a Qiagen All-prep kit. For individual target genes that are recurrently mutated in indolent NHL, classical Sanger sequencing will be performed on PCR amplicons, using primers surrounding the known sites of mutation. To broadly assess mutations, next generation sequencing (e.g., on an Illumina HiSeq 2000 platform) will be employed, using a paired end sequencing strategy of libraries constructed from tumor DNA. DNA will either be sequenced in its entirety from a whole genome library or will be first enriched for exonic sequences using the Agilent Sure Select system, aiming for 30X or 100X average coverage per base, respectively. The sequence fragments will be mapped back to the genome using the BWA algorithm. Of sequences overlapping a particular base pair in the genome, the percent mutant calls greater that 20% with a minimum of 25X coverage will be

considered as an arbitrary threshold for single nucleotide variants (SNVs). SNVs that are not present in the matched normal sample will be considered candidate somatic mutations.

A related technology, RNA-Seq, utilizes RNA from the tumor specimen to create a cDNA library for high-throughput sequencing. RNA-seq will be performed using Illumina kits followed by high-throughput sequencing on an Illumina HighSeq 2000 machine. The cutoffs for coverage and percent mutant calls mentioned above will also be used to identify putative SNVs. RNA sequencing will also be used to read out digital gene expression across the genome as described.

Recent advances in genomic technologies enable GEP at the single cell level, a distinct advantage over conventional GEP which cannot always distinguish tumor vs non-tumor gene expression(95, 96). Single-cell approaches allow identification of the evolution of rare populations of resistant tumor cells, as well as identification of TME cells critical for the survival of the tumor. The Center for Cancer Research (CCR) has recently opened a single cell analysis core facility with expert staff headed by Dr. Michael Kelly within the CCR Genomics Core. This facility has the ability to take purified viably frozen cells banked from patient biopsies and prepare them, using well-validated 10X Genomics technology, for single-cell RNA sequencing. This core is directly integrated with the NCI Sequencing core facility to provide high-quality, deep-sequencing of the single cell RNA-SEQ samples, as well as 'first-pass' data processing and analysis. Data will then be transferred to lymphoma researchers and bio-informaticians in the Staudt lab for further analysis of gene expression patterns and cellular population dynamics.

5.3.6 Metabolic Tumor Imaging

Under the direction of Dr. Ahlman, special research analyses/readings of standard 18F-FDG PETs collected per standard of care will be performed to evaluate metabolic tumor volume and total lesion glycolysis.

5.3.7 DNA Copy Number Analysis

Array comparative genomic hybridization (e.g., on Agilent 240K or Affy SNP 6.0 microarrays) will be used to assess DNA copy number alterations as described, in tumor DNA to yield somatically acquired regions of copy number gain and loss.

5.3.8 Pharmacokinetics (PK) and Anti-drug Antibodies (ADA) Analysis

Validated assays will be used to measure magrolimab serum concentration and presence of anti-magrolimab antibodies. Coded (linked) samples (Section **5.4.2**) will be sent to a contracted laboratory at the request of Gilead Sciences, Inc. for analysis of magrolimab pharmacokinetics and presence of anti-magrolimab antibodies: PPD Laboratories.

PPD will run validated assays to measure magrolimab serum concentration and presence of anti-magrolimab antibodies. See **Appendix F** for additional details.

The laboratory contact information is as follows:

5.3.8.1 Shipping Information

PPD Laboratories
Attn: Specimen Mgmt Dept, LiMajor Pittman
2246 Dabney Road
Richmond, VA 23230

5.3.8.2 Contact

LiMajor Pittman
Phone: 1-804-977-8459
Email: LiMajor.Pittman@ppdi.com

5.3.9 Other Analyses

Other analyses include the following:

- Cell analysis and histological (e.g., H&E), immunohistochemical review and analysis per standard and established research techniques (e.g., PD-1/PD-L1 expression [Dako], FISH for 9p24 amplicon, and other IHC analyses in blood and tissue).
- Cytokine analysis (e.g., IL-6, IL-10, interferon beta, TNF-alpha)
- cfDNA/ctDNA for liquid genotyping as a non-invasive dynamic monitoring of disease as well as monitoring for individual molecular aberrations that herald progression or disease transformation; specifically, amplification and sequencing of the VDJ segment of the immunoglobulin receptor is planned

5.3.10 Future Use

Any blood, tissue, or other (e.g., CSF) products or portions leftover from other analyses will be stored for future research.

5.4 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.4.1 General

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting patients will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section **7.2**.

If the patient withdraws consent his/her data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

5.4.2 Clinical Pharmacology Program (Figg Lab)

5.4.2.1 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) of the Clinical Pharmacology Program under the direction of Dr. Figg will be barcoded, with data entered and stored in the Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined Figg lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All Figg lab personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without Labmatrix access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

5.4.2.2 Sample Storage

Barcoded samples are stored in barcoded boxes in a locked freezers at appropriate temperatures (e.g., -20ºC to -80ºC) according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Labmatrix. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.4.3 Hematopathology Section of Laboratory of Pathology (Tissue samples)

Archival and/or freshly collected and processed tumor tissue may be stored in the Hematopathology Section of Laboratory of Pathology until ready for planned and/or future research assays if the patient has agreed to allowing specimens to be used in future research studies. IRB approval will be obtained before using any samples to conduct studies that are not described within this protocol. Samples will be stored under conditions appropriate to the type of sample and processing (e.g., ambient or frozen).

Tissue that is given to the technician will be assigned an accession number (HP#) in the HP Case Log book; sample tracking also takes place with a FileMaker Pro data base called HP Patient Information and Specimen Inventory. A Patient background sheet may be filled out and filed with any accompanying paperwork, with final reports and any supplemental reports that follow added as completed.

5.4.4 Staudt Lab

5.4.4.1 Sample Data Collection

Patient samples, collected for research under this IRB approved protocol, may be archived in the Staudt laboratory. All data associated with archived clinical research samples is entered into the web-based NCI Labmatrix database, a centralized system with access controlled via centralized login. Access to this database for samples collected from this study is limited to Dr. Staudt and his research staff, each requiring individual login and password. All staff in the laboratory receive annually updated NIH/CITI or other training, as appropriate, and maintain standards of computer security.

The data recorded for each sample may include the patient ID, trial name/protocol number, date drawn/collected, treatment cycle/time point, sample source (e.g., peripheral blood, marrow, tissue, etc.) as well as box and freezer location. All received samples will be given a unique bar code number, which will be added to the sample NCI Labmatrix database. Only this bar code will be recorded on the sample vial and the vials will not be traceable back to patients without authorized access to the NCI Labmatrix database.

5.4.4.2 Sample Storage

Samples are stored in freezers at -80°C (e.g., sera, plasma, tissue samples) or under liquid nitrogen (e.g., cells), according to established stability requirements. These freezers are located onsite under the direction of Dr. Staudt. Access to samples from this protocol for research purposes will be as outlined in this protocol or by permission of the Principal Investigator only.

5.4.5 Nuclear Medicine/Tumor Imaging (Ahlman)

As Dr. Ahlman is also a clinical nuclear medicine clinician reading the images also for standard of care, he will have access to identifiers of the subjects; however, his assessments specifically for the research metabolic tumor imaging analyses will not be recorded in the medical record, but only in the research records similar to other research-specific data and results.

5.4.6 CAT-I Laboratory (Germain Lab)

The CAT-I laboratory (CAT-I) will obtain coded samples from Dr. Roschewski and his staff. Upon sample acquisition, members of the CAT-I laboratory will enter these samples into CEREBRO, an advanced sample labeling system that tracks each sample through every step of the workflow. To meet requirements for availability of primary data and for quality assurance checks, CAT-I will maintain a detailed inventory of the type (slide, tissue, frozen OCT block) and location of each sample in the laboratory. More specifically, frozen OCT blocks and accompanying slides will be physically stored in the CAT- I laboratory. Tissues provided will be fixed, frozen, and stored in the CAT-I's -80°C freezer. The CAT-I laboratory will be locked when CAT-I lab members are not present. Unprocessed samples will be held by the CAT-I or returned upon their request. Finally, the CAT-I will comply with requirements for annual Biospecimen Reporting at the NIH.

5.5 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.5.1 Description of the scope of genetic/genomic analysis

The research correlates for this study are expected to include DNA/RNA sequencing of tumors, including circulating tumor DNA. In addition, whole exome sequencing may include evaluation for known lymphoma mutations. For any genetic studies performed, the results will be deposited in a database such as dbGaP per NIH requirements. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the subject. This is discussed in the consent.

5.5.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Confidentiality for genetic samples will be maintained as described (Section **5.4**). In addition, a Certificate of Confidentiality has been obtained for this study.

5.5.3 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists).

5.5.4 Genetic Counseling

Subjects will be contacted with a request to provide a sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH to have genetic education and counseling to explain this result; at the time of any such event(s), these activities will be funded by the NCI/CCR in consideration of the specific circumstances. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

6.1.1 Summary

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11 compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Day 1 through 30 days after the last dose of study agent was administered. Beyond the 30 day period after the last drug was administered, only adverse events which are serious and related to the study intervention need to be recorded.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in Section **7.2.1.**

6.1.2 Data Collection/Recording Exceptions

6.1.2.1 Abnormal Laboratory Values

An abnormal laboratory value will be recorded as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms

- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

6.1.2.2 Hospitalizations

Hospitalizations or prolonged hospitalization for the following will not be recorded unless one of the other criteria for seriousness are met (Section **8.1.2**):

- Closer monitoring and/or prophylaxis of TLS during any cycle
- Closer monitoring and/or prophylaxis of IRR during any cycle

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?
I will share human data generated in this research for future research as follows:

_X_ Coded, linked data in an NIH-funded or approved public repository.
_X_ Coded, linked data in another public repository
_X_ Coded, linked data in BTRIS (automatic for activities in the Clinical Center)
_X_ Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?
Data will be shared through:

_X_ An NIH-funded or approved public repository. Insert name or names: ClinicalTrials.gov, dbGaP.
_X_ BTRIS (automatic for activities in the Clinical Center)
_X_ Approved outside collaborators under appropriate individual agreements.
_X_ Publication and/or public presentations.

When will the data be shared?
_X_ Before publication.
_X_ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

In general, response rate will be assessed according to the Lugano response criteria for FL, MCL and MZL; and the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for CLL. Notable exceptions are mentioned below.

- iwCLL criteria may also be used for MCL when the disease involves peripheral blood, bone marrow or spleen without significant lymphadenopathy.
- Separate response criteria for splenic marginal zone lymphoma as proposed by Matutes et al.(121)
- For patients with MALT lymphoma of the ocular adnexa, an MRI based response criteria will be used in conjunction with ophthalmologic evaluation.(122)
- Group d'Etudedes Lymphomes de l'Adult (GELA) grading system to define the histologic response of gastric MALT lymphoma will be utilized for gastric marginal zone lymphoma of MALT type.(123)

6.3.1 Response Criteria – FL, MCL and MZL

The Lugano Classification of Response will be used to assess response in subjects with FL, MZL and MCL, with the exception of CLL.

Lugano classification of response criteria with PET (Cheson et al., 2014)(124):

Response and Site	PET-CT Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response** *All of the following:*
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	• Target nodes/nodal masses must regress to ≤1.5 cm in LDi • No extralymphatic sites of disease
	NOTE: *It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.*	
Nonmeasured lesions	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission** *All of the following:*
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size *At interim, these findings suggest responding disease.* *At end of treatment, these findings indicate residual disease.*	• ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites *When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default valve; when no longer visible, 0 x 0 mm. For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation.*
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None

Response and Site	PET-CT Based Response	CT-Based Response
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change form baseline	Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease** *Requires at least 1 of the following:*
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline; *and/or*	An individual node/lesion must be abnormal with: • LDi >1.5 cm, *and* • Increase by ≥ 50% from PPD nadir, *and* • An increase in LDi or SDi from nadir: o 0.5 cm for lesions ≤2 cm o 1.0 cm for lesions >2 cm
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	• In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. • New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	• Regrowth of previously resolved lesions • A new node >1.5 cm in any axis • A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Response and Site	PET-CT Based Response	CT-Based Response

Abbreviations: 5PS, 5-point scale; CT computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trails involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy of myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

6.3.2 Response Criteria – CLL

The response rate in CLL patients will be calculated based on iwCLL response criteria (Hallek et al 2018)(90):

Complete remission (CR)
Requires **all** of the following criteria: • Absolute lymphocyte count <4000/microL (4×10^9/L). • No lymph nodes >1.5 cm in diameter. • No hepatomegaly or splenomegaly. • No constitutional symptoms attributable to CLL.* • Bone marrow recovery as demonstrated by ANC >1500/microL (1.5×10^9/L), platelet count >100,000/microL (100×10^9/L), and hemoglobin concentration >11 g/dL (110 g/L) in the absence of transfusion or growth factor support. • Bone marrow at least normocellular for age, without evidence for typical CLL lymphocytes by morphologic criteria and immunohistochemistry and without nodular lymphoid aggregates.¶
CR with incomplete bone marrow recovery (CRi)
Fulfills all requirements for CR except has persistent neutropenia, anemia, or thrombocytopenia thought to be unrelated to the disease and likely related to drug toxicity. These patients must have a normal bone marrow aspirate and biopsy with no evidence of clonal infiltrates.
Partial remission (PR)
At least **two** of these criteria must be documented: • A decrease in the peripheral absolute lymphocyte count by at least 50% from the level prior to therapy.

- A reduction in previously enlarged nodes by at least 50% with no increase in the size of any single lymph node and no new enlarged lymph nodes. An increase of <25% in a lymph node <1.5 cm is not considered significant.
- A decrease in the size of the liver and/or spleen by at least 50%.

One of the following hematologic parameters must be met in addition to two of the above criteria in order to qualify for a PR:

- Platelet count ≥100,000/microL (100 × 10^9/L) or at least 50% improvement over baseline (if this value was abnormally low at baseline).
- Hemoglobin concentration ≥11 g/dL (110 g/L) or 50% improvement over baseline (if this value was abnormally low at baseline) without red blood cell transfusions or erythropoietin support.

If only one parameter was abnormal before therapy, only one needs to improve to achieve PR.

Nodular PR

Persistent bone marrow nodules on bone marrow biopsy in patients achieving a CR or PR. Lymphoid aggregates should be evaluated with immunohistochemistry to determine whether they are comprised of CLL cells, lymphocytes other than CLL cells, or T cells. If nodules are not composed of CLL cells, a CR can be documented provided all other criteria are met.

Progressive disease (PD)[Δ]

At least one of these criteria must be documented:

- The appearance of a newly enlarged lymph node (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltration.
- An increase of 50% or more in size of a previously involved site (e.g., lymph nodes, spleen, or liver) measuring ≥1.5 cm.
- An increase of 50% or more in the total circulating lymphocyte count with absolute lymphocyte count of 5000/microL (5 × 10^9/L) or greater.[◊]
- Richter's transformation documented by lymph node or other tissue biopsy.
- Development of neutropenia, anemia, or thrombocytopenia attributable to **CLL.**[§]

Stable disease

Patients who do not meet the criteria for a complete remission, partial remission, or progressive disease, have stable disease. Stable disease is therapeutically equivalent to a nonresponse (i.e., refractory disease).

For patients treated with a therapy for a defined treatment duration, response assessment should be performed at least two months after the completion of therapy. For those receiving continued therapies or treatment strategies that include a maintenance phase, response assessment should be performed at least two months after achieving "maximum response" defined as a treatment phase where no additional improvement is seen during at least two months of therapy.

CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma; ANC: absolute neutrophil count.
* These include ≥10% unintentional weight loss within the previous six months, fatigue that interferes with work or usual activities, fevers greater than 100.5°F (>38°C) for ≥2 weeks, or night sweats for >1 month.
¶ Assessment of residual CLL cells in the bone marrow for this purpose is not based on flow cytometry. Assessment for measurable residual disease (MRD, also called 'minimal residual disease') is reserved for clinical trials. Although bone marrow biopsy is required to confirm a CR, it is not always recommended in general practice as it may not impact management. If the above clinical and hematologic parameters are compatible with a CR and the clinician chooses not to perform a bone marrow biopsy, the documented response can be "partial remission."
Δ Transient increases in lymph node size may occur during treatment with novel inhibitors and should not be considered PD.
◊ For patients treated with therapies that may cause lymphocytosis (e.g., kinase inhibitors), an increase in blood lymphocyte count, by itself, does not uniformly indicate an increased tumor burden, but may reflect redistribution of leukemia cells from lymphoid tissues. In such cases, increased lymphocytosis alone is not a sign of treatment failure or progressive disease.

§ Cytopenias cannot be used to determine disease progression during active therapy since they may be due to administered cytotoxic agents. Cytopenias that occur at least three months after the completion of therapy and are accompanied by an infiltrate of clonal CLL cells on bone marrow biopsy can be used to define disease progression. Specific values that define progression include a decrease in hemoglobin level by more than 2 g/dL (20 g/L) or to less than 10 g/dL (100 g/L) or a decrease in platelet count by more than 50% or to less than 100,000/microL (100×10^9/L).

6.3.3 Response Criteria – Splenic Marginal Zone Lymphoma(121)

Partial response: 50% or greater decrease in spleen size. A reduction in previously enlarged nodes (if present) by at least 50% with no increase in the size of any single lymph node and no new enlarged lymph nodes. An increase of <25% in a lymph node <1.5 cm is not considered significant. In addition to the above two criteria, one of the following hematologic parameters must be met in order to qualify for a PR:

- Platelet count ≥100,000/microL (100 × 109/L) or at least 50% improvement over baseline (if this value was abnormally low at baseline).
- Hemoglobin concentration ≥12 g/dL (110 g/L) or 50% improvement over baseline (if this value was abnormally low at baseline) without red blood cell transfusions or erythropoietin support.

Complete response: Resolution of organomegaly, normalization of the blood counts (Hb>12 g/dL; platelets >100,000/uL and absolute neutrophil count > 1500 /uL and no evidence of circulating clonal B cells). No evidence or minor BM infiltration detected by immunohistochemistry.

No response: Patients who do not meet the criteria for a complete remission, partial remission, or progressive disease, have stable disease. Stable disease is therapeutically equivalent to a nonresponse (i.e., refractory disease).

Progressive disease: At least one of these criteria must be documented:

- The appearance of a newly enlarged lymph node (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltration.
- An increase of 50% or more in size of a previously involved site (e.g., lymph nodes, spleen, or liver) measuring ≥1.5 cm.
- Development of neutropenia, anemia, or thrombocytopenia attributable to **SMZL.**

6.3.4 Response Criteria – MALT lymphoma of the ocular adnexa(122)

Partial Response: 50% or greater reduction in the maximum diameter of the lesion from its original tumor size on imaging (CT/MRI) or ophthalmologic evaluation.

Complete Response: Complete resolution of the lesion on imaging (CT/MRI) or ophthalmologic evaluation.

6.3.5 Response Criteria - Gastric MZL of MALT type

Response (score)	Description	Histological Characteristics
CR	Complete histological remission	Normal or empty LP and/or fibrosis with absent or scattered plasma cells and small lymphoid cells in the LP, no LEL
pMRD	Probable minimal residual disease	Empty LP and/or fibrosis with aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM, no LEL
rRD	Responding residual disease	Focal empty LP and/or fibrosis with dense, diffuse or nodular lymphoid infiltrate, extending around glands in the LP, focal LEL or absent
NC	No change	Dense, diffuse or nodular lymphoid infiltrate, LEL usually present

LEL, lymphoepithelial lesions; LP, lamina propria; MM, muscularis mucosa; SM, submucosa.

6.3.6 Definitions

6.3.6.1 Best Overall Response

The best overall response rate (ORR) is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

6.3.6.2 Duration of Response

The duration of response (DOR) is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started), death, or, in the absence of PD, date of last assessment.

6.3.6.3 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from the date of study enrollment until time of disease relapse, disease progression, or death, whichever occurs first.

6.3.6.4 Event-Free Survival

Event-free survival (EFS) is defined as the duration of time from the date of study enrollment until time of disease relapse, disease progression, alternative anti-lymphoma therapy including radiation, or death, whichever occurs first.

6.3.6.5 Overall Survival

Overall survival (OS) is defined as the time from study enrollment until death from any cause.

6.3.6.6 Complete Response Rate

The proportion of patients who achieve a PET-negative complete response (CR) in accordance with the 2014 Lugano classification of the International Working Group Criteria for Non-Hodgkin's Lymphoma(125) or International Workshop Group on CLL (iwCLL) criteria.

6.3.6.7 Complete Molecular Remission Rate

The proportion of patients who achieve both a complete response and are negative on molecular assays for MRD after therapy.

6.3.6.8 Objective Tumor Response Rate

The proportion of patients who achieve at least a partial response (PR) to therapy.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7 NIH REPORTING REQUIREMENTS / DATA SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING/IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis (approximately weekly) when patients are being actively treated on the trial to discuss each patient. The clinical research team will prepare a

monthly report on the occurrence of any grade 3 or 4 hemolytic anemia events. This report will be provided to Sponsor (OSRO) who will share the information with Gilead and Genentech. In the event of a grade 3 or 4 hemolytic anemia event(s), the clinical research team will confer with the Sponsor, Gilead, and Genentech to discuss the full safety profile including SAEs and DLTs. Minutes and formal decisions will be documented. Gilead and Genentech will be informed when decision is made to dose de-escalate due to observed DLTs. Decisions about trial continuation will be made based on the efficacy data from prior patients at appropriate time points per the statistical plan.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting described in Section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.4.2 Safety Monitoring Committee (SMC)

This protocol will be periodically reviewed by an intramural Safety Monitoring Committee. comprising physicians, biostatisticians and a lay member selected based on experience, area of expertise, reputation for objectivity, absence of conflicts of interest and knowledge of or experience with clinical trial research. Initial review will occur as soon as possible after the annual NIH Intramural IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC based on the risks presented in the study. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period. The SMC will operate under the rules of an approved charter that will be written and reviewed at the organization meeting of the SMC. Each review will focus on unexpected protocol-specific safety issues that are identified during the conduct of the clinical trial.

Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see Section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
  - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
  - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
  - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- 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.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Adverse Events of Special Interest (AESI)

There are no AESI with respect to the NCI CCR Sponsor representative for this protocol.

AESI for the pharmaceutical collaborator, Genentech, include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:

- Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN
- Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:
- Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

8.1.6.1 Venetoclax-specific AESI

- Tumor Lysis Syndrome (irrespective of seriousness)

8.1.6.1.1 Obinutuzumab-specific AESI

- All Tumor Lysis Syndrome (irrespective of seriousness, causality or severity)
- Second Malignancies

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in section **8.4**.

8.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in Section **8.4**.

All SAE reporting must include the elements described in **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found here: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions.

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 WAIVER OF EXPEDITED REPORTING TO CCR

As death/hospitalization due to disease progression are part of the study objectives (DOR, PFS) and captured as an endpoints in this study, they will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to Section **8.3**.

8.5 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

Reporting to Gilead Sciences, Inc., and Genentech, Inc., will be per the respective collaborative agreements.

8.6 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known.

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (Section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

8.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm from the first dose until 90 days after the last dose of magrolimab, 30 days after the last dose of venetoclax, 6 months after the last dose of obinutuzumab or whichever is later.

Pregnancy of the patient's partner is not considered to be an AE. The outcome of all pregnancies occurring from the date of the first dose until 90 days after the last dose of magrolimab, 30 days after the last dose of venetoclax, and 6 months after the last dose of obinutuzumab or whichever is later should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected

adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any noncompliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Sponsor and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESIS

10.1.1 Primary Endpoint

- To determine the safety and tolerability of the triplet combination of venetoclax, magrolimab and obinutuzumab in relapsed and refractory indolent B-cell malignancies

10.1.2 Secondary Endpoints

- Overall response rate (ORR = CR+PR) after triplet combination therapy with magrolimab, obinutuzumab, and venetoclax
- Complete molecular remission rate (CMR) by flow cytometry or similar assays as they become available in patients after triplet combination therapy with magrolimab, obinutuzumab, and venetoclax (in CLL patients only)
- Duration of response (DOR)
- Event-free survival (EFS)
- Progression-free survival (PFS)
- Overall survival (OS)

10.2 SAMPLE SIZE DETERMINATION AND STATISTICAL PLAN

The primary endpoint of this trial is to determine the safety and tolerability of the combination of magrolimab and obinutuzumab with venetoclax. We will be assessing this endpoint by using a venetoclax dose-finding scheme. During dose-finding, patients will receive magrolimab and obinutuzumab at fixed doses, and venetoclax will be administered at DL1. If required, dose de-escalation of venetoclax will be explored. Patients will be enrolled in two cohorts for this evaluation: follicular lymphoma (FL) in Cohort 1, marginal zone lymphoma (MZL), chronic lymphocytic leukemia (MCL), and mantle cell lymphoma (CLL) in the Cohort 2. Unless dose de-escalation is required, 6 total patients will be enrolled from Cohort 1 into Arm 1, and 6 total patients will be enrolled from Cohorts 2 into Arm 2. Both Cohorts 1 and 2 will include a single dose de-escalation DL(-1) if needed. A maximum of 6 treated patients will be needed to complete the dose de-escalation scheme (if required) for Cohort 1, Arm 1, and a maximum of 6 treated patients will

be needed to complete the dose de-escalation scheme (if required) for Cohort 2, Arm 2 (total 24 patients).

At the MTD of venetoclax, dose expansion cohorts will enroll patients to assess the secondary clinical response outcomes in a preliminary fashion. The dose expansion cohorts (Cohorts 3, 4, 5 and 6), based on the results of dose-escalation in Cohorts 1 and 2, will open to accrue up to 18 additional FL patients, 6 additional MZL patients, 12 additional MCL patients and 6 additional CLL patients. These numbers were chosen based on the expected number of patients which could be accrued in two years after completion of the dose-finding phase. A total of 42 treated patients will be required to complete the dose expansion phase of the study.

Based on these estimates, up to 24 patients may be required for venetoclax dose-finding. These, in addition to 42 total treated patients required to complete the dose expansion phase brings the total number of patients required to complete the study to 66. To allow for a small number of inevaluable patients and screen failures, the accrual ceiling will be set at 76 patients. It is expected that 3 to 4 years may be required to complete accrual, including dose-finding and expansion cohorts. Patients enrolled in dose-finding cohorts who are treated at the same dose-level as the expansion cohorts may be analyzed together with the dose-expansion cohorts at the end of the study (Cohort 1 with Cohort 3, and Cohort 2 with Cohorts 4, 5 and 6, respectively).

As mentioned earlier in Section **1.2.6.2.1.2**, recent reports indicate that MZL patients may be at a higher risk of infection-related AEs with fatal outcome when obinutuzumab was used in combination with chemotherapy. As an early stopping rule, if ≥2 subjects have infection-related SAEs or any subject experiences a fatal infection-related AEs from the first 6 subjects on study, we will hold further enrollment, and a comprehensive safety analysis will be performed.

In addition, an early stopping rule will be implemented for all histologies, if a substantial number of patients have to discontinue therapy due to unacceptable toxicity. If at any point after the first 20 patients are enrolled, 25% or more patients have been unable to complete therapy due to unacceptable toxicity or if at any point 2 or more deaths or grade 4 hemolytic anemia events occur that are probably or definitely related to study therapy, then study enrollment for all histologies will be suspended for a formal assessment of the overall safety profile of the study design. This early stopping rule is applicable throughout the duration of the study.

10.3 POPULATIONS FOR ANALYSES

10.3.1 Evaluable for Toxicity

All patients who have received at least one dose of any of the study drugs will be evaluable for toxicity.

10.3.2 Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one cycle of treatment (magrolimab+obinutuzumab) therapy, and have had their disease re-evaluated will be considered evaluable for response. (NOTE: Patients who exhibit objective disease progression after receiving at least one cycle of magrolimab+obinutuzumab will also be considered evaluable.)

10.3.3 Evaluable Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-

evaluated will be considered evaluable for non-target disease response assessment. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

Toxicity profile of the combination therapy will be reported, and important toxicities described. Response rates will be reported as percentage, and time-to-event outcomes will be reported using Kaplan-Meier curves.

10.4.2 Analysis of the Primary Endpoints

The type, number and frequency of DLTs to triplet combination therapy will be reported and described.

10.4.3 Analysis of the Secondary Endpoints

The type, number and frequency of DLTs to doublet combination therapy (during the 'window') will be reported and described. The ORR, and CR rate will be determined and reported from individual cohorts and histological diagnosis. CMR rate by flow cytometry or similar assays as they become available will be determined and reported separately for the CLL cohort. Responses will also be reported along with 95% confidence intervals, with waterfall plots, when appropriate. The duration of response (DOR; beginning at the date clinical response is first identified), progression free survival (PFS), event-free survival (EFS), and overall survival (OS) will be estimated using Kaplan-Meier curves, along with 95% confidence intervals at the median when appropriate.

10.4.4 Safety Analyses

The type, grade and frequency of toxicities will be reported. DLTs, MTD of venetoclax in combination with magrolimab and obinutuzumab; and SAEs will be reported as well.

10.4.5 Baseline Descriptive Statistics

Baseline characteristic of all cohorts will be explained including demographics, prior therapies and functional status.

10.4.6 Planned Interim Analyses

No interim analyses are planned

10.4.7 Sub-Group Analyses

None planned.

10.4.8 Tabulation of Individual Participant Data

None planned.

10.4.9 Exploratory Analyses

The following are the exploratory analyses planned:

- Overall response rate (ORR) after doublet-combination therapy with magrolimab and obinutuzumab

- Complete molecular remission rate (CMR) by ctDNA assay or similar assays as they become available after doublet-combination therapy with magrolimab and obinutuzumab
- Complete molecular remission rate (CMR) by ctDNA assay or similar assays as they become available after triplet-combination therapy with magrolimab, obinutuzumab and venetoclax
- Lead time for ctDNA assay in detecting molecular relapse prior to clinical progression
- Identify potential biomarkers and molecular correlates that are associated with response and/or resistance to the study treatment
- Test immunogenicity of magrolimab and asses the effect of anti-drug antibodies (ADA) on the pharmacokinetics, pharmacodynamic markers, efficacy, and safety of magrolimab.

The ORR and CMR rates will be determined and reported from individual cohorts and histological diagnosis. Responses will also be reported with waterfall plots, when appropriate. The exploratory objectives such as seeking to identify potential biomarkers and molecular correlates that are associated with response and/or resistance to the study treatment, will be assessed using descriptive statistics as well as non-parametric methods such as exact Wilcoxon rank sum tests. The analyses will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed.

Magrolimab PK data will be summarized using summary statistics (mean, median, range, standard deviation, etc.) at each time point. The overall rate of ADA occurrence and type of ADA (e.g., transient vs persistent) will be summarized for all patients. PK in ADA positive and negative patients will be tabulated at each timepoint. If relevant, the impact of ADA occurrence on efficacy and safety will be assessed through summary statistics.

11 COLLABORATIVE AGREEMENTS

11.1 CLINICAL TRIAL AGREEMENT (CTA)

11.1.1 Gilead Sciences, Inc.

There is a CTA with Gilead Sciences, Inc. (#01181-20).

11.1.2 Genentech

There is a CTA with Genentech, Inc. (#01182-20).

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR PATIENT SELECTION

This trial is designed as a novel-novel targeted therapy with magrolimab as backbone for patients with indolent lymphomas. Median age for all 4 histologies included in this study are over 60 years of age and male predominance is noted in MZL and CLL. Pregnant or nursing mothers are excluded because of the potential teratogenic effects of therapy. Given the small number of patients on our study, we expect a gender-even to a slightly male predominant patient population for our study.

12.2 PARTICIPATION OF CHILDREN

Since safety data is not available for magrolimab in children, patients <18 years of age will be excluded from the study. Also, most of the histologies of indolent lymphomas we are testing are rare in children.

12.3 RISK/BENEFIT ASSESSMENT

12.3.1 Known Potential Risks

The most common (>10%) adverse reactions with magrolimab are anemia (43%), nausea (41%), fatigue (30%), constipation (39%), diarrhea (39%), infusion-related reactions (33%), headache (32%), dyspnea (30%), pyrexia (39%), cough (27%), thrombocytopenia (25%), decreased appetite (25%), febrile neutropenia (25%), chills (23%), vomiting (23%), dizziness (20%), and hypokalemia (21%), and bilirubin increase (15%), and pneumonia (10%). Other common AEs with magrolimab include hemolysis (≥1% and <10%, SAR 1.2% serious), sepsis (≥1% and <10%, 0.4% serious), and hypotension (≥10%, 0.2% serious). Common AEs with venetoclax-obinutuzumab combination were neutropenia, thrombocytopenia, diarrhea, infections, fatigue and nausea. Severe neutropenia may occur with magrolimab use. Grade 3 (absolute neutrophil count [ANC] 500 to <1000 cells/uL) and Grade 4 (ANC <500 cells/uL) have been reported. Additionally, fatal events of febrile neutropenia have been reported in patients treated with magrolimab. Close hematological monitoring will be performed for all patients during treatment (at least once a month while on therapy). In cases of neutropenia, consider antimicrobial prophylaxis and administration of granulocyte colony-stimulating factor (G-CSF) if clinically appropriate. If febrile neutropenia occurs, administer antibiotics and antimycotics. Dose modifications/delays will be per Section **3.3.2.**

Serious infections (Grades 3 or 4) have been reported in patients treated with magrolimab, including fatal events of pneumonia and sepsis. Patients will be regularly monitored for signs and symptoms of infection during monthly clinic visits while on therapy. For patients with prolonged neutropenia or patients at risk, infection prophylaxis using appropriate antibiotics will be considered in accordance with current guidelines. Dose modifications/delays will be per Section **3.3.2.**

TLS has been observed with venetoclax, but rigorous precautions, slow ramp-up of dose and early detection and treatment has improved the safety profile. Individually, both magrolimab (in FL) and venetoclax (in CLL, FL, MZL and MCL) have shown promising activity.

As noted in Section **3.2**, premedication will be given to reduce the risk of AEs occurring. Subjects will be monitored closely, and manufacturer recommendations for delaying and discontinuing study medications and initiating supportive therapy will be followed.

12.3.1.1 Biopsy Risk

The risks associated with biopsies are pain and bleeding at the biopsy site. In order to minimize pain, conscious sedation or local anesthesia will be used. Rarely, there is a risk of infection at the sampling site. CT guidance may be used for biopsies.

12.3.1.2 Conscious Sedation

The common side effects of conscious sedation include drowsiness, delayed reflexes, hypotension, headache, and nausea. These are generally mild and last no more than a few hours.

12.3.1.3 Bone Marrow Biopsy

Bone marrow biopsy is minimally invasive and is typically a very safe procedure. Usually, the hipbone is numbed with anesthesia. Using a needle, the solid and liquid portion of bone marrow is taken out. This procedure causes some pain. Very rarely, infection or bleeding may occur at the needle site.

12.3.1.4 Radiation Risk

The study will involve radiation from the following sources:

- Up to 7 CT scan of chest abdomen pelvis (1 during screening)
- Up to 4 [^{18}F]-FDG-PET/CT
- Up to 2 CT-guided biopsies as referenced above

Subjects in this study may be exposed to approximately 14.1 rem. This amount is more than would be expected from everyday background radiation. Being exposed to excess radiation can increase the risk of cancer. The risk of getting cancer from the radiation exposure in this study is 1.4 out of 100 (1.4%) and of getting a fatal cancer is 0.7 out of 100 (0.7%).

12.3.1.5 Scans

The radiation risks of the FDG and CT scans are discussed above. In addition to radiation risks, CT scans that employ contrast may cause allergic reactions, injection site reactions abdominal discomfort and fainting. MRIs carry no radiation risks, but are contraindicated in participants with metal in their bodies. In patients that receive gadolinium contrast with MRIs, allergic reactions, injection site reactions and kidney damage may occur.

12.3.1.6 Risk related to blood sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

Up to 6.4 tablespoons of blood may be collected at any day and up to 26.9 tablespoons may be collected within 8 weeks.

12.3.1.7 Non-Physical Risks of Genetic Research

Risk of receiving unwanted information, anxiety and stress at the information, and breach of confidentiality.

12.3.2 Known Potential Benefits

Although the potential for SAEs exists but owing to differing mechanism of action and non-overlapping toxicities, the incidence of them is expected to be much lower than chemotherapy.

12.3.3 Assessment of Potential Risks and Benefits

We are aiming to develop a combination of novel agents that individually appear to be safe. Patients may obtain direct benefit from treatment with this combination with a high response rate and deep remissions.

12.4 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors,

and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location but is not required.

Both the investigator and the subject will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at:

https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements

- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB, and as applicable Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute/Center for Cancer Research has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) collaborators, as applicable. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records

(office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB and Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) will be secured and password protected. At the end of the study, all study databases will be archived at the NIH Clinical Center.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

The clinical investigations outlined will be conducted under an NCI CCR-held IND; IND #148205).

14.1 MAGROLIMAB

Magrolimab is a recombinant IgG4 humanized IgG4 monoclonal antibody of the IgG4 kappa isotype containing a Ser-Pro (S-P) substitution in the hinge region (position 228) of the heavy chain to reduce Fab arm exchange. It comprises a disulfide-linked glycosylated tetramer, consisting of two identical 444 amino acid heavy gamma chains and two identical 219 amino acid kappa light chains. Magrolimab targets the human CD47 antigen.

Molecular Formula: $C_{6462}H_{9960}N_{1718}O_{2027}S_{48}$

14.1.1 Source/ Acquisition and Accountability

Drug (investigational supplies) will be provided by Gilead Sciences, Inc. for use by subjects in this clinical trial.

14.1.2 Toxicity

See Section **1.2.4.4** and Section **12.3.1** for a summary of AEs and SAEs.

14.1.3 Formulation and preparation

Magrolimab drug product is formulated in 0.01% (w/v) Polysorbate 20, 5% (w/v) Sorbitol, and 10 mM Sodium acetate, pH 5.0, and Sterile Water for Injection. The drug product is a sterile, clear to slightly opalescent, colorless, preservative-free liquid supplied at a protein concentration of 20

mg/mL in 10 mL (200 mg) single-use vials. Magrolimab drug product is provided in a liquid dosage form intended for intravenous (IV) infusion.

The desired amount of magrolimab should be withdrawn from the vial(s) and diluted in a polyvinyl chloride (PVC) infusion bag containing 0.9% Sodium Chloride Injection United States Pharmacopeia (USP) to a final concentration of approximately 0.03 to 6.0 mg/mL. The clinical dose will be prepared (diluted in saline) as an IV infusion through a standard infusion set. The initial priming dose will be administered as a continuous IV infusion in 250 mL over 180 minutes to reduce the risk of acute hemagglutination. All other infusions for doses greater than 1 mg/kg will be administered in 500 mL over 120 minutes. The bag should be gently inverted to mix the solution. Before administration, the parenteral drug products should be inspected visually. If particulate matter or discoloration is noted, drug should not be administered, and the sponsor should be notified. The prepared drug solution can be stored at refrigerated temperature between 2°C to 8°C (36°F to 46°F) for up to 16 hours and / or stored at room temperature for up to 8 hours from the preparation start time.

Precautions

- Recommended safety measures for preparation and handling of magrolimab include laboratory coats and gloves.
- Magrolimab cannot be mixed with any other drug in the infusion bag or the administration set.
- Magrolimab should NOT be administered as a bolus injection.

14.1.4 Stability and storage

Magrolimab drug product is shipped refrigerated and must be stored at 2-8°C (36-46°F) until use, with access limited to pharmacy personnel, the Principal Investigator, or a duly designated person. A temperature log must be kept to document the refrigerator temperature. If the temperature is not maintained, the sponsor should be contacted.

Magrolimab should be protected from light. Sufficient protection from light is provided by the secondary container. No specific light protection is needed during preparation of the dosing solution and infusion. DO NOT SHAKE. Magrolimab is not formulated with a preservative. Therefore, once the sterile vials are entered, all dose preparations should be performed aseptically.

14.1.5 Administration procedures

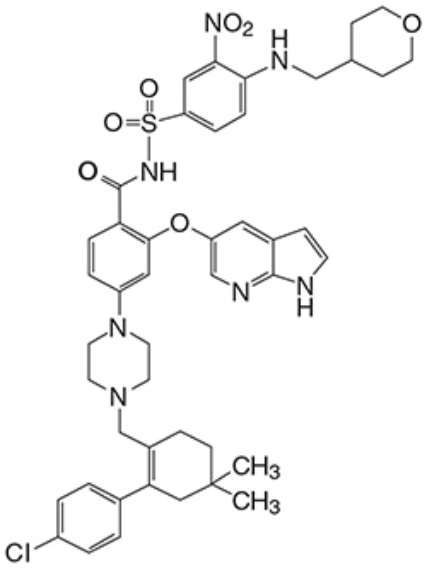
Refer to Section **3.2.1** for administration details.

14.1.6 Incompatibilities

Magrolimab cannot be mixed with any other drug in the infusion bag or the administration set.

14.2 VENETOCLAX (VENCLEXTA®)

Venetoclax is a selective inhibitor of BCL-2 protein. It is a light yellow to dark yellow solid with the empirical formula $C_{45}H_{50}ClN_7O_7S$ and a molecular weight of 868.44. Venetoclax has very low aqueous solubility. Venetoclax has the following chemical structure:



Venetoclax is a small molecule administered orally and is primarily metabolized by cytochrome P450 3A4 (CYP3A4/5). Details of interactions and dose adjustments are mentioned in Section **3.3**. Please refer to the package insert for full drug interactions and toxicities.

14.2.1 Source/Acquisition and Accountability

Venetoclax is a commercially available agent manufactured by Abbvie, but will be provided by Genentech to the NCI (investigational supplies) for dispensing to the study participants as per an arranged research agreement.

14.2.2 Toxicity

See Section **1.2.5.1** for a summary of AEs and SAEs.

14.2.3 Formulation and preparation

Venetoclax comes in 10 mg, 50 mg and 100 mg tablets. Excipients include: copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, calcium phosphate dibasic. In addition, the 10 mg and 100 mg tablet coating contains iron oxide yellow, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc; the 50 mg tablet coating contains iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

- Venetoclax 10 mg film-coated tablets are round, biconvex shaped, pale yellow debossed with “V” on one side and “10” on the other side.
- Venetoclax 50 mg film-coated tablets are oblong, biconvex shaped, beige debossed with “V” on one side and “50” on the other side.
- Venetoclax 100 mg film-coated tablets are oblong, biconvex shaped, pale yellow debossed with “V” on one side and “100” on the other side.

14.2.4 Stability and storage

Venetoclax tablets will be packaged in high-density polyethylene plastic bottles to accommodate the study design. Each bottle will be labeled per local regulatory requirements. A desiccant canister may be included in the bottle. If supplied with a desiccant, the desiccant canister should be returned to the bottle directly after each tablet removal. Store at or below 86°F (30°C).

14.2.5 Administration procedures

See Section **3.2.3** for details regarding venetoclax administration.

14.2.6 Incompatibilities

See **Appendix C** for details regarding medications that have possible interactions with venetoclax.

14.3 OBINUTUZUMAB

14.3.1 Source/Acquisition and Accountability

Obinutuzumab is commercially available agent,but will be provided by Genentech to the NCI (investigational supplies) for dispensing to the study participants as per a research agreement.

14.3.2 Toxicity

See Section **1.2.6.2** for a summary of AEs and SAEs. Additionally, coagulation abnormalities including disseminated intravascular coagulation (DIC) have been reported in patients receiving obinutuzumab for treatment of FL and CLL. In the majority of cases, the events have involved subclinical (asymptomatic) changes in platelets and laboratory coagulation parameters following the first infusion, with spontaneous resolution usually occurring by Day 8. In some cases, the events were associated with IRRs and/or TLS. No specific baseline risk factors for DIC have been identified.

14.3.3 Formulation and Preparation

Obinutuzumab is provided as a single 1000-mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50-mL glass vials containing 40 mL of the 25-mg/mL liquid concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188, and highly purified water (HPW). HPW meets the specified limits of HPW according to Pharm. Eur. and for water for injections (WFI) according to USP.

14.3.4 Stability and Storage

The recommended storage conditions for obinutuzumab drug product are between 2°C and 8°C, protected from light. For further instructions, as well as information on in-use stability, see the packaging label.

14.3.5 Administration procedures

See Section **3.2.2**for details about obinutuzumab administration.

14.3.6 Incompatibilities

No formal drug interaction studies have been performed with obinutuzumab. Please refer to the package insert and PDR for full drug interactions and toxicities.

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16 APPENDICES

APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: GUIDELINES FOR PREGNANCY AND NURSING

Contraception

Magrolimab, venetoclax and/or obinutuzumab may have adverse effects on a fetus in utero. Furthermore, it is not known if magrolimab, venetoclax and/or obinutuzumab have transient adverse effects on the composition of sperm.

Magrolimab is contraindicated in pregnancy. In an enhanced embryo-fetal prenatal and postnatal development study in a pregnant cynomolgus monkey, there was an increased incidence of stillbirths at the high dose, and morbidity and mortality in the offspring at the high dose (secondary to severe anemia). In the clinical development program, pregnant or active breastfeeding women were excluded from participation the clinical studies.

For this trial, male patients will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female patients will be considered of non-reproductive potential if they are either:

1. postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.); **OR**
2. have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening; **OR**
3. have a congenital or acquired condition that prevents childbearing.

Female and male patients of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 90 days after the last dose of magrolimab, 18 months after the last dose of obinutuzumab, and 30 days after the last dose of venetoclax, whichever is later, by complying with one of the following:

1. practice abstinence[†] from heterosexual activity; **OR**
2. use (or have their partner use) contraception methods that result in a failure rate of <1% per year during heterosexual activity.

With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year.

With a pregnant female partner, men must use a condom.

Acceptable methods of contraception are[‡]:

Single method

Use of one of the following is acceptable:

- intrauterine device (IUD)
- vasectomy of a female subject's male partner

- contraceptive rod implanted into the skin

Combination method

Requires use of two of the following:

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study patients of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation, throughout the study period, and up to the time frames after the last dose of trial therapy as noted above. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Use in Pregnancy

If a subject inadvertently becomes pregnant while on study treatment, the subject will immediately be removed from the study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Gilead Sciences, Inc. and Genentech without delay, especially if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Gilead Sciences, Inc. and Genentech and followed as described above.

Use in Nursing Women

It is unknown whether magrolimab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

APPENDIX C: INHIBITORS AND INDUCERS OF CYP3A AND P-GP

A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website and venetoclax FDA label is displayed below.

Inhibitors of CYP3A		**Inducers of CYP3A**	**Inhibitors of P-gp**
Strong inhibitors: INDINAVIR NELFINAVIR RITONAVIR CLARITHROMYCIN ITRACONAZOLE KETOCONAZOLE NEFAZODONE SAQUINAVIR TELITHROMYCIN CONIVAPTAN POSACONAZOLE VORICONAZOLE **Moderate inhibitors:** aprepitant erythromycin diltiazem fluconazole grapefruit juice seville orange juice verapamil	**Weak inhibitors:** cimetidine **All other inhibitors:** amiodarone azithromycin chloramphenicol boceprevir ciprofloxacin delaviridine diethyl-dithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone norfloxacin norfluoxetine star fruit telaprevir troleandomycin voriconazole	carbamazepine efavirenz nevirapine barbiturates glucocorticoids modafinil oxcarbarzepine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's Wort troglitazone	amiodarone azithromycin dronedarone captopril carvedilol cyclosporine felodipine quercitin quinidine ranolazine ticagrelor

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx and https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf

APPENDIX D: STUDY DRUG DIARY (OPTIONAL)

Patient Name: _____ Cycle: _____

Instructions:

- Use this diary to record all doses of oral study medication taken.
- You should bring this study drug diary and each of your study medications (including leftover pills and empty bottles) with you to each clinic visit.
- Contact us if you have any side effects or before starting any new medications or over-the-counter drugs.
- If you have questions at any time, please contact your doctor or nurse.

Study Drugs:

The study medications should be taken as follows; the doses will be assigned to you by your doctor:

Venetoclax	Venetoclax tablets to be taken by mouth, with a glass of water and food
Magrolimab	Magrolimab is given by IV, in the clinic
Obinutuzumab	Obinutuzumab is given by IV, in the clinic

Additional Information:

- The venetoclax should be taken at about the same time each day
- If you do not remember to take all or any of the medications on any day, please tell us. Do not make-up the dose or take extra the following day to make-up for the missed dose.
- If you vomit after taking a dose, you should not take another dose that day. However, if vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another dose may be given.

EXAMPLES – Study Drug Diary (Cycle 2-12):

These are examples of how you might take the study drugs:

- Day 1: Come to clinic. Take the venetoclax when advised by the study staff.
- Days 2 through 14: Take the venetoclax.
- Day 15: Come to clinic. Take the venetoclax when advised by the study staff.
- Days 16-28: Take the venetoclax.

STAFF USE ONLY

Date returned/reviewed: _____ Staff member: _____

Notes/Comments:

Please record the dose/number of pills of each study drug taken in the table below:

Cycle Day	Date	Study Drugs			Comments
		Venetoclax	Obinutuzumab	Magrolimab	
1			In Clinic, IV	In Clinic, IV	
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15				In Clinic, IV	
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

APPENDIX E: CAIRO-BISHOP DEFINITION FOR TLS

The Cairo-Bishop definition proposed in 2004 (**Table 21**), provided specific laboratory criteria for the diagnosis of TLS both at presentation and within seven days of treatment. It also incorporated a grading system to help delineate the degree of severity of TLS (**Table 22**).

Table 21: Cairo-Bishop laboratory TLS definition

Parameter	Value	Change from baseline
Uric acid	≥476 micromol/L (8 mg/dL)	25% increase
Potassium	≥6.0 mmol/L (or 6 mEq/L)	25% increase
Phosphorus	≥1.45 mmol/L (4.5 mg/dL) for adults	25% increase
Calcium	≤1.75 mmol/L (7 mg/dL)	25% increase

Laboratory TLS is defined as any two or more abnormal serum values, as mentioned in the above table (**Table 21**), present within three days before or seven days after instituting therapy in the setting of adequate hydration (with or without alkalization) and use of a hypouricemic agent.

Clinical TLS is defined as laboratory TLS plus one or more of the following that was not directly or probably attributable to a therapeutic agent: increased serum creatinine concentration (≥1.5 times the upper limit of normal [ULN]), cardiac arrhythmia/sudden death, or a seizure.

Table 22: Cairo-Bishop clinical TLS definition and grading

Complication	Grade					
	0	1	2	3	4	5
Creatinine	≤ 1.5 x ULN	1.5 x ULN	>1.5-3.0 x ULN	> 3.0-6.0 x ULN	> 6.0 x ULN	Death
Cardiac arrhythmia	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with HF, hypotension, syncope, shock)	Death
Seizure	None	-	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death

APPENDIX F: MAGROLIMAB PK AND ADA SAMPLE COLLECTION, PROCESSING, AND SHIPPING INSTRUCTION

Sample Collection, Processing, and Shipping Instructions (PK/ADA)

A Phase 1 Study of Venetoclax with Obinutuzumab and Magrolimab (VENOM) in Relapsed and Refractory Indolent B-cell Malignancies

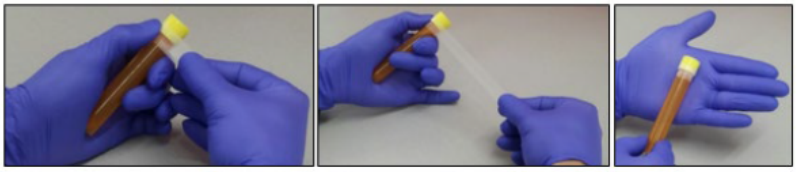
Red Top Serum Separator Tube SST (PK, ADA)

1. Fill a Red top SST COMPLETELY, as far as the vacuum will allow.
2. Mix immediately by gently inverting the tube 5 times.
3. Allow blood to clot undisturbed for 30 minutes (max. 60 minutes), tube standing upright.
4. Centrifuge tube within 1 hour of collection for 10-15 minutes at 1800 g until clot and serum are separated by a well –formed polymer barrier. *If serum and cells have not completely separated, re-centrifuge the specimen for an additional 6-8 minutes.*
5. Transfer serum, using a transfer pipette, into the Transport Tube (s).
6. Allow enough space between serum and tube caps to account for expansion during freezing. Do not overfill.
7. Record the subject ID number on the specimen label.
8. Wrap a small piece of parafilm around the cap of the transport tube. See parafilm instructions below.
9. Store serum samples for a minimum of 8 hours at **-80°C** until shipment to **PPD Richmond**.

Visit	Collection Tube	Tube Label	Shipping Temp
C1D1, C3D1, C5D1, C9D1, C13D1	1 x 3.5mL Red SST	Collection Tube: **PK SST** Transport Tube: **PK 1** **PK 2**	Frozen
C1D1, C3D1, C5D1, C9D1, C13D1	1 x 3.5mL Red SST	Collection Tube: **ADA SST** Transport Tube: **ADA 1** **ADA 2**	Frozen

Parafilm Instructions For Transport Tubes

1. Obtain a small piece of provided parafilm.
2. Hold tight against the cap of the transport tube and the side of the tube. Be sure to use half the parafilm to cover the cap and half of the parafilm to cover the top part of the tube.
3. While holding the end of the parafilm in place, gently pull and stretch the parafilm. Be careful not to pull too tight or it will break.
4. Wrap the stretched parafilm around the outside of the cap and top of the tube.



SHIPMENT PREPARATIONS

SPECIMEN	SHIPPING FREQUENCY	COURIER/ DESTINATION	SHIPPING TEMPERATURE
PK	Primary – Weekly Backup – With next shipment of primary samples	PPD Richmond	Frozen
ADA	Primary – Weekly Backup – With next shipment of primary samples	PPD Richmond	Frozen

SPECIMEN SHIPPING INSTRUCTIONS

Electronic Packing List (EPL) Instructions (PK, ADA):

For each specimen collected, please record the subject ID, visit, and collection date. Please send a copy of the EPL in the below tabular format to RichmondPPDShipments@ppdi.com, RichmondSMOpeners@ppdi.com, and LiMajor.Pittman@ppdi.com.

Sponsor	Protocol	Subject ID	Visit	Collection Date	Collection Time	Sample type (e.g. PK, ADA)
Forty Seven, Inc.	*VENOM*	*XXXX*	*C1D1*	*01/01/1990*	*HH:MM AM*	*PK*

Shipping address:

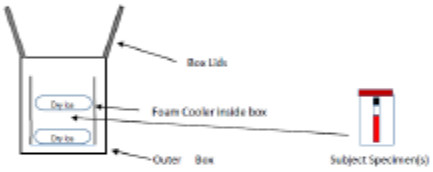
PPD Laboratories
Attn: Specimen Mgmt Dept, LiMajor Pittman
2246 Dabney Road
Richmond, VA 23230

LiMajor Pittman
Phone: 1-804-977-8459
Email: LiMajor.Pittman@ppdi.com

Packaging Specimens into the Frozen Shipper (PK, ADA)

When packing a frozen shipper please follow the below instructions. Ensure that there is sufficient layering of dry ice both under and on top of the frozen specimens, such that the specimens are 'sandwhiched' between dry ice.

+ Dry Ice



1. Place specimens in absorbent wrap(s). Ensure that the screw cap lids on the polypropylene tubes are firmly in place and threaded properly. Dry ice may cause the lids to loosen while in transit.
2. Place the absorbent wrap(s) into a specimen transport bag, and seal bag closed.
3. Using insulated gloves, place a layer of dry ice in the bottom of the foam cooler, completely covering the bottom of the cooler.
4. Fold and place the transport bag containing frozen samples on top of the layer of dry ice.
5. Fill the remaining portion of the cooler with dry ice, completely covering the transport bag and bottom layer of dry ice.

Note: The amount of dry ice is critical to maintain constant temperature within the shipper during transport.

6. Replace the foam lid on the insulated container.
7. Secure the flaps of the shipper and tape the box closed.
8. Please include a copy of the electronic packing list within the shipment.
9. Ship at your courier's earliest convenience.

APPENDIX G: STUDY CALENDAR

Procedure	**Screening**	**Baseline**	**Window Portion†**		**Triplet Combination Therapy$^{\Delta}$**	**Response-Based Therapy**	**Disease Evaluations**		**End of Treatment or PD**	**Active Monitoring/ Surveillance Follow-Up**		
			C -2 D1	C -1 D1	C1-C6 D1	C7-C12 D1	Window C-1/ Pre-C1, Cycles 6 & 12	Cycles 3 & 9		Safety (Day 30)	Follow-Up (Prior to PD)	Survival (Post-PD)
Scheduling Window (Days):	-28 to -1[1]		-28[2] -14* or -7^	-3	-3	-3	Last 7 days of the cycle		Treatment discon./PD[3]	+7	Every 3 or 6 months[4]	Every 3 months[5]
Confirmation of Diagnosis	X											
Physical Exam[6]	X	X	X	X	X	X			X	X	X	
ECOG PS	X	X	X	X	X	X			X	X	X	
CBC with Differential[7]	X	X	X*	X	X	X			X	X	X	
Chemistry Panels[8]	X	X	X*	X	X	X			X	X	X	
LDH	X	X	X*	X	X	X			X	X	X	
Total protein		X	X*	X	X	X			X	X	X	
PT/INR and aPTT	X	X	X	X	X	X			X	X	X	
Urinalysis	X	X	X*	X	X	X			X	X	X	
Pregnancy Test (urine/serum; WOCBP)	X	X	X^	X	X	X			X	X		
Hepatitis and HIV Testing	X											
Haptoglobin		X										
Quantitative serum immunoglobulin (IG) levels		X	X	X	X	X			X	X	X	
Beta-2 microglobulin		X	X	X	X	X			X	X	X	
Direct Anti-Globulin (DAT)	X	X	X	X	X	X			X	X	X	
RBC Phenotyping, Type and Screen		X										
Lymphocyte Phenotype (T, B, NK cell subsets)		X	X	X	X	X			X	X	X	
Peripheral Blood Flow Cytometry[9]	X		X (C-2 D8, 15)				X		X			

Procedure	Screening	Baseline	Window Portion†		Triplet Combination Therapy$^{\Delta}$	Response-Based Therapy	Disease Evaluations		End of Treatment or PD	Active Monitoring/ Surveillance Follow-Up		
			C -2 D1	C -1 D1	C1-C6 D1	C7-C12 D1	Window C-1/ Pre-C1, Cycles 6 & 12	Cycles 3 & 9		Safety (Day 30)	Follow-Up (Prior to PD)	Survival (Post-PD)
Scheduling Window (Days):	-28 to -1[1]		-28[2] -14* or -7^	-3	-3	-3	Last 7 days of the cycle		Treatment discon./PD[3]	+7	Every 3 or 6 months[4]	Every 3 months[5]
Bone Marrow Aspiration (with flow cytometry)/ Biopsy[10]	X					X			X			
CT Scans or MRI[11]	X	X					X	X	X		X	
^{18}F-FDG-PET/CT Scan[12]		X		X			X		X			
Symptoms/Adverse Events, Concomitant Medication Reviews	X	X	X	X	X	X			X	X		
Research Tissues (archival/fresh biopsy, bone marrow biopsy/aspiration)[13]		See Research Sample Calendar in Section **5.1**										
Research Saliva/Buccal (baseline), Blood Samples[14]		See Research Sample Calendar in Section **5.1**										
Survival Status												X

†**Window Portion:** Applies only to patients enrolled in the dose expansion cohorts.

$^{\Delta}$Additional monitoring for TLS during C1 of triplet combination therapy is described in **Section 4.1.2.**

NOTE: Perform any other assessments and/or tests as clinically indicated at the discretion of the investigator.

---

[1] Screening and Baseline evaluations should be performed within 28 days prior to enrollment and dosing, respectively, with the following exceptions: Confirmation of diagnosis (no time limit); HIV antibody, Hepatitis B surface antigen and Hepatitis C antibody (within 3 months); Bone marrow assessments (within 12 months). See Section **2.2**. **NOTE:** Any screening tests performed within the time frame for baseline do not need to be repeated.

[2] Within 28 days prior to dosing in Window on Cycle -1 Day 1, unless otherwise noted to be within 14 days (*) or 7 days (^).

[3] To be done at treatment discontinuation (+/- 2 weeks) or may coincide with the safety follow-up visit. If treatment is discontinued for a reason other than disease progression, assessments should be repeated at the time of progression. If subject to initiate new anti-cancer therapy assessments should occur before the first dose of the new therapy.

[4] Follow-up prior to disease progression to occur about every 3 months (+/- 2 weeks) for first 2 years after therapy, every 6 months for years 3-5 (+/- 4 weeks), and then annually (+/- 6 weeks) at the discretion of investigator.

[5] After disease progression or initiation of new anti-cancer therapy, contact for survival about every 3-6 months (+/- 4 weeks).

[6] Physical exams to include history, vitals, weight, and height (screening only).

[7] Complete Blood Count with Differential will be performed prior to each dose and 3-6 hours after the first and second doses of magrolimab - Cycle 1, Days 2 and 8 for dose-finding arms (Arms 1 and 2), and Cycle -2, Days 2 and 8 for dose-escalation arms (Arms 3 and 4).

[8] Chemistry panels include: Acute care, Hepatic, and Mineral and 24-hour urine creatinine clearance (if needed to measure CrCl).

[9] Peripheral blood flow cytometry for diagnostic and staging purposes; repeat in follow-up to assess disease status and response. See also Section **5** for flow cytometry to be collected also for research purposes.

[10] Bone marrow aspiration (± flow cytometry)/biopsy within 12 months prior to starting treatment, unless repeat at screening/baseline felt to be clinically indicated (see Section **2.2**); repeat in follow-up to confirm response or progression only if bone marrow involvement is present at baseline.

[11] CT scans (preferred) of chest, abdomen and pelvis to be performed at each disease evaluation; may be adjusted to assess additional known sites of disease, as needed. Scans are to be done after completion of window with magrolimab and obinutuzumab (i.e., after 2 cycles of treatment; up to 7 days prior to Cycle 1, Day 1 pre-dose); after Cycle 3, Cycle 6, and Cycle 9 (if applicable), up to 7 days prior to next cycle; after Cycle 12 (if applicable), 21-28 days after completion of the treatment

[12] PET scans to be performed at baseline, after completion of the window with magrolimab and obinutuzumab, after Cycles 6 and 12 (if applicable), and at the end of treatment; repeat additionally if clinically indicated

[13] If adequate archival tissue at baseline, fresh tumor biopsy is optional. Optional "on-treatment" and bone marrow sampling will be performed, as indicated in Section **5.**

[14] Samples for correlative research blood and saliva (preferred)/buccal swab samples to be collected as indicated in Section **5**.