Academic and Community Cancer Research United (ACCRU)

A Phase 2 Trial of the Combination of Polatuzumab Vedotin, Venetoclax and Rituximab and Hyaluronidase Human for Relapsed and Refractory Mantle Cell Lymphoma

For any communications regarding this protocol, please contact the person indicated on the Protocol Resource page. This is a stand-alone document found on the ACCRU web site [redacted].

Study Chair:

ACCRU: [redacted]

FDA IND:
Sponsor/Investigator: [redacted]

Statistician: [redacted]

Drug Availability

Drug Company Supplied: rituximab**,** venetoclax, polatuzumab vedotin, rituximab and hyaluronidase human

√ Study contributor(s) not responsible for patient care.

[redacted]

Document History	**(effective date)**
Initial Version	09/28/2020
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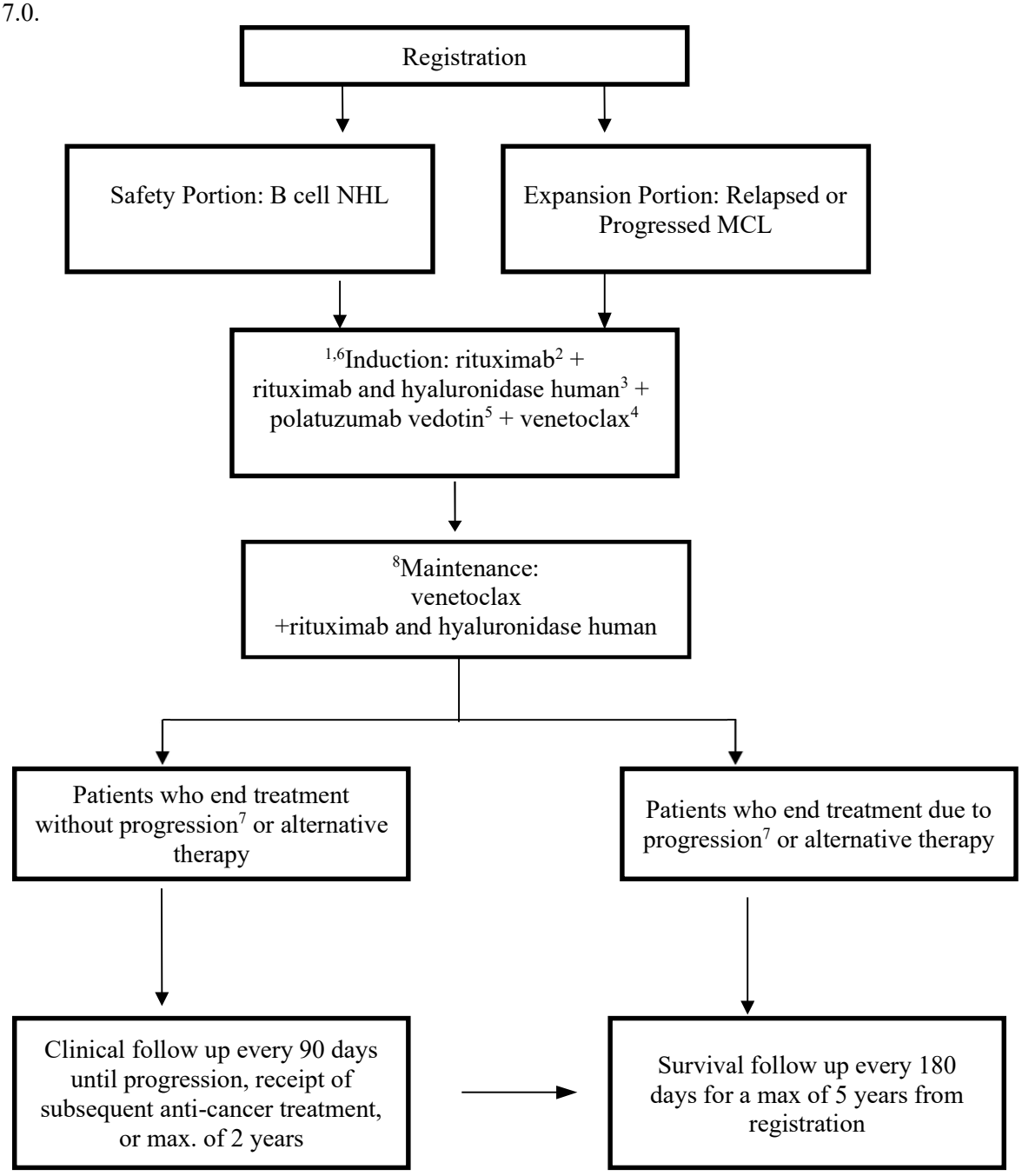
Schema

For the safety portion only: Prior to discussing protocol entry with the patient, call the ACCRU Registration Office ([redacted] or email [redacted] for dose level and to ensure that a place on the protocol is open to the patient.

First 6-12 patients with Relapsed/Refractory B cell NHL treated in safety portion as described in section 7.0.



If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.
[1] Induction cycle length = 21 days
[2] rituximab given day 1 of cycle 1 only
[3] rituximab and hyaluronidase human on day 1 of cycle 2+
[4] venetoclax daily
[5] polatuzumab vedotin on day 1
[6] Total of 6 cycles for induction (See Section 7.2)
[7] Progressive disease is based on either PET-CT based or CT based response criteria
[8] Maintenance for 1 year (see section 7.3); Cycle length = 30 days

Generic name: venetoclax Brand name(s): Venclexta Availability: McKesson	Generic name: polatuzumab vedotin Brand name(s): Polivy Availability: McKesson
Generic name: rituximab and hyaluronidase human Brand name(s): Rituxan Hycela Availability: McKesson	Generic name: rituximab Brand name(s): Rituxan Availability: McKesson

1.0 **Background**

1.1 Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin lymphoma that is considered incurable with conventional therapy. While fit younger MCL patients who receive aggressive induction therapy followed by autologous stem cell transplant (ASCT) may have a prolonged overall survival (OS) with responses up to and beyond 5-8 years, there are no curative regimens for older patients who cannot undergo treatments of this intensity. For relapsed patients, ibrutinib, lenalidomide, and bortezomib are all FDA-approved options however these do not represent curative approaches. While ibrutinib has a high overall response rate (ORR) of 67% in heavily pre-treated patients, the 2-year progression-free survival (PFS) is only 31%, and patients who progress on ibrutinib have a dismal prognosis, with an overall survival of 3 months. Acalabrutinib has recently received accelerated approval for relapsed MCL based on Phase 1 data which demonstrated an ORR of 80% and a 12-month PFS of 67% in ibrutinib naïve patients, the longer-term durability and the outcome for patients who progress on this agent are still unknown. Moreover, this drug is not approved for ibrutinib treated patients, and strategies in MCL that do not rely on BTK targeting remain an unmet medical need. Novel approaches to improve outcomes for patients with relapsed/refractory MCL are an urgent unmet medical need.

Therapies derived from a biologic understanding of MCL pathogenesis should lead the development of the next generation of therapeutic platforms for MCL. The hallmarks of MCL are the chromosomal translocation t(11;14) (q13;q32), resulting in overexpression of the cell cycle protein cyclin D1 and cell cycle dysregulation, and constitutive B cell receptor (BCR) complex signaling. Crosslinking of BCR by antigen triggers the phosphorylation of CD79 and initiates activation of multiple tyrosine kinases including Bruton's tyrosine kinase (BTK) which plays a critical role in amplifying the B cell activation signal and activating downstream pathways. Aberrant TLR and chemokine signaling further enhances BCR signaling. Recent studies have shown that high levels of constitutive BCR signaling in MCL correlated with high surface expression of CD79,and was associated with resistance to BTK inhibition and decreased survival. High expression of CD79 also leads through ERK kinase and other downstream mediators to up-regulation of the anti-apoptotic protein BCL-2 and its family members, a primary driver of MCL pathogenesis.

1.2 Polatuzumab vedotin

1.21 Background on Polatuzumab Vedotin

CD79b is a cell-surface antigen whose expression is restricted to all mature B cells except plasma cells. It is expressed in a majority of B cell−derived malignancies, including nearly all NHL and CLL samples tested (Dornan et al. 2009). Antibodies bound to CD79b are rapidly internalized, which makes CD79b ideally suited for targeted delivery of cytotoxic agents (Polson et al. 2007; Polson et al. 2009). Polatuzumab vedotin (DCDS4501A) is an antibody−drug conjugate (ADC) that contains a humanized IgG1 anti−human CD79b monoclonal antibody (MCDS4409A) and a potent anti-mitotic agent, mono-methyl auristatin E (MMAE), linked through a protease-labile linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl. MMAE has a mode of action that is

similar to that of vincristine, which is a component of standard chemotherapy (e.g., R-CHOP used for treatment of lymphoma). Following binding at the cell-surface epitope and internalization of the ADC by the targeted cell, MMAE is released following cleavage of the linker by lysosomal enzymes. MMAE then binds to tubulin and disrupts the microtubule network, resulting in inhibition of cell division and cell growth (Doronina et al. 2003). This therapeutic approach takes advantage of the specific targeting capability of the antibody, the cytotoxic activity of MMAE, and the increased potency of MMAE compared with vincristine. It is hypothesized that polatuzumab vedotin in combination with other novel agents will provide enhanced efficacy and safety to patients with NHL.

1.22 Preclinical Studies with Polatuzumab Vedotin

Comprehensive pharmacologic, pharmacokinetic (PK), pharmacodynamic, and toxicology studies were conducted to support the entry of polatuzumab vedotin into clinical trials. Because polatuzumab vedotin specifically recognizes CD79b on B cells of humans but not on those of the cynomolgus monkey, rat, or mouse–a surrogate ADC (DCDS5017A) that binds to cynomolgus monkey CD79b was generated to assess the antigen-dependent activities in cynomolgus monkeys. The structure, binding epitope, and binding affinity of the surrogate ADC are similar to that of polatuzumab vedotin. Polatuzumab vedotin has demonstrated efficacy in nonclinical mouse xenograft models of human CD79b-positive NHL. Additionally, polatuzumab vedotin when combined with rituximab plus chemotherapy (R-CHP or bendamustine) demonstrated better anti-tumor activity compared with polatuzumab vedotin as single agent or compared with a current standard-of-care regimen (R-CHOP or rituximab plus bendamustine [BR]) in xenograft models of NHL. The pharmacokinetics and safety of polatuzumab vedotin and the surrogate ADC were characterized in repeat-dose toxicity studies in rats and cynomolgus monkeys. Polatuzumab vedotin and the surrogate ADC were well tolerated in both species at the tested doses. The predominant antigen-independent findings associated with polatuzumab vedotin or surrogate ADC exposure were reversible bone marrow toxicity and associated peripheral blood cell effects in both monkeys and rats. The PK profiles of polatuzumab vedotin and the surrogate ADC suggested that the pharmacokinetics of the ADC were driven mainly by the antibody component (similar serum concentration−time profile between ADC and total monoclonal antibody). Refer to the polatuzumab vedotin Investigator's Brochure for complete details of the biochemical composition and nonclinical studies.

1.23 Clinical Studies with Polatuzumab Vedotin

Clinical data on polatuzumab vedotin in patients with NHL or CLL are available from one completed Phase I/Ib study (DCS4968g) and the ongoing Phase Ib/II studies (GO27834, GO29044, GO29834, BO29561, and GO29365) in patients with B-cell lymphoma. DCS4968g evaluated polatuzumab vedotin as a single agent and in combination with rituximab in patients with R/R B-cell lymphoma. GO27834 is evaluating polatuzumab vedotin in combination with either obinutuzumab or rituximab in patients with R/R FL or DLBCL. GO29044 is

evaluating polatuzumab vedotin in combination with R-CHP or G-CHP in patients with newly diagnosed or R/R B-cell lymphoma. GO29365 is evaluating polatuzumab vedotin in combination with bendamustine plus rituximab or obinutuzumab in patients with R/R FL or DLBCL. GO29834 is evaluating polatuzumab vedotin in combination with lenalidomide and either obinutuzumab or rituximab in patients with R/R FL or DLBCL. BO29561 is evaluating polatuzumab vedotin in combination with atezolizumab and either obinutuzumab or rituximab in patients with R/R FL or DLBCL. Available safety results and efficacy results from these studies are summarized in Section 1.231 and Section 1.232 respectively. For more detailed clinical information on polatuzumab vedotin, including clinical pharmacology data, refer to the polatuzumab vedotin Investigator's Brochure.

1.231 Clinical Safety of Polatuzumab Vedotin

Clinical safety data are available from 327 patients with NHL or CLL who received polatuzumab vedotin as a single agent (DCS4968g), in combination with rituximab (DCS4968g and GO27834), in combination with obinutuzumab (GO27834), in combination with obinutuzumab or rituximab plus CHP (GO29044), and in combination with obinutuzumab or rituximab plus bendamustine (GO29365). In Study DCS4968g, Grade ≥ 3 adverse events were reported in 74% of patients with R/R B-cell lymphoma who received single−agent polatuzumab vedotin; the most common (reported in ≥ 5% of patients) Grade ≥ 3 adverse events were neutropenia (38% of patients), anemia and peripheral sensory neuropathy (9% each), and leukopenia (6%). In the dose-escalation phase of Study DCS4968g, dose-limiting toxicities (DLTs) of Grade 4 neutropenia occurred in 1 of 10 DLT-evaluable patients treated with 2.4 mg/kg polatuzumab vedotin and 1 of 9 DLT-evaluable patients treated with 2.4 mg/kg polatuzumab vedotin in combination with rituximab. polatuzumab vedotin at a dose of 2.4 mg/kg given every 3 weeks was chosen as the recommended Phase II dose (RP2D) when administered as a single agent and in combination with rituximab. The overall safety profile of polatuzumab vedotin (1.8 mg/kg and 2.4 mg/kg doses) in combination with rituximab was comparable to that of single agent polatuzumab vedotin. In Study GO27834, the most frequent (≥ 5%) Grade ≥ 3 adverse events were neutropenia (19 of 79 patients [24%]), diarrhea (5 of 79 patients [6%]), and febrile neutropenia (4 of 79 patients [5%]). No fatal adverse events were reported for the combination.

Serious adverse events were reported for 37% of all patients treated with polatuzumab vedotin alone or in combination with rituximab in Studies DCS4968g and GO27834 combined. The most frequently reported (≥ 2%) serious adverse events were febrile neutropenia (5%), pyrexia (4%), and diarrhea (2%). In Studies DCS4968g and GO27834 combined, 33%−41% of patients discontinued polatuzumab vedotin because of an adverse event. The most frequently reported adverse events leading to discontinuation were peripheral sensory neuropathy, peripheral neuropathy, and peripheral motor neuropathy. In Study GO29044, Grade

≥ 3 adverse events were reported in 19 of 40 patients (48%) with B-cell lymphoma who received polatuzumab vedotin (1.8 mg/kg) in combination with obinutuzumab or rituximab plus CHP. The most frequent events (≥ 10% of patients) were fatigue (33%), diarrhea (33%), and nausea (30%). Serious adverse events were reported for 33% of patients in this treatment group. In Study GO29365, Grade ≥ 3 adverse events were reported in 11 of 21 patients (52%) with B-cell lymphoma who received polatuzumab vedotin in combination with rituximab plus bendamustine and in 17 of 28 patients (61%) who received polatuzumab vedotin in combination with obinutuzumab plus bendamustine. The most frequent events (≥ 10% of patients) were nausea (43%), diarrhea (41%), and fatigue (35%). Serious adverse events were reported for 33% of patients receiving polatuzumab vedotin in combination with rituximab plus bendamustine and 39% of patients receiving polatuzumab vedotin in combination with obinutuzumab plus bendamustine. A total of 44 deaths have been reported: 11 deaths in patients treated with single agent polatuzumab vedotin and 33 in patients treated with polatuzumab vedotin combined with rituximab or obinutuzumab. The majority of deaths were judged as related to disease progression.

1.232 Clinical Efficacy of Polatuzumab Vedotin

Polatuzumab vedotin demonstrated clinical activity as a single agent. In Study DCS4968g, at the 2.4-mg/kg dose, objective responses (CR or PR) were observed in 7 of 16 patients (44%) with R/R indolent B−cell lymphoma (FL, marginal zone lymphoma [MZL], or small lymphocytic lymphoma [SLL]) and 14 of 27 patients (52%) with R/R DLBCL. At a dose of 1.8 mg/kg, a PR was observed in 2 of 4 patients with DLBCL and in 2 of 2 patients with MCL, and no objective responses were observed in the 5 patients with CLL. The median duration of response was 6.2 months (95% CI: 3.3, 19.3 months) for the 2.4 mg/kg dose and 6.6 months (95% CI: 2.3, 11.4 months) for the 1.8 mg/kg dose. At the 2.4-mg/kg dose, median PFS was 7.9 months (95% CI: 3.0, 11.6 months) for patients with indolent B-cell lymphoma and 5.0 months (95% CI: 2.3, 6.8 months) for patients with DLBCL. Median PFS was 4.6 months (95% CI: 1.4, 13.9 months) for patients with DLBCL treated at the 1.8-mg/kg dose.

Polatuzumab vedotin also demonstrated clinical activity when administered in combination with rituximab. In Study DCS4968g, at a dose of 2.4 mg/kg, objective responses were observed in 7 of 9 patients with indolent B-cell lymphoma, DLBCL, or MCL (78%); 2 of the 7 patients had CRs. Median duration of response among these patients was 12.3 months (95% CI: 4.3, not estimable [NE]). Median PFS was 12.5 months (95% CI: 6.9, 17.4 months). Preliminary data for patients in Study GO27834 who received polatuzumab vedotin (2.4 mg/kg) in combination with rituximab, objective responses were observed in 14 of 20 patients with R/R FL (70%; 9 patients with CRs) and 21 of 39 patients with R/R DLBCL (54%; 8 patients with CRs). For patients who received

polatuzumab vedotin (1.8 mg/kg) in combination with rituximab, objective responses were observed in 15 of 20 patients with FL (75%; 6 patients with CRs). Median duration of response was 12.9 months (95% CI: 6.7, NE) and 13.2 months (95% CI: 7.2, 21.2) for patients who received polatuzumab vedotin 1.8 mg/kg (FL) or 2.4 mg/kg (FL or DLBCL), respectively. At the 2.4 mg/kg dose, median PFS was 15.1 months (95% CI: 11.8, NE) among the 20 patients with FL and 5.6 months (95% CI: 4.2, 12.7) among the 39 patients with DLBCL. Among the 20 patients with R/R FL treated with 1.8 mg/kg polatuzumab vedotin in combination with rituximab, median PFS was 18.1 months (95% CI: 9.9, NE). For patients in Study GO27834 who received polatuzumab vedotin (1.8 mg/kg) in combination with obinutuzumab, overall responses were observed in 8 of 12 patients with R/R FL (67%; 1 patient with CR) and 3 of 15 patients with R/R DLBCL (20%; 0 patients with CR). Preliminary data from Study GO29044 in patients treated with polatuzumab vedotin (1.0−1.8 mg/kg) in combination with R-CHP showed overall responses in 29 of 31 patients (94%; 24 patients with CRs). When polatuzumab vedotin (1.4 or 1.8 mg/kg) was combined with G-CHP, overall responses were seen in 10 of 12 patients (83%; 10 patients with CRs). Preliminary data from GO29365 in FL patients treated with polatuzumab vedotin (1.8 mg/kg) in combination with bendamustine showed overall responses in 7 of 7 patients (100%; 2 patients with CRs) when combined with rituximab and in 3 of 4 patients (75%; 1 patient with CR) when combined with obinutuzumab. Patients with DLBCL treated with polatuzumab vedotin (1.8 mg/kg) in combination with bendamustine showed overall responses in 3 of 7 patients (43%; 2 patients with CRs) when combined with rituximab and in 6 of 8 patients (75%; 2 patients with CR) when combined with obinutuzumab.

While development is currently focused on FL and DLBCL early studies demonstrated promising activity in MCL. In a phase I/Ib study of single agent polatuzumab vedotin 6 of 7 patients with relapsed/refractory MCL achieved a response (Lancet Oncol 2015; 16: 704–15).

1.3 Venetoclax

1.31 Background on Venetoclax

Venetoclax (synonymous with ABT-199 and GDC-0199) is a highly selective, orally available small−molecule Bcl-2 family protein inhibitor that binds with high affinity (dissociation constant [Ki] < 0.10 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-XL and Bcl-w (> 480- and > 2000-fold lower affinity than to Bcl-2, respectively). Overexpression of anti−apoptotic Bcl-2 family proteins is associated with resistance to chemotherapy, and antagonism of the action of these proteins might overcome resistance and enhance response to therapy. Anti−apoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, making them compelling targets for anti-tumor therapy.

1.32 Preclinical Studies with Venetoclax

In vitro, venetoclax demonstrated broad cell-killing activity against a panel of lymphoma and leukemia cells, including B-cell FL, mantle cell lymphoma (MCL), DLBCL, and acute myeloid leukemia. Venetoclax was especially potent against cell lines that expressed high levels of Bcl-2. Leukemia and lymphoma cell lines that bear the t(14;18) translocation were significantly more sensitive to venetoclax than wild−type cell lines. Venetoclax inhibited subcutaneous (SC) murine xenograft growth of human tumor cell lines derived from acute lymphoblastic leukemia and NHL. The PK profile of venetoclax was evaluated in multiple animal species. In mice, rats, monkeys, and dogs, low plasma clearance and low volumes of distribution characterized the venetoclax PK profile. Half-lives ranged from 2.2 hours in monkeys to 12 hours in dogs. Food had a marked effect on the oral bioavailability in dogs. Venetoclax demonstrated high protein binding to human, rat, dog, and monkey plasma proteins (> 99.9%). In rats, venetoclax was widely distributed into liver, kidneys, spleen, heart, lungs, small intestine, and white fat, but was poorly distributed in testes, brain, muscle, and bone. Liver metabolism was the major route of elimination with biliary excretion of the parent drug playing the secondary role in rats. Venetoclax showed moderate metabolic stability in in vitro hepatic systems across species tested, except for low to moderate stability in dog hepatocytes. In vitro, venetoclax is metabolized by cytochrome (CYP) 3A4 and is a moderate inhibitor of CYP2C8 and a potent inhibitor of CYP2C9. It is not a potent inhibitor of CYP3A4, CYP1A2, CYP2B6, CYP2C19, or CYP2D6 (IC50 > 30 μM) and does not induce CYP3A4 or CYP1A2 at concentrations up to 10 μM. Venetoclax has the potential to inhibit P-glycoprotein (P-gp). A more detailed discussion of the nonclinical activity of venetoclax, including pharmacokinetic, toxicology, and metabolism, is provided in the current venetoclax Investigator's Brochure.

1.33 Clinical Studies with Venetoclax

As of 28 November 2014, a total of 639 patients had been dosed with venetoclax in AbbVie and Genentech/Roche oncology studies. Doses administered in venetoclax clinical studies ranged from 20 to 1200 mg. A total of 345 patients with CLL/SLL and 155 patients with NHL have been treated with venetoclax as single agent or in combination. Two studies, GP28331 and GO27878, include the combination of obinutuzumab and venetoclax in CLL and NHL, respectively. In addition, Study BO25323, a randomized Phase III study evaluating the efficacy of obinutuzumab plus venetoclax compared with obinutuzumab plus chlorambucil in patients with previously untreated CLL, has recently been initiated. For more detailed clinical information on venetoclax, including results in the CLL cohorts of the clinical studies and clinical pharmacology data, refer to the venetoclax Investigator's Brochure.

1.331 Clinical Pharmacokinetics and Pharmacodynamics

Preliminary PK data with venetoclax are available from ongoing Studies

M12-175, M12-630, and M13-365 in patients with hematologic malignancies. The venetoclax formulation currently used in clinical studies is a tablet formulation with strengths of 10, 50, and 100 mg. The tablet formulation was orally administered after a low-fat meal. Food increased the bioavailability of venetoclax by 3- to 4-fold. Preliminary PK results indicated that the absorption of venetoclax after the oral dosing was relatively slow. Venetoclax plasma concentrations peaked at approximately 6 hours after dosing. The mean terminal-phase elimination half-life of venetoclax was approximately 17 hours, and the mean oral clearance was approximately 13 L/hr after a single dose. There was no apparent difference in the pharmacokinetics of venetoclax in patients with CLL/SLL or NHL. The combined data from patients with CLL/SLL and NHL suggested that venetoclax exposure was approximately dose proportional across the 150- to 900-mg dose levels. In the limited number of patients to date, co-administration of BR did not show apparent effect on venetoclax pharmacokinetics.

1.332 Safety and Activity Data for Venetoclax

Study M12-175, the first in-human venetoclax monotherapy dose-escalation study, is ongoing in patients with R/R CLL/SLL and NHL. Two DLTs have been reported in patients with NHL who were treated with venetoclax in Study M12-175. Both DLTs occurred at the 600-mg dose in Cohort 5 (which enrolled a total of 10 patients and had a 300-mg lead-in dose and 600-mg designated cohort dose). One patient experienced a DLT of serious Grade 3 febrile neutropenia, and the other patient experienced a DLT of non-serious Grade 4 neutropenia. Dosing was interrupted and patients were treated with medication; the events resolved, and the patients restarted therapy at a reduced venetoclax dose of 300 mg. No DLTs were reported in Cohorts 6−8, with the maximum dose studied of 1200 mg. The most common adverse events in the NHL cohort of Study M12-175 were nausea, anemia, diarrhea, and fatigue, all occurring in ≥ 20% of patients. Grade ≥ 3 hematologic toxicity was less common in patients with NHL than in patients with CLL. In Study M12-175, 13% of patients with NHL experienced Grade ≥ 3 neutropenia and 10% experienced Grade ≥ 3 thrombocytopenia. As of 4 December 2014, a total of 105 patients with R/R NHL had been enrolled (70 in the dose-escalation cohorts and 35 in the safety expansion cohort) and evaluated for objective response following the International Working Group criteria (patients with Waldenstrom's macroglobulinemia [WM] were evaluated using the International Workshop-WM criteria). In the dose-escalation cohorts, the objective response rate (ORR) was 57%, the CR rate was 11%, and median time in the study was approximately 6 months. In the safety expansion cohort, the ORR was 17%, the CR rate was 3%, and median time in the study was approximately 3 months. This group had limited follow-up at the time of the clinical cutoff.

Study M12-630 is a study of venetoclax in combination with BR in patients with R/R NHL. Patients receive this regimen for 6 cycles. In

Study M12-630, preliminary efficacy data are available for 27 patients (17 male patients [63%]) with R/R NHL as of 7 October 2014. Hematologic toxicity in Study M12-630 (venetoclax in combination with BR in patients with NHL) was not significantly greater than that expected with BR alone. The ORR was 64% (18 of 27 evaluable patients): 4 patients (14%) with CR and 14 patients (50%) with PR. An additional 3 patients (11%) had stable disease. Efficacy data are not yet available for the other NHL studies listed. Data on venetoclax and human pregnancy or venetoclax and drug abuse and drug dependency are not available. Additional details on the clinical activity and safety of venetoclax are provided in the venetoclax Investigator's Brochure.

1.4 Rationale for Study Combination

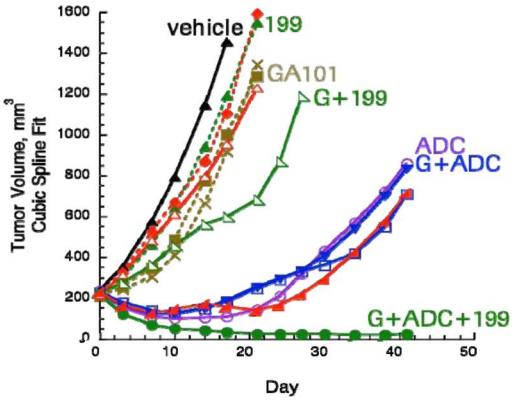
This study will evaluate the activity of a novel triplet combination of rituximab and hyaluronidase human, polatuzumab vedotin, and venetoclax for relapsed MCL.

B-cell lymphoma, including MCL, express the CD20 antigen, and anti-CD20 therapy (rituximab) has been demonstrated to provide enhanced anti-tumor activity in combination with other agents, leading to increased response rates, PFS, and OS[1].

Polatuzumab vedotin is an ADC designed for the targeted delivery of MMAE, a potent microtubule inhibitor to lymphoma cells that express CD79b. MMAE has a mechanism of action that is similar to that of vincristine. Venetoclax is a specific inhibitor of the Bcl-2 anti−apoptotic protein expressed in many NHL cells. Bcl-2 is overexpressed in most FL and many DLBCLs as a consequence of the t(14;18) chromosomal translocation or gene amplification and is associated with a poor prognosis in multiple tumor types (Cory and Adams 2002; Cory et al. 2003; Reed 2008; Iqbal et al. 2011). Bcl-2 has been shown to contribute to resistance of malignant cells to chemotherapies with varied mechanisms of action, consistent with its role as an inhibitor of the final common steps of apoptosis and is likely to play a role in resistance to the pro-apoptotic activities of immunotherapy and chemotherapy. In solid and hematologic tumor models, anti-mitotic drugs (taxanes and auristatin) were shown to modulate Bcl-2 pro-survival proteins to induce cell death in vitro (Haldar et al 1996; Poruchynsky et al. 1998; Wertz et al. 2011). MMAE in polatuzumab vedotin may be able to down regulate Mcl-1, a known resistant factor for venetoclax. Therefore, the addition of venetoclax, a Bcl-2 inhibitor, to a polatuzumab vedotin-containing regimen may have the potential to significantly enhance the anti-lymphoma activity and to result in improved clinical outcomes. Nonclinical data that support the triplet combination of CD 20 antibody, polatuzumab vedotin, and venetoclax include WSU-DLCL2 model in CB17 severely compromised immunodeficient (SCID) mice that demonstrated significantly improved anti-tumor activity of the triplet combination over the activity of any treatment regimen alone or doublet combination (obinutuzumab plus venetoclax or obinutuzumab plus polatuzumab vedotin; see Figure 1).

Progress has been made in the treatment of MCL, however cure is still not attainable for most patients, and options to prolong remission and survival for relapsed patients remain limited. There is a need for the continued development of safe and effective therapies for patients with relapsed disease after front line therapy, and particularly for patients who relapse or progress on ibrutinib who have a dismal prognosis.

Figure 1



There is a strong scientific rationale for combining these agents. Recent studies have shown that high levels of constitutive BCR signaling in MCL correlated with high surface expression of CD79,and was associated with resistance to BTK inhibition and decreased survival. High expression of CD79 also leads through ERK kinase and other downstream mediators to up-regulation of the anti-apoptotic protein BCL-2 and its family members, a primary driver of MCL pathogenesis. The contribution of impaired immune activation to ibrutinib resistance is unknown. We hypothesize that by targeting CD79 expressing B cells in conjunction with enhancing apoptosis through Bcl-2 inhibition we will abrogate the effects of constitutive BCR signaling, and that this regimen will be highly active in relapsed MCL. Preclinical data supporting the triplet combination of obinutuzumab, polatuzumab vedotin, and venetoclax has been demonstrated in a WSU-DLCL2 model in CB17 severely compromised immunodeficient (SCID) mice showing significantly improved anti-tumor activity of the triplet combination over the activity of any treatment regimen alone or doublet combination (Figure 1) Existing data from protocol GO29833 demonstrate that these agents can be safely combined in other B cell NHL without significant overlapping toxicity. For patients with relapsed MCL who progress after BTK inhibition, treatment options and survival are profoundly limited, and the use of these agents in earlier line therapy may potentially have an adverse effect on OS. Treatments with manageable toxicity and a high CR rate remain an unmet medical need for patients with relapsed MCL, as well as for unfit and elderly patients who cannot tolerate aggressive induction regimens. While venetoclax has high ORR in relapsed MCL, the CR rate remains suboptimal at around 21%. This novel triplet regimen has the potential to both increase ORR and deepen CR extending chemotherapy free remission, and decreasing toxicity by sparing patients cytotoxic chemotherapy, and improving upon individual agents used as part of current standard of care. If this trial confirms high activity and tolerability, this regimen may have a place as first line therapy of older and unfit patients, potentially replacing components of standard systemic chemotherapy and enhancing both efficacy and tolerability, or as a standard of care second line salvage regimen for BTK naïve or resistant patients.

1.5 Correlative Research

1.51 Studies have shown that achieving MRD negativity in the peripheral blood and in the bone marrow prior to consolidation correlates with improved outcome in MCL regardless of the treatment approach and molecular remission is regarded as an independent predictor of clinical outcome (23-26). Thus, molecular

monitoring can be used to guide treatment decisions to intensify treatment interventions in some patients and avoiding unnecessary treatments in others. In addition to its potential use in response-adaptive treatment strategies, MRD status in clinical remission after treatment has been shown to be predictive of subsequent PFS (23, 27, 28). MRD assessment by real-time quantitative PCR (RQ-PCR) has been the most standardized technique (29), but more recently, a novel commercial assay that uses multiplex PCR and next-generation sequencing (NGS) of immunoglobulin and T-cell receptor rearrangements to detect and quantify gene sequences in DNA from peripheral blood or bone marrow samples has been available. The ClonoSEQ® assay, formerly ClonoSight™, measures the level of MRD and is able to detect 1 in 1 million cells (30). Based on data that showed that the MRD assessment with ClonoSEQ® in B-ALL and multiple myeloma patients correlated with EFS and PFS, respectively (31), FDA granted marketing authorization of ClonoSEQ in September 2018 (32) for myeloma and leukemia, and its use for MCL is currently under investigation. We will evaluate MRD in responding patients at EOI to learn the role of maintenance therapy, may contribute to deepening remission and extending progression free survival. Other NSG based MRD tests may also be evaluated in addition to ClonoSEQ using residual material.

1.52 The contribution of immune dysregulation to lymphomagensis is significant, but the impact of response to therapy on restoration of normal immune function in MCL has not been studied**.** Moreover, immune dysfunction and restoration can manifest in multiple ways, including changes in cell subset frequency, altered expression of costimulatory proteins, or impaired cytokine production[22]. Using high parameter, single cell technologies, we will correlate immune profiles with clinical features and EOI response. The restoration of immune function may suggest improved anti-tumor immune surveillance, and potentially be correlated with deeper or prolonged response. Our findings may uncover mechanisms that could be targeted with immunotherapy, or combination approaches in future trials.

We have previously identified immunological differences amongst patients with different therapeutic outcomes. Using our Checkpoint Ligand panel, which identifies subsets of myeloid cells, DC, and measures the expression of many ligands of checkpoint molecules, we evaluated pre- and post-treatment samples from melanoma patients, clustering the data for all patients and overlaying a density gradient to indicate the frequency of cells defined by each cluster. This method allowed comparison across patient groups. We selected clusters that differed between the two patient groups and found that they comprised GAL9+ and OX40L+ GAL9+ cells, compared the frequency of cells expressing these markers for each patient group, and observed a statistically significant difference between responders and non-responders. These preliminary data demonstrate our ability to acquire, visualize, statistically analyze, and interpret complex data. We are also able to identify functional traits that differ across patient groups, using a novel new single cell technology for measurement of cytokine secretion, which enumerates 39-cytokines simultaneously from 20,000 cells per chip (IsoLight by IsoPlexus, Bramford, CT) (Rossi J, Paczkowski P, Shen YW, et al. Preinfusion polyfunctional anti-CD19 chimeric antigen receptor T cells are associated with clinical outcomes in NHL. Blood 2018;132:804-14.

We applied this technology to melanoma patients on an immunotherapy trial and found that non-responders had more Granzyme B+ cells and molecules than responders. Notably, these cells did not secrete the delivery molecule perforin, demonstrating our ability to deeply characterize cells. Although our most developed data is in melanoma, these assays have been performed in lymphoma. In Hodgkins lymphoma (HL), our cytokine secretion analysis demonstrated that patients who fail therapy have higher levels of IL9 (p=0.0028) and IL22 (p=0.021) at diagnosis compared to those who respond to treatment. We have also identified a suite of cytokines that increase over the course of disease treatment (including IL4, IL5, IL10; p=0.001) only in patients who fail therapy (ASH abstract 128366).

1.53 Mantle cell lymphoma international prognostic index (IPI) prognostic score is a continuous variable derived from 4 factors including age, ECOG PS, LDH and WBC count, and classifies MCL patients into 3 risk groups (low-risk, intermediate-risk, and high-risk) with differential survival (33). Other markers at diagnosis that have been shown to be prognostic in MCL are Ki-67 proliferation index (34, 35) and complex cytogenetics (36). Complex karyotype is defined as 3 or more detectable chromosomal abnormalities. Ki-67 staining performed on the tissue biopsy at diagnosis will be used to calculate the proliferation index, defined as the percentage of Ki-67 positive lymphoma cells, and to categorize patients into < 10%, 10-30% and > 30% subgroups. The MIPI score, proliferation index and complex cytogenetics status at MCL diagnosis will be correlated with the MRD rate prior to the 4th cycle of the proposed regimen. The interim MRD positivity alone and also in combination with the at-diagnosis prognostic factors will be tested for association with the treatment response at EOI according to the Lugano 2014 response criteria based on PET-CT scans.

2.0 Goals

2.1 Primary Endpoint

2.11 To evaluate the end of induction (EOI) complete response rate (CR) for treatment with the regimen of rituximab and hyaluronidase human + polatuzumab vedotin + venetoclax (RSc+Pola+Ven) in relapsed/ refractory MCL.

2.2 Secondary Endpoints

2.21 To evaluate the EOI overall response rate (ORR) for the combination of RSc+Pola+Ven in relapsed/ refractory MCL.

2.22 To evaluate the best response (CR, PR) in patients who continue on to maintenance therapy and evaluate the improvement in the depth of response.

2.23 To evaluate the progression free survival (PFS) and overall survival (OS) for the combination of RSc+Pola+Ven in relapsed/ refractory MCL.

2.24 To compare the ORR, CR, PFS, and OS in ibrutinib refractory compared to ibrutinib naïve patients.

2.25 To evaluate regimen-related toxicity for patients treated with RSc+Pola+Ven.

2.3 Correlative Research

2.31 To evaluate changes in minimal residual disease (MRD) status in both responding and non-responding patients at EOI and end of maintenance and compared to baseline as well as correlate MRD status with PFS and OS.

2.32 To evaluate changes in systemic immune profiles and T cell activation induced by treatment with RSc+Pola+Ven.

2.33 To evaluate the prognostic importance of high-risk cytogenetic alterations, and other risk stratification scores in patients with relapsed/refractory MCL receiving RSc+Pola+Ven.

2.34 To evaluate features of the tumor microenvironment in patients with relapsed/refractory MCL receiving RSc+Pola+Ven.

2.35 To evaluate molecular features associated with response in PDX models from patients with relapsed/refractory MCL receiving RSc+Pola+Ven.

3.0 Patient Eligibility

For patients in the safety run in, prior to discussing protocol entry with the patient, call the ACCRU Registration Office ([redacted]) or email at [redacted] to ensure that a place on the protocol is open to the patient.

NOTE: Waivers to eligibility criteria are not allowed per ACCRU policy

3.1 Registration – Inclusion Criteria

3.11 Age ≥ 18 years.

3.12 Pathologically confirmed relapsed or primary refractory mantle cell lymphoma with concurrent or prior tissue sample IHC positive for cycle in D1 or that is positive for FISH or cytogenetics for t(11;14).

NOTE: Safety Portion only: MCL or indolent B cell NHL (FL (grades I-IIIa) MZL), or SLL stratified as low risk for TLS, relapsed or progressed after at least two lines of therapy, or one line of a BTK inhibitor containing therapy, or Autologous Stem Cell Transplant (AutoSCT). No limit to prior lines of therapy.

NOTE: Expansion Portion only: MCL relapsed or progressed after at least two lines of therapy, or one line of a BTK inhibitor containing therapy, or Autologous Stem Cell Transplant (AutoSCT). No limit to number of prior therapies. May have received prior BTK inhibitor therapy.

3.13 Measurable disease as defined with at least one lesion measuring ≥ 1 x 1.5cm by PET/CT using Lugano criteria.

3.14 ECOG Performance Status of 0, 1, or 2. (Form is available on the ACCRU web

site under Study Resources -> Forms)

3.15 The following laboratory values obtained ≤ 14 days prior to registration.

- Absolute neutrophil count (ANC) ≥1000/mm^3
- Platelet count ≥75,000/mm^3
- Hemoglobin ≥9.0 g/dL
- International normalized ratio ≤ 1.5 x ULN for patients not receiving therapeutic anticoagulation
- Partial thromboplastin time (PTT) or activated PTT (aPTT) ≤ 1.5 x ULN
- Adequate liver function, as indicated by: AST and ALT ≤ 2.5 × ULN
- Total bilirubin < 1.5 × ULN (or ≤ 3 × ULN for patients with documented Gilbert syndrome)
- Adequate renal function as indicated by: calculated Cr clearance ≥45 ml/min using the modified Cockcroft-Gault formula (eCCr; with the use of ideal body mass [IBM] instead of mass):

$$\text{eCCr} = \frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [0.85 \text{ if female}]}{72 \text{ x serum creatinine (mg/dL)}}$$

Or, if serum creatinine is in μmol/L:

$$\text{eCCr} = \frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [1.23 \text{ if male, } 1.04 \text{ if female}]}{\text{serum creatinine (μmol/L)}}$$

3.16 Negative serum pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.
NOTE: A female of childbearing potential is a sexually mature female who:
1) has not undergone a hysterectomy or bilateral oophorectomy; or
2) has not been naturally postmenopausal for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months).

3.17 Able to provide informed written consent, and ability to comply with study related procedures.

3.18 Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.19a Willing to provide tissue samples for mandatory correlative research (see Section 17.0).

3.19b For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of <1% per year during the treatment period and for at least 30 days after the last dose of venetoclax or 18 months after the last dose of rituximab and hyaluronidase human, whichever is longer.

For men: agreement to remain abstinent (refrain from heterosexual intercourse)

or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 6 months after the last dose. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose to avoid exposing the embryo.

3.2 Registration – Exclusion Criteria

3.21 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.22 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.23 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.24 Receiving any other investigational or chemotherapeutic agent which would be considered as a treatment for the primary neoplasm.

3.25 Known CD20-negative status at relapse or progression.

3.26 Prior allogeneic SCT.

3.27 Completion of autologous SCT ≤ 100 days prior to registration.

3.28 Treatment with radioimmunoconjugate ≤ 12 weeks prior to registration.

3.29a Monoclonal antibody or Antibody-drug Conjugate (ADC) therapy within 5 half-lives or 4 weeks prior to registration, whichever is longer.

3.29b Radiotherapy, chemotherapy, hormonal therapy, or targeted small-molecule therapy within 2 weeks prior to registration (with the exception of ibrutinib to prevent tumor flare, patients taking ibrutinib who are progressing must discontinue ibrutinib 2 half-lives or 2 days prior to initiating protocol therapy)

3.29c Clinically significant toxicity (other than alopecia) from prior therapy that has not resolved to Grade ≤ 2 (per NCI CTCAE v5.0) prior to registration.

3.29d Current Grade > 1 peripheral neuropathy.

3.29e Any history of CNS lymphoma or leptomeningeal infiltration

3.29f Treatment with systemic corticosteroids > 20 mg/day prednisone or equivalent Patients who are receiving corticosteroids ≤ 20 mg/day, prednisone or equivalent, for non-lymphoma treatment reasons must be documented to be on a stable dose for ≥ 4 weeks prior to registration. If corticosteroid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, up to 100 mg/day of prednisone or equivalent can be given for a maximum of 5 days, but all tumor assessments must be completed prior to start of corticosteroid treatment.

3.29g History of severe allergic or anaphylactic reaction or known sensitivity to humanized or murine monoclonal antibodies, rituximab, polatuzumab vedotin, or venetoclax.

3.29h Active bacterial, viral, fungal, or other infection.

3.29i Requirement for warfarin treatment (because of potential DDIs that may increase the exposure of warfarin).

3.29j Treatment with the following agents ≤7 days prior to registration – Strong and moderate CYP3A inhibitors such as fluconazole, ketoconazole, and clarithromycin (see Appendix I for examples) – Strong and moderate CYP3A inducers such as rifampin and carbamazepine (see Appendix I for examples). If subject is taking proton pump inhibitors, subject is willing to avoid co-administration and stagger venetoclax dosing.

3.29k Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade that contains Seville oranges), or star fruit ≤ 3 days prior to registration.

3.29l Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis.

3.29m Active hepatitis B or hepatitis C infection.
NOTE: Patients who have been successfully treated and cleared their virus as evidenced by a negative Hep B or Hep C PCR are eligible.

3.29n Known history of HIV positive status or known infection with human T-cell leukemia virus 1. For patients with unknown HIV status, HIV testing will be performed at screening.

3.29o History of PML (Progressive Multifocal Leukoencephalopathy).

3.29p Vaccination with a live virus vaccine ≤ 28 days prior to registration.

3.29q History of other malignancy that could affect compliance with the protocol or interpretation of results, with the exception of the following: Curatively treated carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal- or squamous-cell skin cancer, Stage I melanoma, or low-grade, early-stage localized prostate cancer

3.29r Any previously treated malignancy that has been in remission without treatment for ≤ 3 years prior to registration.

3.29s Evidence of any significant, uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the previous 6 months, unstable arrhythmia, or unstable angina) or significant pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm).

3.29t Major surgical procedure other than for diagnosis ≤ 28 days prior to Day 1 of Cycle 1, or anticipation of a major surgical procedure during the course of the study.

3.29u Inability or unwillingness to swallow pills.

3.29v History of malabsorption syndrome or other condition that would interfere with enteral absorption.

3.29w History of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) or active bowel inflammation (e.g., diverticulitis).

4.0 Test Schedule

Tests and Procedures	Days Prior to Registration		Induction (21-day cycles)					EOI [1]	Maintenance (12 months)	EOM [2]	Post- Treatment clinical follow-up period (q3m for 2 years +/- 14 days)
	≤ 30 days	≤ 14 days	Cycle 1 (±1 d)			Cycle 2 (±2 d)	Cycles 3-6 (±2 d)	After last induction dose	Monthly (30days) (±1 week)	35 days after last dose (±14 days)	
			D1	D8	D15	D1	D1		D1		
Complete Medical history	X										
ECOG Performance Status	X		X	X	X	X	X	X	X	X	X
Physical exam, weight and vital signs (blood pressure, pulse, O2)[4]	X		X	X	X	X	X	X	X	X	X
Height	X										
12-lead EKG[8]	X										
MUGA/echocardiogram[8]	X										
Hematology (CBC and diff)		X	X[16]	X	X	weekly[18]	X	X	X	X	
Chemistry Labs [7]		X	X [16]	X	X	X	X	X	X	X	
Coagulation (INR, aPTT [or PTT], and PT)		X									
Serum Pregnancy test [3]		X[3]	X[3]			X[3]	X[3]	X	X[3]	X[3]	
HIV [14], HBV [13], HCV [6]	X										
Quantitative IgA, IgG, IgM			X					X		X	X
Optional Whole blood for MRD[17]			X					X		X	
Optional Immunology Research Blood [12 R]			X[12]				X[12]	X[12]	X[12]		X[12]

Tests and Procedures	Days Prior to Registration		Induction (21-day cycles)					EOI [1]	Maintenance (12 months)	EOM [2]	Post- Treatment clinical follow-up period (q3m for 2 years +/- 14 days)
	≤ 30 days	≤ 14 days	Cycle 1 (±1 d)			Cycle 2 (±2 d)	Cycles 3-6 (±2 d)	After last induction dose	Monthly (30days) (±1 week)	35 days after last dose (±14 days)	
			D1	D8	D15	D1	D1		D1		
Review Patient Medication Diary[15]				X	X	X	X	X	X		
Optional tissue specimen [R]					X[11]			X[11]			
Mandatory tissue specimen [19 R]	X										
Concomitant medications	X		To be recorded continually until end of treatment								
Adverse Event Assessment[5]	X		To be assessed continually								
PET-CT scan	X							X	X[9]	X	X[9]
Bone marrow biopsy and aspirate	X [10]							X[10]			

[1] End of induction (EOI) is between 28-42 days after the last induction dose of rituximab and hyaluronidase human and polatuzumab vedotin.

[2] End of maintenance (EOM) visit may take place at 35 days +/- 14 days from the last dose of venetoclax treatment.

[3] For women of childbearing potential only. Must be done ≤7 days prior to registration, D1 of each induction cycle, Day 1 of each maintenance cycle, and end of maintenance. Test done ≤7 days prior to cycle1 day 1 can serve as cycle 1 day 1 test.

[4] For first infusion only, vital signs to be collected prior to dosing, every 15 minutes (+/- 5 minutes) during dosing and 30 minutes (+/- 10 minutes) after treatment completion until vital signs normalize or return to baseline. For vital signs that are normal/return to baseline at the 30 minutes (+/- 10 minutes) assessment, no additional vitals are required**.** For subsequent infusions, vital signs should be collected prior to dosing and every 30 minutes (+/- 10 minutes) during dosing. After treatment completion: Patients who have never had a documented infusion reaction, post-dosing vital signs may be obtained at 30 minutes post infusion for the second infusion, and thereafter at 15 minutes after treatment completion. Additionally, O2 should be monitored as a vital sign during each visit. In cycle 1 if the investigator feels that the patient is at significant risk of tumor lysis patients should be monitored for tumor lysis per institutional standard.

[5] Adverse events will be assessed at the end of each induction cycle, EOI, EOM, and end of each maintenance cycle, and during clinical follow up

[6] At screening, testing should be performed for HIV antibody, hepatitis C antibody, and HBs antigen. These tests could be repeated later during the course of the study if clinically indicated.

[7] Chemistry laboratory analysis includes albumin, amylase, lipase, urea or BUN, creatinine, ALT, AST, LDH, serum alkaline phosphatase, direct and total bilirubin, glucose, total protein, sodium, potassium, chloride, HCO3 (CO2; venous blood), calcium, phosphorous. These labs must be done and reviewed before infusion. If labs for baseline are done within one week of starting therapy, they do not need to be repeated unless they are abnormal and need to be repeated per SOC. Serum chemistry will be obtained prior to administering venetoclax (predose) and 8 and 24 hours after dosing for the first dose only. Laboratory samples should be sent and analyzed immediately. This will be done for each ramp up dose.

[8] Patients with known cardiac dysfunction are required to have EKGs and assessments of left ventricular ejection fraction at screening and as clinically indicated afterwards.
[9] PET/CT in maintenance and post treatment every 6 months or per standard of care.
[10] Baseline bone marrow biopsy and aspirate can be collected within 90 days of registration if negative. However, if bone marrow is positive after most recent therapy (even if greater than 90 days prior to registration), bone marrow biopsy and aspirate does not need to be repeated, but must be recorded as positive on the pre-treatment staging. Repeat Bone Marrow biopsy only in patients who are bone marrow positive at baseline and a CR at EOI to confirm EOI CR. Repeat Bone Marrow biopsy not needed in maintenance.
[11] Tissue specimen optional at the end of cycle 1 and optional at the time of progression. See Section 17.0 for additional details.
[12] Draw at baseline (drawn after registration but prior to cycle 1 treatment), day 1 of cycle 3, day 1 of cycle 7, day 1 of final maintenance cycle, and one year after completion of maintenance if patient is a CR. See Section 14.0 for further details.
[13] Screen all patients for hepatitis B (HBV) infection before initiating treatment with Rituxan. For patients who show evidence of prior hepatitis infection, consult an expert in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during Rituxan treatment (see Section 9.5).
[14] If HIV testing is done ≤ 180 days prior to registration it does not need to be repeated.
[15] Patients will be required to keep a medication diary for venetoclax using the diary in Appendix V. Sites will be required to upload medication diary to RAVE at the end of each cycle.
[16] Hematology and chemistry will be obtained prior to administering venetoclax (predose) and 8 and 24 hours after the first dose only. Laboratory samples should be sent and analyzed immediately.
[17] MRD Testing to be completed at Mayo Clinic Rochester for patients who consent to optional collection.
[18] Subjects must return to the consenting ACCRU institution for CBC evaluation, or have outside laboratory CBC every 7 days during the first 6 weeks of therapy
[19] Tissue is to be submitted no more than 30 days *after* registration. See Section 17.0 for more details.
[R] Research funded

4.1 Survival Follow-up

	Survival Follow-up Phase [1]				
	Every 90 days until subsequent treatment or PD[2]	At subsequent treatment or PD[2]	After subsequent treatment or PD[2] q. 180 days	Death	New Primary
Survival Follow Up	X	X	X	X	At each occurrence

[1] If a patient is still alive 5 years after registration and they have completed protocol therapy, no further follow-up is required.
[2] Progressive disease is based on either PET-CT based or CT based response criteria
NOTE: A +/-14 day window is allowed for all survival follow-up visits.

5.0 Grouping Factors:

5.1 Cohort: Safety portion vs. expansion portion

5.2 Venetoclax Dosing Safety Lead-In: Dose 0 vs Dose -1

5.3 Previous ibrutinib exposure: ibrutinib naïve vs. ibrutinib pre-treated

NOTE: To ensure equal distribution of both ibrutinib naïve and pretreated patients at the dose level determined during the safety run-in, a minimum of 25 patients must be ibrutinib naïve. Therefore, accrual of ibrutinib pretreated patients will stop after 26 Ibrutinib pretreated patients are accrued

6.0 Registration Procedures

6.1 Site Procedures

6.11 Study staff will need to complete the required training prior to gaining access to the registration application. This is located on the ACCRU web page at [redacted] Refer to Study Resources → Applications. Near the bottom of the page there will be a link to the "Research Registration Application Training." After training is complete, study staff must complete the "Attestation of Training" and send to the ACCRU Registration Office at [redacted]

6.12 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with ACCRU. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS). If the necessary documentation is not submitted in advance of attempting patient registration, the randomization will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals is required until the study has been closed through your IRB.

6.2 Safety Portion

Prior to discussing protocol entry with the patient, call the ACCRU Registration Office [redacted] to ensure that a place on the protocol is open to the patient.

6.21 To register a patient, fax [redacted] a completed eligibility checklist to the Academic and Community Cancer Research United (ACCRU) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.3 Expansion Portion

6.31 To register a patient, access the ACCRU web page at [redacted] go to the Study Resources → Application section and click on "Registration" and enter the registration application. The registration application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Instructions for the registration application are available on the above web page under the Study Resources → Application section. Please refer to the "Research Registration Application Training" or Quick Reference Guide for instructions.

Prior to initiation of protocol study intervention, this process must be completed in its entirety and a ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted] If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to the Research Registration Application training on the ACCRU website under Study Resources → Applications.

6.4 Safety and Expansion Portions

6.41 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19a, and 17.1).

An optional correlative research component is part of this study, there will be an option to select if the patient is to be registered onto this component (see Sections 14.1 and 17.1).

- Patient has/has not given permission to give his/her blood sample for research testing.
- Patient has/has not given permission to give his/her tissue sample for research testing.

6.42 Prior to accepting the registration, registration application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.43 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her blood sample(s)

for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her blood sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her sample(s) to outside researchers.

6.44 Treatment cannot begin prior to registration and must begin ≤ 21 days after registration.

6.45 Pretreatment tests/procedures (see Section 4.0) must be completed within guidelines specified on the test schedule.

6.46 All required baseline symptoms (see Section 10.52) must be documented and graded.

6.47 Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist or hematologist.

6.48 Blood draw kit is available on site.

7.0 Protocol Treatment

Safety Portion: An initial 6 patients will receive rituximab via IV on day 1 of cycle 1. On day 1 of cycles 2-6 patients will receive rituximab and hyaluronidase human subcutaneously. On day 1 of cycles 1-6 patients will receive polatuzumab vedotin via IV. Patients will also receive venetoclax daily during all cycles. See Table 7.2 for details.

Expansion Portion: After confirming the optimal and safe tolerable dose of venetoclax, patients will continue with the same schedule of rituximab and hyaluronidase human. The safety portion will determine the frequency of venetoclax dosage.

7.1 Treatment Schedule - Use actual weight or estimated dry weight if fluid retention

Pretreatment medication

Agent	Dose	Route	Day
Dexamethasone[1]	10-20 mg	IV or PO	Within 1 hour of R/ScHyc/Pola
Acetaminophen[1]	650mg	PO	Within 1 hour of R/ScHyc/Pola
Benadryl[1]and	25-50 mg	IV[2]	30 minutes prior to R/ScHyc/Pola
Ranitidine or	50 mg		
Cimetidine or	300 mg		
Famotidine	20 mg		
Allopurinol	100mg	PO	Three times daily from day 1 of cycle 1 to day 1 of cycle 3.

Acyclovir	400mg	PO	Twice daily
Bactrim DS	1 tablet three times a week	oral	Continuously during treatment. Monday/Wednesday/Friday

1. If taken within 8 hours of Rituximab and polatuzumab, each premedication will only need to be taken once per cycle
2. Benadryl can be taken PO or IV

7.2 Induction (Cycles 1-6):

- Patients will receive rituximab 375mg/m^2 IV on day 1 of cycle 1, and rituximab and hyaluronidase human SQ day 1 of cycles 2-6
- Patients will receive polatuzumab vedotin 1.8 mg/kg IV on Day 1 of each 21-day cycle for a total of 6 cycles.
- Patients will receive venetoclax PO 20 mg beginning on day 1 of cycle 1. On day 7 of cycle 1 they will begin ramp-up increasing over 5 weeks to 400 mg po daily days 1-21 cycles 1-6. If not tolerated venetoclax will be dose reduced.
- Missed/skipped/vomited doses will not be made up (i.e. the patient should not double their dose if the previous dose was missed).
- For first infusion only, vital signs to be collected prior to dosing, every 15 minutes (+/- 5 minutes) during dosing and 30 minutes (+/- 10 minutes) after treatment completion until vital signs normalize or return to baseline. For vital signs that are normal/return to baseline at the 30 minutes (+/-10 minutes) assessment, no additional vitals are required**.** For subsequent infusions, vital signs should be collected prior to dosing and every 30 minutes (+/- 10 minutes) during dosing. After treatment completion: Patients who have never had a documented infusion reaction, post-dosing vital signs may be obtained at 30 minutes post infusion for the second infusion, and thereafter at 15 minutes after treatment completion. Additionally, O2 should be monitored as a vital sign during each visit. In cycle 1, if the investigator feels that the patient is at significant risk of tumor lysis, patients should be monitored for tumor lysis per institutional standard.
- When study treatments are given on the same day, they will be administered sequentially in the following order:

  Order of Administration (See section 15 for individual drug instructions)

  1) Venetoclax[#] (No time constraints)
  2) Rituximab/rituximab and hyaluronidase human (if no reaction 30 minutes after completion, patient can receive polatuzumab vedotin)
  3) Polatuzumab vedotin

  [#] First dose of venetoclax will be given at the treatment center. All other doses may be taken at home

Table 7.2a Induction (21 Day Cycles)

Agent	**Dose**	**Route**	**Day[2]**
Rituximab	375mg/m^2	IV	Day 1 Cycle 1
Rituximab and hyaluronidase human[1]	1,400 mg/23,400 Units	SQ over 5 minutes	Day 1 Cycles 2-6
Polatuzumab vedotin	1.8 mg/kg	IV	Day 1 Cycles 1-6
Venetoclax	20 mg week 1 increasing over 5 weeks up to 400 mg po daily days 1-21 cycles 1-6 [3] See table 7.2b below	PO	Daily for Days 1-21 Cycles 1-6

1. Rituximab IV is given in cycle 1, rituximab and hyaluronidase human is started on Cycle 2; All patients must receive and tolerate one full dose of rituximab by IV before starting with rituximab

and hyaluronidase human.
2. A +/- 3 day window is allowed for day 1 of treatment during induction.
3. If 400 mg days 1-21 is not tolerated in the safety portion, venetoclax will dose reduced as outlined in Section 7.61.

Table 7.2b Dosing Schedule for venetoclax Ramp-Up

	Venetoclax Daily Dose
Week 1 (Cycle 1 week 1)	20 mg
Week 2 (Cycle 1 week 2)	50 mg
Week 3 (Cycle 1 week 3)	100 mg
Week 4 (Cycle 2 week 1)	200 mg
Week 5 and beyond (Cycle 2 week 2 and beyond)	400 mg

After completion of induction treatment, patients will continue to receive daily venetoclax treatment (during Month 1) until response is assessed at EOI. Patients who have a CR, or PR at EOI will then receive venetoclax and rituximab and hyaluronidase human in maintenance as outlined in Table 7.3. Polatuzumab will not be given in maintenance. All therapy will be discontinued if response assessments at EOI indicate that a patient is not eligible for post- induction treatment (referred to as maintenance). Maintenance treatment will continue for 12 months or until disease progression.

7.3 Maintenance (Cycles 7-18):

Table 7.3 (30 Day Cycles)

Agent	**Dose**	**Route**	**Day[2]**
venetoclax maintenance	400mg daily for up to 1 year	PO	*Daily for Days 1-21
Rituximab and hyaluronidase human	1,400 mg/23,400 Units	SQ over 5 minutes	First dose 6 weeks after end of rituximab and hyaluronidase human and polatuzumab vedotin induction treatment (+/- 2 weeks) Remaining treatments thereafter will be every 60 days for 1 year.[1]

1. Since cycle length is 30 days, rituximab and hyaluronidase human maintenance is given once every other cycle. A total of 6 rituximab and hyaluronidase human treatments during the maintenance phase.
2. A +/- 7 day window is allowed for day 1 of treatment during maintenance.
   NOTE: No polatuzumab vedotin will be administered.
3. All subjects who get a dose reduction of Venetoclax during induction, will be maintained on the same corresponding dose in maintenance.
   * If 400 mg days 1-21 is not tolerated in the ***safety run-in***, venetoclax will be given 400 mg days 1-10.
4. For Venetoclax dose reductions in Maintenance refer to Table 8.21.

7.4 For this protocol, the patient must return to the consenting ACCRU institution for CBC evaluation, or have outside laboratory CBC every 7 days during the first 6 weeks of therapy, every 30 days during maintenance, and every 3 months during clinical follow-up (Active Monitoring Phase).

7.5 Study treatment by a local medical doctor (LMD) is not allowed.

7.6 Safety Portion: Rules for Dose De-escalation

Dose de-escalation will be considered if the initial safety portion dose level (venetoclax 400 mg days 1-21) per Table 7.2a proves excessively toxic, with 2 or more subjects having excessive significant toxicity as defined in Section 7.7. Dose de-escalation will proceed per section 7.6.1.

7.61 The first cohort of three patients will be treated at the starting dose level of Venetoclax (400 mg days 1-21) and observed for at least 63 days (3 cycles) from the start of treatment to assess toxicity. If significant toxicity as defined in Section 7.7 is observed in 0 or 1 of these 3 patients, 3 new patients will be accrued and treated at same dose level of Venetoclax (400 mg days 1-21) and observed for 3 cycles. After enrolling 6 patients on Venetoclax dose level of 400 mg days 1-21, if ≤1 patient experience significant toxicity, then this dose will be considered safe and the rest of the patients in expansion cohort will be treated at this dose level of Venetoclax. However, if 2 or more out of the first 3 or 6 patients experience significant toxicity, then the dose of venetoclax may be de-escalated to 300mg days 1-21. In this case, another safety analysis using similar 3+3 design approach will be conducted at the reduced dose level of venetoclax.

7.7 Definitions of significant toxicity

7.71 Toxicity will be measured per NCI-CTCAE version 5. For this protocol, significant toxicity will be defined as an adverse event occurring during the first 3 cycles of treatment that is possibly, probably, or definitely related as follows: NOTE: **All significant non-hematologic toxicities must be resolved to a minimum of grade 1 for ongoing treatment at any cycle of treatment.**

7.711 **Non-Hematological significant toxicities.** Any Grade 3 or Grade 4 non-hematological toxicity that is possibly, probably or definitely attributable to the regimen of RSC+Pola+Ven is considered a significant toxicity, including the following:

- Non-hematologic toxicity that causes a delay of >14 days in initiating cycle 2.
- Any type of grade 3-4 hypersensitivity reaction (i.e.: allergic reaction, anaphylaxis, serum sickness, skin disorders, etc.), regardless of attribution, that necessitate discontinuation of study drug.
- Any type of grade 3-4 immune related adverse event or immune system disorder including skin reactions.
- Grade 3 or greater colitis and bowel perforation
- Grade 3 ALT/AST elevation
- Grade 3 or greater TLS

NOTE: The following events are exclusions and are **NOT** considered a significant toxicity for this protocol, regardless of attribution or specific type:

- Grade 3 nausea, vomiting, diarrhea, or oral mucositis with < 3 days

duration.
- Grade 3 fever.
- Grade 3 peripheral sensory neuropathy that is decreased by at least one grade within 7 days.
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive (i.e.: decreased by at least one grade) to oral supplementation within 7 days.
- Grade 3 hypertriglyceridemia that returns to < Grade 2 prior to the beginning of cycle 2.
- Grade 3 hyperglycemia that returns to < Grade 2 (with or without the use of insulin or oral diabetic agents) prior to the beginning of cycle 2.

7.713 **Hematological significant toxicity.** The following hematological toxicity possibly, probably or definitely attributable to the regimen of RSC+Pola+Ven is considered a significant toxicity:
- Grade 4 neutropenia for > 7 days without growth factor support
- Grade 4 febrile neutropenia
  NOTE: Grade 4 non-febrile neutropenia will not be a significant toxicity but should warrant growth factor support on subsequent doses.
- Platelet count < 25,000/uL on 2 separate days, or requiring a platelet transfusion on 2 separate days within a 7-day period
- Myelosuppression that causes a delay of > 14 days in initiating cycle 2
- Grade 3 thrombocytopenia with grade > 2 bleeding

NOTE: Growth factors are allowed per treating investigator's discretion in patients at high risk for febrile neutropenia after cycle 2, or in a patient who has demonstrated neutropenia on previous doses. Patients who are otherwise eligible per protocol with demonstrated bone marrow infiltration, may be treated with prophylactic growth factor support.

7.8 Patients will be required to keep a medication diary for venetoclax using the diary in Appendix V. Sites will be required to upload medication diary to RAVE at the end of each cycle.

8.0 Dosage Modification Based on Adverse Events

Dose modification guidelines are provided specifically for venetoclax, polatuzumab vedotin, rituximab, and rituximab/hyaluronidase human in the tables below. In addition, Venetoclax dose reductions will be discussed in Section 8.21.

If the patient requires a dose reduction, no dose re-escalation (e.g. no return to the baseline dose) is permitted.

Additional dose reductions may be employed at investigator discretion as clinically appropriate to ensure patient safety, and exact modification, timing, and reasons should be recorded.

8.1 Assessment of Safety

The safety plan for patients in this study is based on clinical experience with rituximab, rituximab and hyaluronidase human, polatuzumab vedotin, and venetoclax. The anticipated important safety risks of rituximab, rituximab and hyaluronidase human, polatuzumab vedotin, and venetoclax are outlined below. Please refer to the rituximab, rituximab and hyaluronidase human, polatuzumab vedotin, and venetoclax Investigator's Brochures for a complete summary of safety information.

8.2 Venetoclax Dose Reduction and Re-Escalation Steps

The dose of venetoclax may be reduced. If administration of chemotherapy is delayed, the administration of Pola and R/SC should be delayed for the same timeframe; for example, if polatuzumab and rituximab and hyaluronidase are delayed, administration of venetoclax should also be delayed so that they are given together beginning on Day 1 of the same cycle.

For non-hematologic toxicities, dosing of Pola and R/SC may be resumed upon resolution to Grade 1 or baseline status. Resumption of dosing without complete resolution of toxicity may only be considered after careful weighing of the benefits and risks with the patient. A dose delay of 21 days is permitted for immunochemotherapy to allow recovery of hematologic toxicities to Grade 2 or non-hematologic toxicities to Grade 1 or baseline status for the first episode. Actions for recurrent hematologic adverse events are described in Table 8.31. If treatment is delayed for more than 3 weeks, the patient should be withdrawn from study treatment except in exceptional circumstances which may be discussed with the study chair. (NOTE: Lymphopenia is not considered a cytopenic toxicity, as it is an expected outcome of therapy). Patients who discontinue all study treatment for adverse events should proceed to clinical follow up and remain in the study.

The dose of venetoclax may be reduced according to the following dose reduction steps based on the starting dose.

Table 8.21: Venetoclax Dose Reduction Steps during Induction and Maintenance (Duration of Venetoclax in Maintenance is 1 year).

Venetoclax Dose Reduction		
Starting Dose (Dose 0)	**Step 1 (Dose -1)**	**Step 2 (Dose -2)**
400 mg (days 1-21)	300mg (days 1-21)	200mg (days 1-21)
300mg (days 1-21)	200mg (days 1-21)	100mg (days 1-21)
200mg (days 1-21)	100mg (days 1-21)	50mg (days 1-21)
100mg (days 1-21)	50mg (days 1-21)	20mg (days 1-21)
50mg (days 1-21)	20mg (days 1-21)	

8.3 Toxicities during Induction Treatment

Table 8.31: Guidelines for Management of Hematologic Toxicities That Occur During Induction Treatment.

Event	Action to Be Taken
Grade 3 or 4 Hematogic Toxicity [1]	For patients who have had one or no prior venetoclax or polatuzumab vedotin dose reduction: • Withhold study treatment.[1] • Administer RBCs or platelets as required. • If patient has not already initiated G-CSF, initiate prophylactic G-CSF for current and subsequent cycles. • Resume venetoclax and polatuzumab vedotin at same dose after interruption for 1st occurrence, once the toxicity has resolved to Grade 1 or baseline level • Resume venetoclax and polatuzumab vedotin at one level dose reduction after interruption for 2nd occurrence, once the toxicity has resolved to Grade 1 or baseline level. Refer to table 8.21 for dose reduction steps. • For patients who develop platelet count of 20,000/L while receiving LMWH, reduce the dose of LMWH. For patients who develop platelet count of 20,000/L while receiving platelet inhibitors, consider temporarily withholding platelet inhibitors. **No more than 2 dose level reductions in venetoclax and polatuzumab vedotin are allowed during induction**. • Consider discontinuation of study drug for patients who require withholding study drug for more than 21 days. **For patients who have had two prior venetoclax dose reductions:** • Permanently discontinue study treatment. • For grade 4 thrombocytopenia ≥ 7 days or grade 3 thrombocytopenia with ≥ grade 2 bleeding resume venetoclax and polatuzumab at one dose level dose reduction after the toxicity has resolved to Grade 1 or baseline level

(G-CSF) granulocyte colony-stimulating factor; (LMWH) low molecular weight heparin.

[1] Treatment delays apply to all toxicities; dose modifications apply only to toxicities that are considered to be related to any of the study treatment components. Toxicities that occur during the cycle and subside prior to the next cycle should not trigger the suggested dose modifications.

Table 8.32: Guidelines for Management of Non-Hematologic Toxicities That Occur During Induction

Event	Action to Be Taken
General guidance for treatment delays and discontinuation	• If study treatment is withheld for 21 days because of a toxicity that is attributable to study treatment, permanently discontinue study treatment. • When a treatment cycle is delayed because of toxicity resulting from any component of the regimen, all study treatment should be held and resumed together to remain synchronized.
TLS	• Withhold study treatment. [a] • Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. • If symptoms have resolved completely, resume rituximab and hyaluronidase human and polatuzumab at full dose and resume venetoclax at current dose. • During venetoclax ramp-up, if venetoclax was withheld for 7 days or less, resume venetoclax at same dose level or at one lower dose level, as determined by the investigator (based on risk assessment, including tumor burden status). Refer to Table 8.21 for dose reduction steps. • During venetoclax ramp-up, if venetoclax was withheld for more than 7 days, the dose must be resumed at one lower dose level, with the exception of the first dose (20 mg). Refer to Table 8.21 for dose reduction steps. • If resolved within 24 to 48 hours of last dose, resume venetoclax at the same dose. • For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose. Refer to Table 8.21 for dose reduction steps. • For any events of clinical TLS, resume at a reduced dose following resolution. Refer to Table 8.21 for dose reduction steps.
New-onset neurologic manifestations suggestive of PML	• Withhold study treatment. [a] • Consult with a neurologist if PML is suspected. • If PML is ruled out, resume rituximab and hyaluronidase human, polatuzumab vedotin and venetoclax at current dose. • If PML is confirmed, permanently discontinue study treatment.
AST, ALT, or bilirubin increase: Grade 3 (or 10x ULN for patients with liver involvement)	• Withhold study treatment. [a] • If improvement to Grade 1, resume rituximab and polatuzumab vedotin at full dose and resume venetoclax at next lower dose for current and subsequent cycles per guidelines in Table 8.21. No more than 2 dose level reductions from original dose of venetoclax are allowed during induction. Patients who have had two prior dose reductions should be permanently discontinued. Refer to Table 8.21 for dose reduction steps. • Permanently discontinue study treatment for life-threatening liver toxicity.
Infections and Infestations; AE: Hepatitis viral	• Discontinue therapy and treat hepatitis

Table 8.32: Guidelines for Management of Non-Hematologic Toxicities That Occur During Induction (cont.)

Event	Grade	Action to Be Taken
Peripheral Neuropathy	Grade 4	• Permanently discontinue polatuzumab vedotin and all other study treatment.
	Grade 2 or 3	1. Delay study treatment. [a] 2. If improvement to Grade 1 within 21 days, resume study treatment for current and subsequent cycles as follows: a. Resume rituximab or rituximab and hyaluronidase human at full dose b. Resume venetoclax at current dose [a] c. For patients who started at 1.8 mg/kg, resume polatuzumab vedotin at the permanently reduced dose of 1.4 mg/kg;
Other non-hematologic toxicities (i.e., not described above), excluding alopecia, nausea, and vomiting	Grade 3 or 4	**For patients who have had no prior dose reductions:** • Withhold study treatment. [a] • If improvement to Grade 1 or baseline, resume rituximab and polatuzumab vedotin at full dose and resume venetoclax at next lower dose [a] for current and subsequent cycles per guidelines. **For patients who have had one prior dose reduction:** Grade 4 events • Permanently discontinue study treatment. Grade 3 events • Withhold study treatment. [a] • If improvement to Grade 1 or baseline, rituximab and polatuzumab vedotin at full dose and resume venetoclax at next lower dose [a] for current and subsequent cycles per guidelines. No more than two dose *level* reductions *from the original dose* of venetoclax are allowed *during induction*. **For patients who have had two prior dose reductions:** • Permanently discontinue study treatment.
	Grade 2	• Withhold study treatment. [a] • If improvement to Grade 1 or baseline, resume rituximab and polatuzumab vedotin, and venetoclax at full dose.

IRR-infusion-related reaction; PML-progressive multifocal leukoencephalopathy; TLS-tumor lysis syndrome; ULN-upper limit normal.

[a] Treatment delays apply to all events; dose modifications apply only to events that are considered to be related to any of the study treatment components. Toxicities that occur during the cycle and subside prior to the next cycle should not trigger the suggested dose modifications.

8.4 Toxicities during Maintenance Treatment provides guidelines for management of toxicities that occur during maintenance treatment.

Table 8.43: Guidelines for Management of Toxicities That Occur during Maintenance Treatment

Event	Action to Be Taken
Hematologic toxicity: Grade 3 or 4	Withhold rituximab and hyaluronidase human and venetoclax • Administer G-CSF for neutropenia per institutional guidelines. • Administer RBCs or platelets as required. • If improvement to Grade 2, resume rituximab and hyaluronidase human at full dose and resume venetoclax next lower dose (Refer to table 8.21 for dose reduction steps.) Patients who are not eligible for further venetoclax dose reductions should be permanently discontinued. • If study treatment is withheld for 21 days, permanently discontinue study treatment.
Non-hematologic toxicity: Grade 2	Withhold rituximab and hyaluronidase human and venetoclax If improvement to Grade ≤ 1 or baseline, resume rituximab and hyaluronidase human at full dose and resume venetoclax at next lower dose (Refer to table 8.21 for dose reduction steps). o [a] for subsequent cycles per guidelines o Patients who are not eligible for further venetoclax dose reductions should be permanently discontinued. • If study treatment is withheld for 21 days, permanently discontinue study treatment.
Infections and Infestations: Hepatitis Viral	• Discontinue therapy and treat hepatitis

G-CSF granulocyte colony-stimulating factor.

Table 8.44: Prophylaxis and Assessments for Tumor Lysis Syndrome

	High Risk	Regular Risk
Definition	• Bulky disease defined as: Any lymph node ≥ 10 cm on the screening CT scan • Circulating lymphoma cells • Other characteristics deemed by the investigator to confer high risk of TLS	• All other patients not meeting definition of high risk
Hospitalization	Required for intensive monitoring during initial dose of venetoclax (See Hospitalization section below)	Not required, but may be hospitalized per discussion with the investigator and Medical Monitor
Assessments	On the day of the initial visit with administration of venetoclax (Cycle 1, Day 1): Serial vital signs will be recorded • Patients who demonstrate electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring as per standard of care and outlined in Appendix II. • Patients still at risk of TLS before the subsequent dose should receive adequate prophylaxis and monitoring.	

LDH=lactate dehydrogenase; TLS=tumor lysis syndrome Obinutuzumab, rituximab, polatuzumab vedotin, and venetoclax-F. Hoffman-La Roche Ltd Protocol GO29833, Version 4

8.5 Management of Adverse Reactions for polatuzumab

Table 8.51 Management of Peripheral Neuropathy, Infusion-Related Reaction, and Myelosuppression

Event	Dose Modification
Grade 2–3 Peripheral Neuropathy	• Hold polatuzumab dosing until improvement to Grade 1 or lower. • If recovered to Grade 1 or lower on or before Day 14, restart polatuzumab with the next cycle at a permanently reduced dose of 1.4 mg/kg. • If a prior dose reduction to 1.4 mg/kg has occurred, discontinue polatuzumab. • If not recovered to Grade 1 or lower on or before Day 14, discontinue polatuzumab.
Grade 4 Peripheral Neuropathy	• Discontinue polatuzumab.
Grade 1–3 Infusion-Related Reaction	• Interrupt polatuzumab infusion and give supportive treatment. • For the first instance of Grade 3 wheezing, bronchospasm, or generalized urticaria, permanently discontinue polatuzumab. • For recurrent Grade 2 wheezing or urticaria, or for recurrence of any Grade 3 symptoms, permanently discontinue polatuzumab. • Otherwise, upon complete resolution of symptoms, infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion related symptoms, the rate of infusion may be escalated in increments of 50 mg/hour every 30 minutes. • For the next cycle, infuse polatuzumab over 90 minutes. If no infusion-related reaction occurs, subsequent infusions may be administered over 30 minutes. Administer premedication for all cycles.
Grade 4 Infusion-Related Reaction	• Stop polatuzumab infusion immediately. Give supportive treatment. • Permanently discontinue polatuzumab.
Grade 3–4 Neutropenia[a,b]	• Hold all treatment until ANC recovers to greater than 1000/microliter. • If ANC recovers to greater than 1000/microliter on or before Day 7, resume all treatment without any additional dose reductions. Consider granulocyte colony-stimulating factor prophylaxis for subsequent cycles, if not previously given.
Grade 3–4 Thrombocytopenia [a,b]	• Hold all treatment until platelets recover to greater than 75,000/microliter. • If platelets recover to greater than 75,000/microliter on or before Day 7, resume all treatment without any additional dose reductions.
Infections and Infestations: Hepatitis Viral	• Discontinue therapy and treat hepatitis

[a] Severity on Day 1 of any cycle.
[b] If primary cause is due to lymphoma, dose delay or reduction may not be needed.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetic's may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and

following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (ASCO), Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33:3199-3212.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for intravenous hydration and correction of electrolyte imbalances.

9.5 Carriers of hepatitis B virus (HBV) should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for up to several months following Rituxan therapy. In patients who develop viral hepatitis, Rituxan and any concomitant chemotherapy should be discontinued and appropriate treatment, including antiviral therapy, initiated. There are insufficient data regarding the safety of resuming Rituxan therapy in patients who develop hepatitis subsequent to HBV reactivation.

9.6 Prohibited Medications or Therapies

9.61 CYP3A Inhibitors/Inducers

Treatment with strong and moderate inhibitors or inducers of CYP3A is not allowed during this trial. See Appendix I for more information. In addition, grapefruit or grapefruit products, Seville organs or products from Seville organs, and Star fruit should be avoided for the duration of the trial due to their effect on CYP3A4.

9.62 Proton pump inhibitors

If subject is taking proton pump inhibitors, subject should be advised to avoid co-administration and stagger venetoclax dosing.

9.63 Treatment with warfarin is prohibited due to potential DDIs that may increase the exposure of warfarin.

9.64 Vaccination with a live virus vaccine is prohibited during this trial.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all adverse events to the sponsor as described within the protocol. Refer to the adverse event and serious adverse event sections of the protocol for detailed information.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: 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:
[redacted]

a. Adverse event monitoring and reporting is a routine part of every clinical trial.
b. Identify the grade and severity of the event using the CTCAE version 5.0.
c. Determine whether the event is expected or unexpected (see Section 10.2).
d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
f. Determine if other reporting is required (see Section 10.5).
g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.53 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

10.31 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.53).*

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported.
General disorders and administrations site conditions	Fatigue	≤Grade 3
	Malaise	≤Grade 3
Blood and lymphatic system disorders	Febrile Neutropenia	≤Grade 3
	Neutrophil count decreased	≤Grade 3
	Thrombocytopenia	≤Grade 3
Investigations	Blood bilirubin increased	≤Grade 3
Metabolism and nutrition disorders	Tumor lysis syndrome	≤Grade 3

These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administrationof study drug
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

*Report any clinically important increase in the **rate** of a serious suspected adverse reaction (at your study) site over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

*An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

A list of known/expected AEs is reported in the investigator brochure, package insert or the literature, including AEs resulting from a drug overdose

10.311 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days with an attribution of **possible, probable, or definite** to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease that cannot be attributed to a CTCAE term associated with Grade 5 should be reported as **Grade 5 "Disease progression"** under the system organ class (SOC) of General Disorders and Administration Site Conditions. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.312 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.313 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.314 Pregnancy

Prior to obtaining private information about a pregnant woman and her

infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting [redacted] the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

10.4 Expedited Adverse Event Reporting Requirements for IND/IDE Agents

10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting via the **MedWatch form** for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour; 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Special Instructions:

Follow site-specific reporting guidelines.

1) Submit SAE's using the MedWatch form 3500A. [redacted] or found on the ACCRU web site) along with the ACCRU Safety Reporting Cover Page (found on the ACCRU web site under Study Resources → Forms) to the ACCRU SAE Coordinator via email at [redacted]

2) The ACCRU SAE Coordinator will forward to Genentech at [redacted]

3) The ACCRU SAE Coordinator will forward to ACCRU IND Coordinator [redacted] as appropriate. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

4) ACCRU must be notified via email at [redacted] if the following occurs:

- 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.
- This event will require expedited reporting and will be treated like a serious adverse event with regard to reporting timeframes.

Genentech Adverse Events of Special Interest (AESI): AEs of Special Interest are defined by Genentech as a potential safety problem identified as a result of ongoing safety monitoring of their products. As such, surveillance for the AESIs below MUST be undertaken <u>at each treatment evaluation</u>. The following events are events of special interest and will require expedited reporting <u>AT ANY GRADE</u> and will be treated like a serious adverse event with regard to reporting timeframes.

<u>Events of clinical interest for this trial include:</u>

Potential drug-induced liver injury (DILI) as defined by Hy's Law

a. Investigations
   i. Alanine aminotransferase increase
   ii. Aspartate aminotransferase increase

b. Metabolism and nutritional disorders
    i. Tumor Lysis Syndrome
c. Secondary Malignancies
    i. Treatment related secondary malignancy

Adverse Event	Form(s) Needed	Site timeline to report to ACCRU	ACCRU timeline to report to sponsor
Non-Serious Adverse Event (Sections 10.52-10.53)	Adverse Events form (see CRF packet)	At each evaluation	Quarterly
Adverse Events of Special Interest (Section 10.41 special instructions)	Adverse Events of Special Interest Form**	At each occurrence	Within 1 business day of receipt
	Adverse Events form (if criteria in 10.5 is met)		Quarterly
Pregnancy (Section 10.314)	MedWatch Form**	At each occurrence	Within 1 business day of receipt
Serious Adverse Events (Section 10.41)*	MedWatch Form**	At each occurrence	Within 1 business day of receipt
	Adverse Events form (see CRF packet)		Quarterly

*If an adverse event meets the criteria for both an AE of Special Interest and a Serious Adverse Event, please report only as a Serious Adverse Event.
** MedWatch form can be found on the ACCRU website.

10.42 Reporting of re-occurring SAEs
ALL SERIOUS adverse events that meet the criteria outlined in Table 10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures

involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Baseline and Adverse Events Evaluations

The following pre-treatment symptoms/conditions are to be graded at baseline and at each evaluation using CTCAE v5.0 grading.

System Organ Class (SOC)	Adverse Event/Symptoms	Baseline	Each evaluation
Nervous system disorders	Peripheral Sensory Neuropathy	X	X
Blood and lymphatic system disorders	Anemia	X	X
Investigations	Neutrophil count decreased	X	X

10.53 **Case Report Forms** - Academic and Community Cancer Research United (ACCRU)
Submit the following AEs not specified in Section 10.5. Submit via appropriate Academic and Community Cancer Research United (ACCRU) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

10.531 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.532 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure

10.533 Grade 5 AEs (Deaths)
-Any death <u>within 30 days</u> of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure requires expedited reporting within 24-hours .
-Any death <u>more than 30 days</u> after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.54 Late occurring adverse events are any adverse events that occur during Clinical

Follow-Up and Survival Follow-Up reporting periods. These are reported in compliance with Section 4.0 and Section 18.0.

10.55 Reconciliation: ACCRU agrees to conduct reconciliation for the product. Genentech and ACCRU will agree to the reconciliation periodicity and format but agree at maximum to exchange quarterly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

10.56 Quarterly Report: ACCRU will provide Genentech with accrual and a toxicity report on a quarterly basis.

10.57 IND Annual Reports: All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech.

11.0 Treatment Evaluation

Lugano Classification Response Criteria

11.1 Response Considerations

Schedule of Evaluations: PET/CT scans are required at baseline for all patients. For the purposes of this study, patients should be reevaluated for disease progression at the end of induction therapy and every 6 months during maintenance or per standard of care. Definitions for clinical response for patients with lymphoma are from the recently revised Cheson's et al criteria published in 2014, derived from the original criteria published in 2007. (Cheson et al, 2014) [Cheson et al, 2007). Lymph node measurements should be taken from the CT portion of the PET/CT, or other dedicated CT scans where applicable. Measurement of lymphadenopathy for purposes of assessing for PR will be determined by adding the sum of the products of the maximal perpendicular diameters of measured lesions (SPD). The PPD of a single node is sufficient to evaluate for PD (see Table 11.2). Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is onlyassessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically and pathologically negative.

Response is based on PET/CT based on the revised 2014 Lugano Classification. (Cheson et al, 2014).

Progressive disease is based on either PET-CT based or CT based response criteria. PET confirmation of progressive disease is per physician discretion.

11.2 Lugano Classification Response criteria (Cheson et al, 2014)

	PET-CT Based Response	**CT-Based Response**
Complete Response	**Complete metabolic response (CR)**	**Complete radiologic response (CR) (all of the following)**

Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, 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	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	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 Response	**Partial metabolic response (PR)**	**Partial remission (PR) (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 value 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
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 (SD)**	**Stable disease (SD)**
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 from baseline	Not Applicable
Progressive disease	**Progressive metabolic disease (PD)**	**Progressive disease (PD) requires at least 1 of the following**
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	PPD progression: 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 0.5 cm for lesions ≤2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, 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 (eg, 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

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 trials 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 six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two 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 (eg, liver, spleen, kidneys, 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 (eg, 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 (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).
†PET Deauville 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.

12.0 Descriptive Factors

12.1 International Prognostic Index (IPI) [Shipp et al, 1993]: low risk (0 or 1 risk factors) vs. low intermediate (2 risk factors) vs. high intermediate (3 risk factors) vs. high (4 or 5 risk factors)

Risk Factors	0 points	1 point
Age	≤ 60 yrs.	> 60 yrs.
Serum LDH	≤ 1 x normal	> 1 x normal
ECOG PS	0 or 1	≥2
Stage	I or II	III or IV
Extranodal involvement	≤1 site	>1 site

Total number of risk factors = sum of the number of points for each prognostic factor.

12.2 Mantle Cell Lymphoma International Prognostic Index (Formula-based MIPI): Scores determine risk group: Low risk (<5.7) vs. Intermediate risk (≥5.7-<6.2) vs. High risk (≥ 6.2).

The MIPI score is calculated by this formula: [0.03535 × age (years)] + 0.6978 (if ECOG > 1)+ [1.367 × $\log_{10}$(LDH/ULN)]+ [0.9393 × $\log_{10}$(WBC count per μL)].

Note: The MIPI score will be calculated in Rave once the components are entered.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who achieve a CR or PR at EOI will receive post induction maintenance treatment with rituximab and hyaluronidase human + venetoclax for up to one year (see Section 7.0).

13.2 Patients who complete post-induction maintenance treatment will continue to clinical

follow-up, every 90 days (3 months) +/- 14 days for 2 years.

13.3 Patients who complete 2 years of clinical follow-up will continue to survival follow up for a maximum of 5 years from registration.

13.4 Patients who go off treatment for adverse events will proceed to clinical follow up.

13.5 Patients who receive alternative therapy or develop progression by CT-based criteria or by PET-CT based criteria at any time while receiving therapy or while in clinical follow-up will go to survival follow up.

13.6 Patients who go off protocol treatment for reasons other than progression or alternative therapy will go to clinical follow-up.

13.7 Additional reasons for study treatment discontinuation.

13.71 Patients will go to survival follow-up if pregnancy occurs.

13.72 If a patient develops any medical condition that the investigator determines may jeopardize the patient's safety if they continue to receive study treatment they will be removed from treatment and continue to clinical follow up.

13.8 Reasons for patient discontinuation from study. No further follow up of any kind will be required.

13.81 Patient withdrawal of consent for all follow-up

13.82 Study termination or site closure

13.83 Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator

13.9a A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Survival follow-up will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material and the off-treatment form must be submitted. No further data submission is necessary.

13.9b A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the survival follow-up phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Survival follow-up will be required per Section 18.0 of the protocol.

13.9c A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the Off Treatment Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Correlative Study	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline (Drawn after registration but prior to cycle 1 treatment)	Day 1 Cycle 3	End of Induction Day 1 Cycle 7	End of Maintenance Day 1 Cycle 18	One year post final maintenance treatment for patients who remain in CR[1]	Temperature/ Conditions
MRD	Optional	Blood	EDTA (purple)	10ml (1)	X		X	X		Ambient
Banking	Optional	Blood	EDTA (purple)	10ml (4)	X	X	X	X	X	Ambient
Banking	Optional	Blood	Streck CF DNA	10ml (2)	X	X	X	X	X	Ambient

[1] +/-8 weeks

After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.2 for detailed shipping instructions.)

14.2 Blood/Blood Products Handling

14.21 Kits are provided for this study.

The kit contains supplies and instructions for collecting, processing, and shipping specimens.

Participating institutions may obtain kits by e-mailing the Mayo Hematology Research Tissue Bank at [redacted] E-mail requests should include the site address, contact information and number of kits being requested.

Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow 3 to 4 business days to receive the kits.**

14.22 Label specimen tubes with the protocol number, the patient's initials (last, first, middle), study patient ID number (if available) and date of blood collection.

14.23 Collect all peripheral blood according to specific kit instructions (see table above).

14.24 Shipping

Specimens must be shipped the same day they are drawn.

Ship the EDTA and Streck whole blood tubes in the provided Styrofoam kits; no cold pack is required but may be used. The Fed Ex air bill is pre-addressed.

Ship specimens via Priority Overnight service on **Monday – Thursday**

(Friday only if you coordinate with lab contact) directly to:

[redacted]

Please send email message to [redacted] The message should include the study name, sample type, Fed Ex air bill tracking number, contact name and telephone number. Phone calls if necessary, to [redacted]

Shipping costs will be covered by the study if these kits and Fed Ex air bills are used for shipping specimens. Each kit contains the required tubes.

14.3 Handling and storage of specimens

14.31 Blood samples: Plasma (from Streck cfDNA BCT® and EDTA tubes) and buffy coat (containing peripheral blood mononuclear cells from EDTA tubes) will be harvested and stored. In addition, aliquots of peripheral blood mononuclear cells will be cryopreserved. 10 mL EDTA tube will be forwarded to BAP for MRD testing.

14.4 Study Methodology and Storage Information

14.41 All research blood samples (plasma, cells) will be stored for future correlative research.

14.42 Return of Genetic Testing Research Results
Future correlative research may involve DNA and/or RNA extracted from banked blood or blood cell specimens. Results of the research involving these DNA and/or RNA are not currently anticipated to have clinical relevance to the patient or their family members, and the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sough regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

IND number 152666

Investigator brochure will be made available on the ACCRU website.

15.1 Venetoclax (ABT-199, GDC-0199, Venclexta®)

15.11 **Background:** Venetoclax is a small-molecule B-cell lymphoma-2 (Bcl-2) family inhibitor in the biarylacylsulfonamide chemical class. Venetoclax binds with high affinity to antiapoptotic protein Bcl-2 and with lower affinity to other antiapoptotic Bcl-2 family proteins, like Bcl-XL and Bcl-w.

15.12 **Formulation**: Venetoclax is available as 10, 50, and 100 mg tablets. The excipients are: copovidone, colloidal silicon dioxide, Polysorbate 80, sodium stearyl fumarate and calcium phosphate dibasic. Venetoclax 10 mg and 100 mg coating contains iron oxide yellow, polyvinyl alcohol, polyethylene glycol, talc, and titanium oxide. Venetoclax 50 mg coating contains iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc.

High Dose venetoclax tablets are available as 160 and 200 mg tablets. The excipients are: copovidone, colloidal silicon dioxide, polysorbate 80, and sodium stearyl fumarate. The coating contains iron oxide yellow, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

15.13 **Preparation and storage**: The clinical supply for all formulations can be stored at not more than 25°C (77°F). Actual labeled storage conditions may be more conservative based on country specific regulations.

15.14 **Administration:** Venetoclax tablets should be taken orally once daily with a meal and water. Do not chew, crush, or break tablets. If the patient misses a dose of venetoclax within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible and resume the normal daily dosing schedule. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the next day. If the patient vomits following dosing, no additional dose should be taken that day.

15.15 **Pharmacokinetic information:**
Absorption: The maximum plasma concentration of venetoclax was attained 5 to 8 hours after dosing. In subjects with CLL, venetoclax showed minimal accumulation, and steady-state AUC increased proportionally over the dose range of 150 to 800 mg.
Food increased the bioavailability of venetoclax by approximately 3- to 5-fold.
Distribution: Venetoclax is highly bound to plasma proteins with unbound fraction (fu) < 0.01. Blood-to-plasma concentration ratios show venetoclax do not partition preferentially into the cellular compartment.
Metabolism: Biotransformation of venetoclax in humans primarily involves enzymatic oxidation on the dimethyl cyclohexenyl moiety to form metabolites. One of the metabolites, M5, undergoes CYP- mediated cyclization at the α-carbon of piperazine to generate M27. In human, M27 was identified as a major metabolite with an inhibitory activity against BCL-2 that is at least 58-fold lower than venetoclax *in vitro*.
Half-life elimination: 17-41 hours following a single dose of venetoclax
Excretion: Venetoclax is primarily eliminated as metabolites in feces (99.9 ± 5.0%) with negligible renal elimination (< 0.1%). Based on the population pharmacokinetic analysis, age, sex, race, weight, mild or moderate hepatic impairment and mild, moderate, or severe renal impairment do not have a

clinically meaningful effect on venetoclax clearance.
Special patient populations: Venetoclax should not be administered to pregnant women. It is not known whether venetoclax is excreted in human milk, so venetoclax should not be administered to nursing mothers.

Hepatic Impairment: Mean venetoclax AUC exposures in subjects with severe hepatic impairment were approximately 2.3- to 2.7-fold higher as compared with subjects with normal hepatic function. On the basis of these results, a dose adjustment in patients with severe hepatic impairment is recommended.

15.16 **Potential Drug Interactions:** Venetoclax is predominately metabolized by CYP3A4 in vitro, thus CYP3A4 inhibitors or inducers are expected to cause changes in venetoclax exposures. Venetoclax should not be used with strong CYP3A inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole) at initiation and during ramp-up phase. Concomitant use of venetoclax with moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil), or strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort), or moderate CYP3A inducers (e.g., bosentan, efavirenz, etavirine) should be avoided. For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, concomitant use of strong and moderate CYP3A inhibitors may be allowed with venetoclax dose reductions. If a strong CYP3A inhibitor must be used after the ramp-up phase, reduce the venetoclax dose by at least 75%. If a moderate CYP3A inhibitor must be used, reduce the venetoclax dose by at least 50%.

Advise patients to avoid consuming grapefruit products, Seville oranges, or starfruit during treatment with venetoclax.

Venetoclax should be administered using caution with weak inhibitors or inducers of CYP3A, substrates or inhibitors of P-gp, BCRP, or OATP1B1/B3. If a P-gp inhibitor must be used, reduce the venetoclax dose by at least 50%. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax. Avoid co-administration with proton pump inhibitors, and stagger venetoclax dosing with H2-receptor antagonists and antacids as described in the USPI.

If venetoclax is co-administered with warfarin, the international normalized ratio (INR) should be monitored closely.

Live-virus vaccines should not be given within 28 days prior to the initiation of study treatment, at any time during study treatment, or in the 30 days following last dose of study treatment.

15.17 **Known potential toxicities**:
Very common (≥ 10%): edema, skin rash, hyperglycemia, hyperkalemia, hypoalbuminemia, hypocalcemia, hyponatremia, hypophosphatemia, abdominal pain, constipation, diarrhea, nausea, stomatitis, vomiting, anemia, leukopenia, lymphocytopenia, neutropenia, thrombocytopenia, increased serum aspartate aminotransferase, dizziness, fatigue, headache,

arthralgia, musculoskeletal pain, cough, dyspnea, lower respiratory infection, pneumonia, upper respiratory infection, fever
Common (≥ 1% to < 10%): febrile neutropenia, tumor lysis syndrome, sepsis
Frequency not defined: hemolytic anemia

Tumor lysis syndrome (TLS) is an important identified risk for venetoclax in oncology studies, especially in CLL and MCL. The risk is during the first 5 weeks of ramp-up period. 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.

Serious infection is an important identified risk for venetoclax. Serious infections, including sepsis and fatal events, have been reported in the oncology clinical studies; these events are confounded by the underlying disease, comorbidities, and prior or concomitant immunosuppressive medications in the majority of cases. Serious infections occur with and without neutropenia, and to date, no clear relationship has been noted between the onset of neutropenia events and serious infectious events in the context of venetoclax. Prophylactic antibiotic treatment is recommended/required (depending on the combination) in all protocols as a preventative measure.

15.18 **Drug procurement:** Investigational venetoclax will be provided free of charge to study participants.

Genentech will supply investigational supply to McKesson . Each participating ACCRU treating location will order the drug from McKesson. Submit the Drug Order Request Form (found on the ACCRU web site) to:

McKesson
[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of venetoclax and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.19 **Nursing Guidelines:**

15.191 Agent should be taken with a meal and water. Patients should be instructed not to crush, chew, or break tablet. Patients who miss their dose by more than 8 hours should not make up dose.

15.192 Assess patients medication both prescription and over the counter. Venetoclax should not be taken with strong CYP3A inhibitors.

15.193 Patients should be advised not to consume grapefruit, Seville oranges, or starfruit or their juices while taking venetoclax.

15.194 Patients who are also taking Coumadin while on venetoclax should be advised to have their INR checked more frequently.

15.195 Venetoclax can cause tumor lysis syndrome. Patients should be monitored closely during the ramp up phase, including monitoring electrolytes, and renal function.

15.196 Cytopenias are very common. Instruct patient to report any unusual bruising or bleeding and/or signs or symptoms of infection to the study team.

15.197 Gastrointestinal side effects are common and include nausea, vomiting, diarrhea, and constipation. Treat symptomatically and monitor for effectiveness of intervention.

15.198 Rarely patients can experience URI symptoms, cough and pneumonia. Instruct patients to report any cough, shortness of breath and/or chest pain to study team.

15.199 Patients who have severe hepatic impairment should have a dose adjustment

15.199a Live virus vaccines should not be given within 28 days prior to initiation of treatment, during treatment, or for 30 days afterwards. See Section 9.6 Prohibited Medications or Therapies.

15.199b Monitor LFT's.

15.199c Due to high risk of infection/sepsis, prophylactic antibiotic treatment is recommended and in some situations required, given combinatorial regimens.

15.19a Temperature excursions that occur at the site should be reported by the site using the Genentech Temperature Excursion Form found on the ACCRU web site for this study and emailed to:

[redacted]

Any shipment deviations (those not occurring at the site) should be reported to McKesson via email to:

[redacted]

15.2 **Polatuzumab Vedotin (RO5541077, Polivy™):**

Investigator brochure will be made available on the ACCRU website.

15.21 **Background:** Polatuzumab vedotin is an antibody-drug conjugate that contains a humanized immunoglobulin-G1 (IgG1) anti-human CD79b monoclonal antibody and a potent anti-mitotic agent, monomethyl auristatin E (MMAE), linked through a protease-labile linker. CD79b is a surface antigen that is expressed on mature B cells, with the exception of plasma cells. CD79b is expressed in a

majority of the B-cell-derived malignancies, including B-cell lymphomas and chronic lymphocytic leukemia (CLL). MMAE exerts its cytotoxicity by binding to microtubules and inhibiting microtubule polymerization, inhibiting cell division, and inducing apoptosis.

15.22 **Formulation**: Polatuzumab vedotin is available as: freeze-dried lyophilisate containing 140 mg of polatuzumab vedotin as a white to grayish-white lyophilized powder in a single-dose vial for reconstitution and further dilution. Reconstitution with sterile water for injection (SWFI) results in a colorless, liquid solution composed of 20 mg/mL polatuzumab vedotin in polysorbate-20 (8.4 mg), sodium hydroxide (3.80 mg), succinic acid (8.27 mg), sucrose (288 mg).

15.23 **Preparation and storage:**
Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not use beyond the expiration date shown on the carton. Do not freeze. Do not shake.

Polatuzumab vedotin is a cytotoxic drug. Follow applicable special handling and disposal procedures.

1. Reconstitute immediately before dilution.
2. More than one vial may be needed for a full dose. Calculate the dose, the total volume of reconstituted polatuzumab vedotin solution required, and the number of polatuzumab vedotin vials needed.
3. Reconstitute each 140 mg polatuzumab vedotin vial by using a sterile syringe to slowly inject 7.2 mL of Sterile Water for Injection, USP with the stream directed toward the inside wall of the vial to obtain a concentration of 20 mg/mL of polatuzumab vedotin.
4. Swirl the vial gently until completely dissolved. Do not shake.
5. Inspect the reconstituted solution for discoloration and particulate matter. The reconstituted solution should appear colorless to slightly brown, clear to slightly opalescent, and free of visible particulates. Do not use if the reconstituted solution is discolored, is cloudy, or contains visible particulates. Do not freeze or expose to direct sunlight.
6. If needed, store unused reconstituted polatuzumab vedotin solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 48 hours or at room temperature (9°C to 25°C, 47°F to 77°F) up to a maximum of 8 hours prior to dilution. Discard vial when cumulative storage time prior to dilution exceeds 48 hours.
7. Dilute polatuzumab vedotin to a final concentration of 0.72–2.7 mg/mL in an intravenous infusion bag with a minimum volume of 50 mL containing 0.9% Sodium Chloride Injection, USP, 0.45% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP.
8. Determine the volume of 20 mg/mL reconstituted solution needed based on the required dose.
9. Withdraw the required volume of reconstituted solution from the polatuzumab vedotin vial using a sterile syringe and dilute into the intravenous infusion bag. Discard any unused portion left in the vial.
10. Gently mix the intravenous bag by slowly inverting the bag. Do not shake.
11. Inspect the intravenous bag for particulates and discard if present.

12. If not used immediately, store the diluted polatuzumab vedotin solution as specified in the table. Discard if storage time exceeds these limits. Do not freeze or expose to direct sunlight.

Diluent Used to Prepare Solution for Infusion	Diluted polatuzumab vedotin Solution Storage Conditions*
0.9% Sodium Chloride Injection, USP	Up to 24 hours at 2°C to 8°C (36°F to 46°F) or up to 4 hours at room temperature (9 to 25°C, 47 to 77°F)
0.45% Sodium Chloride Injection, USP	Up to 18 hours at 2°C to 8°C (36°F to 46°F) or up to 4 hours at room temperature (9 to 25°C, 47 to 77°F)
5% Dextrose Injection, USP	Up to 36 hours at 2°C to 8°C (36°F to 46°F) or up to 6 hours at room temperature (9 to 25°C, 47 to 77°F)

15.24 **Administration:**

Polatuzumab vedotin must be administered using a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2- or 0.22-micron pore size) and catheter. Do not mix polatuzumab vedotin with or administer as an infusion with other drugs.

Administer the initial dose of polatuzumab vedotin over 90 minutes. Monitor patients for infusion-related reactions during the infusion and for a minimum of 90 minutes following completion of the initial dose. If the previous infusion was well tolerated, the subsequent dose of polatuzumab vedotin may be administered as a 30-minute infusion and patients should be monitored during the infusion and for at least 30 minutes after completion of the infusion.

If a planned dose of polatuzumab vedotin is missed, administer as soon as possible. Adjust the schedule of administration to maintain a 21-day interval between doses.

15.25 **Pharmacokinetic information:**

Absorption: Mild accumulation for both acMMAE (antibody- conjugated MMAE) and total antibody is observed for the q3w dosing regimen of polatuzumab vedotin with the steady state reached approximately after 3 cycles of dosing.
Distribution: The acMMAE central volume of distribution estimated based on population PK analysis is 3.15 L. For human, MMAE plasma protein binding is 71% to 77% and the blood to plasma ratio is 0.79 to 0.98, in vitro.
Metabolism: In vitro studies indicate that MMAE is predominantly metabolized by CYP3A4/5.
Half-life elimination: The acMMAE terminal half-life is approximately 12 days (95% CI: 8.1 to 19.5 days) at Cycle 6 with predicted clearance of 0.9 L/day. The unconjugated MMAE terminal half-life is approximately 4 days after the first polatuzumab vedotin dose.
Distribution and Excretion: Following IV administration of radiolabeled polatuzumab vedotin (tritium radiolabel on MMAE) to rats, the percentage of

injected radioactivity recovered in rats over 14 days was approximately 103% in feces and approximately 5% in urine.

Avoid the administration of polatuzumab vedotin in patients with moderate or severe hepatic impairment (bilirubin greater than 1.5 × ULN). Patients with moderate or severe hepatic impairment are likely to have increased exposure to MMAE, which may increase the risk of adverse reactions. Polatuzumab vedotin has not been studied in patients with moderate or severe hepatic impairment. No adjustment in the starting dose is required when administering polatuzumab vedotin to patients with mild hepatic impairment (bilirubin greater than ULN to less than or equal to 1.5 × ULN or AST greater than ULN).

Patients with mild or moderate renal impairment have similar conjugate (acMMAE) and unconjugated MMAE exposures as the patients with normal renal function. PK in patients with severe renal impairment has not been studied.

15.26 **Potential Drug Interactions:**
In vitro studies indicate that MMAE is predominantly metabolized by CYP3A4/5. MMAE is a weak time-dependent inhibitor of CYP3A4/5 but does not competitively inhibit CYP3A4/5 at clinically relevant concentrations. MMAE does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. MMAE is not an inducer of CYP enzymes. Concomitant use of polatuzumab vedotin with ketoconazole (strong CYP3A inhibitor) is predicted to increase unconjugated MMAE AUC by 45%. Concomitant use of polatuzumab vedotin with rifampin (strong CYP3A inducer) is predicted to decrease unconjugated MMAE AUC by 63%. Unconjugated MMAE is not predicted to alter the AUC of concomitant drugs that are CYP3A substrates (e.g., midazolam). In vitro data indicate that MMAE is a P-gp substrate. In vitro, MMAE is not a substrate of OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MRP2, or BCRP. MMAE does not inhibit P-gp, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, BSEP, MRP2, or BCRP at clinically relevant concentrations.

Patients who are receiving strong CYP3A4 inhibitors and p-gp inhibitors concomitantly with vc-MMAE ADCs should be closely monitored for adverse events.

Polatuzumab vedotin is being studied in combination with other drugs including rituximab, obinutuzumab, bendamustine, cyclophosphamide, doxorubicin and prednisone/prednisolone, venetoclax, lenalidomide, and atezolizumab, and it is not fully known whether or how the addition of polatuzumab vedotin might affect the safety and efficacy of other drugs, or vice versa.

15.27 **Known potential toxicities:**
Serious Adverse Drug Reactions: pneumonia, sepsis, neutropenic sepsis, septic shock, upper respiratory tract infection, rhinovirus infection, neutropenia, febrile neutropenia, leukopenia, peripheral motor neuropathy, peripheral sensory neuropathy, diarrhea, abdominal pain, vomiting, pyrexia, asthenia

Potential Risks: anemia, thrombocytopenia, infections, progressive multifocal leukoencephalopathy, infusion related reactions, immunogenicity (anti-drug

antibodies), hepatic toxicity (hyperbilirubinemia, transaminase [AST or ALT] elevation), reproductive toxicity, fatigue, hyperglycemia, renal toxicity (increased serum creatinine), gastrointestinal toxicity (nausea, constipation, anorexia), pulmonary toxicity (interstitial lung diseases), joint pain/arthralgia/skeletal pain, alopecia, cardiac arrhythmias, ocular toxicity, dysgeusia, tumor lysis syndrome, genotoxicity/carcinogenicity (myelodysplastic syndrome)

There is also a risk of embryo-fetal toxicity. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 9 months after the last dose and for 6 months after the last dose of polatuzumab vedotin for male patients with female partners of reproductive potential.

15.28 **Drug procurement:** Investigational supply is provided free of charge to study participants.

F. Hoffmann-La Roche will supply investigational supply to McKesson. Each participating ACCRU treating location will order the drug from McKesson. Submit the Drug Order Request Form (found on the ACCRU web site) to:

McKesson
[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of polatuzumab and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.29a Nursing Guidelines:

15.291 Cytopenias are common, including febrile neutropenia. Monitor CBC w/diff and instruct patient to report fever or sign/symptoms and/or unusual bruising or bleeding of infection to the study team. Sepsis has been reported.

15.292 Patients may experience infusion related reactions. Monitor and treat per protocol.

15.293 Monitor LFT's

15.294 Monitor renal function

15.295 Gastrointestinal side effects that have been seen are diarrhea, nausea, vomiting and constipation. Treat symptomatically and monitor for effectiveness.

15.296 Instruct patients to report any dyspnea, cough or chest pain as interstitial

lung toxicity has been seen.

15.297 Patients may experience joint pain/arthralgia/skeletal pain. Treat symptomatically and monitor for effectiveness.

15.298 Patients may experience Tumor lysis syndrome. Monitor labs appropriately.

15.299 Instruct females of child bearing potential of the risks to a fetus and that they should use effective contraception throughout treatment and for 9 months after their last dose. For male patients they should use effective contraception throughout treatment and for 6 months after drug discontinuation.

15.29b Temperature excursions that occur at the site should be reported by the site using the Genentech Temperature Excursion Form found on the ACCRU web site for this study and emailed to: [redacted]

Any shipment deviations (those not occurring at the site) should be reported to McKesson via email to: [redacted]

15.3 **Rituximab and Hyaluronidase Human (Rituxan Hycela®):**

Investigator brochure will be made available on the ACCRU website.

15.31 **Background:** Rituximab is a monoclonal antibody directed against the CD20 antigen on B-lymphocytes. CD20 regulates cell cycle initiation; and, possibly, functions as a calcium channel. Rituximab binds to the antigen on the cell surface, activating complement-dependent cytotoxicity; and to human Fc receptors, mediating cell killing through an antibody-dependent cellular toxicity.

Hyaluronidase increases the absorption rate or rituximab-containing products by increasing permeability of subcutaneous tissue through temporary depolymerization of hyaluronan; at the recommended doses, hyaluronidase acts locally, and the effects are reversible. Permeability of the subcutaneous tissue is restored in 24 to 48 hours.

15.32 **Formulation**: Rituximab and hyaluronidase human is supplied as a ready-to- use liquid formulation with rituximab at a concentration of 120 mg/mL. It is available as individually packaged single dose: 1400mg/23400 units per 11.7 mL. The drug product is a sterile, colorless to yellowish, clear to opalescent liquid that contains 2,000 U/mL recombinant human hyaluronidase (rHuPH20, manufactured in a Chinese hamster ovary [CHO] cell line) acting as a permeation enhancer, histidine/histidine-HCl (buffer), α,α-trehalose (tonicity adjuster), methionine (stabilizer), and polysorbate 80 (surfactant) in water for injection at pH 5.5.

15.33 **Preparation and storage**: Store vials at refrigeration temperature, 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Protect vials from direct sunlight. Once transferred from the vial to the syringe, the

solution of rituximab and hyaluronidase human is physically and chemically stable for 48 hours at 2°C − 8°C and subsequently for 8 hours at 30°C in diffuse daylight. Rituximab and hyaluronidase human is ready to use. To avoid needle clogging, attach the hypodermic injection needle to the syringe immediately prior to administration. Rituximab and hyaluronidase human is compatible with polypropylene and polycarbonate syringe material and stainless-steel transfer and injection needles. Visually inspect the product for particulate matter and discoloration prior to administration. Rituximab and hyaluronidase human should be a clear to opalescent and colorless to yellow liquid. Do not use if particulates or discoloration is present.

15.34 **Administration:**
NOTE: All patients must receive at least one full dose of rituximab by intravenous infusion before starting treatment with rituximab and hyaluronidase human.

Inject rituximab and hyaluronidase human into the subcutaneous tissue of the abdomen over approximately 5 to 7 minutes and never inject into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars. No data are available on performing the injection at other sites of the body.

Inject 11.7 mL of rituximab and hyaluronidase human 1400 mg/23400 units subcutaneously into the abdomen over approximately 5 minutes.

15.35 **Pharmacokinetic information**:
Duration: CLL patients remained B-cell depleted until month 9, where signs of repletion were seen. In follicular lymphoma patients, B-cell repletion begins after 6 months.
Absorption: Model based simulations showed that a fixed dose of 1400 mg rituximab SC would achieve C_{trough} values non-inferior to those observed with rituximab IV 375 mg/m^2 administered q2m or q3m in maintenance and q3w in induction.
Distribution: Vdss subcutaneous 8.52L (CLL); 8.09L (FL) **Bioavailability (compared to IV rituximab):** 63.4% (CLL); 64.6% (FL)
Half-life elimination: 32 days (CLL); 34.1 days (FL)

15.36 **Potential Drug Interactions:**
Increased Effect/Toxicity: Monoclonal antibodies may increase the risk for allergic reactions to rituximab due to the presence of HAC antibody. Antihypertensive medications may exacerbate hypotension.
Decreased Effect: Currently recommended not to administer live vaccines during rituximab treatment. Inactivated vaccines should be complete at least 2 to 4 weeks prior to starting therapy. Rituximab may diminish the effects of sipuleucel-T.

Immunosuppressants: Rituximab may enhance the adverse/toxic effects of immunosuppressants, including:certolizumab pegol, pimecrolimus, tacrolimus, fingolimod, leflunomide, natalizumab, roflumilast,and to a lesser extent of denosumab,ophthalmic chloramphenicol, trastuzumab.

Myelosuppressants: Rituximab may enhance the adverse/toxic effects of

myelosuppressants, including: abatacept, belimumab, clozapine, deferiprone, dipyrone, promazine, and tofacitinib.

15.37 **Known potential toxicities:**
Consult the Investigator's Brochure and package insert for the most current and complete information. Refer to the package insert pertaining to the following boxed warnings: Progressive multifocal leukoencephalopathy (PML); Hepatitis B virus reactivation; and severe and sometimes fatal mucocutaneous reactions.

Common known potential toxicities, > 10%:
Central nervous system: Fatigue, chills, paresthesia, headache, peripheral neuropathy, paresthesia
Dermatologic: Alopecia, dermatological reaction, erythema, skin rash (including severe mucocutaneous reactions)
Gastrointestinal: Nausea, constipation, vomiting, diarrhea, abdominal pain
Hematologic & oncologic: Neutropenia, anemia, leukopenia, febrile neutropenia, thrombocytopenia
Immunologic: Antibody development, anti-rituximab antibodies
Infection: Serious infection
Local: Erythema at injection site
Neuromuscular & skeletal: arthralgia, asthenia
Respiratory: Cough, upper respiratory tract injection, dyspnea, pneumonia
Miscellaneous: Fever

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Peripheral edema, chest pain, hypertension, hypotension
Central nervous system: insomnia, dizziness
Dermatologic: Pruritis
Endocrine & metabolic: Weight loss
Gastrointestinal: Decreased appetite, dyspepsia, stomatitis, upper abdominal pain
Genitourinary: Urinary tract infection
Hematologic & oncologic: Lymphocytopenia
Infection: Influenza
Local: Infusion site reaction
Neuromuscular & skeletal: Limb pain, ostealgia, back pain, muscle spasm, myalgia
Ophthalmic: Conjunctivitis
Respiratory: Nasopharyngitis, oropharyngeal pain, bronchitis, sinusitis, flu-like symptoms, respiratory tract infection

Frequency not defined:
Fulminant hepatitis, hepatic failure, hypersensitivity reaction, JC virus infection, reactivation of HBV, infusion-related reaction, tumor lysis syndrome, gastrointestinal perforation

Rare known potential toxicities, <1% (Postmarketing and/or case reports):
Bone marrow depression, bronchiolitis obliterans, hypogammaglobulinemia (prolonged), interstitial pulmonary disease, intestinal obstruction, intestinal perforation, Kaposi sarcoma, Lupus-like syndrome, optic neuritis, pancytopenia, pleurisy, polyarthritis, progressive

multifocal leukoencephalopathy, serum sickness, uveitis, vasculitis (systemic, with rash), viral infection

Maternal IgG enters breast milk and rituximab has been reported to be excreted at low concentrations in human breast milk. Given that the clinical significance of this finding for infants is unknown, rituximab should not be administered to nursing mothers.

15.38 **Drug procurement:** Investigational supply is provided free of charge to study participants by F. Hoffmann-La Roche.

F. Hoffmann-La Roche will supply investigational supply to McKesson . Each participating ACCRU treating location will order the drug from McKesson. Submit the Drug Order Request Form (found on the ACCRU web site) to:

McKesson
[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of rituximab and hyaluronidase human and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.381 Temperature excursions that occur at the site should be reported by the site using the Genentech Temperature Excursion Form found on the ACCRU web site for this study and emailed to:
[redacted]

Any shipment deviations (those not occurring at the site) should be reported to McKesson via email to:
[redacted]

15.39 Nursing Guidelines:

All patients must receive at least one full dose of rituximab by intravenous infusion before starting treatment with rituximab and hyaluronidase human.

15.391 Patients should not receive live vaccines during rituximab treatment. Inactivated vaccines should be administered 2-4 weeks prior to starting therapy.

15.392 Patients may experience reactivation of Hepatitis B (HBV). Patients who are at risk of hepatitis B virus should be screened prior to initiation of therapy.

15.393 Inject rituximab and hyaluronidase human into the subcutaneous tissue of

the abdomen over approximately 5 to 7 minutes and never inject into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars.

15.394 Assess patient's concurrent medications as those that are on immunosuppression and/or myelosuppresive agents can see increased effects from those drugs while receiving rituximab.

15.395 Cytopenias are common and can be long term. Monitor CBC. Instruct patient to report signs and symptoms of infection, excessive bruising and/or bleeding to the health care team

15.396 GI disturbances (Nausea, abdominal pain and less commonly diarrhea, vomiting, dyspepsia) headache, and weakness are common side effects. Treat as necessary. Monitor for effectiveness

15.397 Monitor for injection site reactions and treat as needed.

15.398 Reports of PML (progressive multifocal leukoencephalopathy) has been seen. Instruct patient to report any changes in cognition, level of consciousness, headache, lethargy, or progressive weakness to the study team immediately.

15.4 **Rituximab (Rituxan®, C2B8)**

Refer to package insert for complete, up-to-date information.

15.41 **Background**: rituximab is a monoclonal antibody directed against the CD20 antigen on B-lymphocytes. CD20 regulates cell cycle initiation; and, possibly, functions as a calcium channel. rituximab binds to the antigen on the cell surface, activating complement-dependent cytotoxicity; and to human Fc receptors, mediating cell killing through an antibody-dependent cellular toxicity.

15.42 **Formulation**: Commercially available for injection, solution [preservative free]: 10 mg/mL (10 mL, 50 mL) [contains Polysorbate 80].

15.43 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store vials at refrigeration temperature do not freeze or shake. Protect vials from direct sunlight. Withdraw the necessary amount of rituximab and dilute to a final concentration of 1-4 mg/mL with 0.9% NaCL or D_5W. Gently invert the bag to mix the solution; do not shake. Solutions for infusion are stable at 2ºC to 8ºC for 24 hours and at room temperature for an additional 24 hours.

15.44 **Administration:** Do not administer I.V. push or bolus. Refer to treatment section for specific infusion instructions. Suggested administration guidelines are:
Initial infusion: Start rate of 50 mg/hour; if there is no reaction, increase

the rate by 50 mg/hr every 30 minutes, to a maximum of 400 mg/hour. Subsequent infusions: If patient did not tolerate initial infusion follow initial infusion guidelines. If patient tolerated initial infusion, start at 100 mg/hour; if there is no reaction; increase the rate by 100 mg/hour every 30 minutes, to a maximum of 400 mg/hour.
Note: If a reaction occurs, slow or stop the infusion. If the reaction abates, restart infusion at 50% of the previous rate.

Accelerated infusion rate (90 minutes): Accelerated infusion rate is not an option for cycle 1. It is an option in cycle 2 and beyond for patients who have had a mild reaction and cannot yet be transitioned to rituximab and hyaluronidase human. For patients with previously untreated follicular NHL and diffuse large B-cell NHL who are receiving a corticosteroid as part of their combination chemotherapy regimen, have a circulating lymphocyte count <5000/mm^3, or have no significant cardiovascular disease. After tolerance has been established (no grade 3 or 4 infusion-related event) at the recommended infusion rate in cycle 1, a rapid infusion rate may be used beginning with cycle 2. The daily corticosteroid, acetaminophen, and diphenhydramine are administered prior to treatment, then the rituximab dose is administered over 90 minutes, with 20% of the dose administered over the first 30 minutes and the remaining 80% is given over 60 minutes. If the 90-minute infusion in cycle 2 is tolerated, the same rate may be used for the remainder of the treatment regimen (through cycles 6 or 8).

15.45 **Pharmacokinetic information:**
Duration: Detectable in serum 3-6 months after completion of treatment; B-cell recovery begins ~6 months following completion of treatment; median B-cell levels return to normal by 12 months following completion of treatment
Distribution: RA: 3.1 L; GPA/MPA: 4.5 L
Absorption: Immediate and results in a rapid and sustained depletion of circulating and tissue-based B cells
Half-life elimination: Proportional to dose; wide ranges reflect variable tumor burden and changes in CD20 positive B-cell populations with repeated doses:
Following first dose: Mean half-life: 3.2 days Following fourth dose: Mean half-life: 8.6 days CLL: Median terminal half-life: 32 days NHL: Median terminal half-life: 22 days RA: Mean terminal half-life: 18 days GPA/MPA: 23 days

Excretion: Uncertain; may undergo phagocytosis and catabolism in the reticuloendothelial system

15.46 **Potential Drug Interactions:**
Increased Effect/Toxicity: Monoclonal antibodies may increase the risk for allergic reactions to rituximab due to the presence of HAC antibody. Antihypertensive medications may exacerbate hypotension.
Decreased Effect: Currently recommended not to administer live vaccines during rituximab treatment. Inactivated vaccines should be complete at least 2 to 4 weeks prior to starting therapy. rituximab may

diminish the effects of sipuleucel-T.

Immunosuppressants: rituximab may enhance the adverse/toxic effects of immunosuppressants, including:certolizumab pegol, pimecrolimus, tacrolimus, fingolimod, leflunomide, natalizumab, roflumilast,and to a lesser extent of denosumab,ophthalmic chloramphenicol, trastuzumab.

Myelosuppressants: rituximab may enhance the adverse/toxic effects of myelosuppressants, including: abatacept, belimumab, clozapine, deferiprone, dipyrone, promazine, and tofacitinib.

15.47 **Known potential adverse events:** Consult the package insert for the most current and complete information. Refer to the package insert pertaining to the following boxed warnings: Severe infusion reactions; Progressive multifocal leukoencephalopathy (PML); Tumor lysis syndrome leading to acute renal failure; and severe and sometimes fatal mucocutaneous reactions (lichenoid dermatitis, paraneoplastic pemphigus, Stevens-Johnson syndrome, toxic epidermal necrolysis and vesiculobullous dermatitis).
Common known potential toxicities, > 10%: Cardiovascular: Peripheral edema, hypertension
Central nervous system: Fatigue, chills, neuropathy, headache, insomnia, pain
Dermatologic: Skin rash, pruritus, night sweats Endocrine & metabolic: Weight gain Gastrointestinal: Nausea, diarrhea, abdominal pain
Hematologic: Lymphocytopenia, anemia, leukopenia, neutropenia, thrombocytopenia, cytopenia, febrile neutropenia
Hepatic: ALT increased Hypersensitivity: Angioedema Immunologic: Antibody development Infection: Infection, bacterial infection
Neuromuscular & skeletal: Weakness, muscle spasm, arthralgia
Respiratory: Cough, rhinitis, epistaxis
Miscellaneous: Infusion related reaction, fever

Less common known potential toxicities, 1% - 10%: Cardiovascular: Hypotension, flushing
Central nervous system: Dizziness, anxiety, migraine, paresthesia
Dermatologic: Urticaria
Endocrine & metabolic: Hyperglycemia, increased lactate dehydrogenase
Gastrointestinal: Vomiting, dyspepsia Infection: Viral infection, fungal infection
Neuromuscular & skeletal: Back pain, myalgia,
Respiratory: Dyspnea, throat irritation, bronchospasm, upper respiratory tract infection, sinusitis

Rare known potential toxicities, <1% (Postmarketing and/or case reports):
Acute mucocutaneous toxicity, acute renal failure (associated with tumor lysis syndrome), acute respiratory distress, anaphylactoid reaction/anaphylaxis, angina pectoris, aplastic anemia, arthritis (polyarticular), bone marrow depression, bronchiolitis obliterans, cardiac

arrhythmia, cardiac failure, cardiogenic shock, encephalitis, fulminant hepatitis, gastrointestinal perforation, hemolytic anemia, hepatic failure, hepatitis, hypogammaglobulinemia (prolonged), hypoxia, increased serum immunoglobulins (hyperviscosity syndrome in Waldenstrom's macroglobulinemia), interstitial pneumonitis, intestinal obstruction, Kaposi's sarcoma (progression), laryngeal edema, lichenoid dermatitis, lupus-like syndrome, mucositis, myelitis, MI, nephrotoxicity, optic neuritis, pancytopenia, paraneoplastic pemphigus, pleurisy, pneumonia, pneumonitis, polymyositis, progressive multifocal leukoencephalopathy, pure red cell aplasia, reactivated pure red cell aplasia, reactivated tuberculosis, reactivation of HBV, reversible posterior leukoencephalopathy syndrome, serum sickness, Stevens-Johnson syndrome, supraventricular arrhythmia, toxic epidermal necrolysis, uveitis, vasculitis with rash, ventricular fibrillation, ventricular tachycardia, vesiculobullous dermatitis, viral reactivation (includes JC virus [PML], cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C), wheezing

15.48 **Drug procurement:** Investigational supply is provided free of charge to study participants by F. Hoffmann-La Roche.

F. Hoffmann-La Roche will supply investigational supply to McKesson. Each participating ACCRU treating location will order the drug from McKesson. Submit the Drug Order Request Form (found on the ACCRU web site) to:

McKesson
[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of rituximab and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.49a Temperature excursions that occur at the site should be reported by the site using the Genentech Temperature Excursion Form found on the ACCRU website for this study and emailed to: [redacted]

Any shipment deviations (those not occurring at the site) should be reported to McKesson via email to:
[redacted]

15.49b Nursing Guidelines

Do not administer as an IV push or bolus since it increases the risk of a hypersensitivity reaction.

Hypotension, bronchospasms, and angioedema have occurred in association with Rituxan infusion. Because of this it is recommended that patients be pre-medicated with acetaminophen and diphenhydramine before infusion. Stop infusion for severe reaction. Infusion may be restarted at 50% rate after resolution of symptoms. It is recommended that diphenhydramine, acetaminophen, epinephrine, bronchodilators, IV saline, and corticosteroids are available for immediate use in the event of a hypersensitivity reaction during administration.

Patients should be cautioned to withhold their anti-hypertensive medication for 12 hours prior to drug administration.

Patients with preexisting cardiac conditions including arrhythmias and angina have had recurrences of these events during Rituxan therapy and should be monitored throughout the infusion and immediate post-infusion period.

It has been found that patients with bulky disease (lesion >10 cm in diameter) have an increased incidence of adverse events. Monitor for signs and symptoms of tumor lysis syndrome, and acute renal failure.

An infusion-related symptom complex consisting of fever and chills/rigors occurs in the majority of patients during the first infusion. These reactions generally occur within 30 minutes to 2 hours of beginning the first infusion and resolve with slowing or stopping the infusion and giving supportive care. The incidence of adverse reactions decreased from 80% to 40% with subsequent infusions.

Cytopenias are common and can be long term. Monitor CBC. Instruct patient to report signs and symptoms of infection, excessive bruising and/or bleeding to the health care team.

GI disturbances (Nausea, abdominal pain and less commonly diarrhea, vomiting, dyspepsia) headache, and weakness are common side effects. Treat as necessary. Monitor for effectiveness.

Adequate birth control measures should be used during therapy and for 12 months following therapy. Women should not breastfeed while drug is detectable in serum.

15.49c Endocrine and metabolic disturbances can be seen (hyper/hypoglycemia, hypocalcemia, hypocholesterolemia, hyperphosphatemia, hyperuricemia. Monitor labs and for signs or symptoms of these conditions. Treat accordingly.

16.0 **Statistical Considerations and Methodology**

16.1 Overview:

This is a single arm Phase II study of combination of polatuzumab vedotin, venetoclax

and rituximab and hyaluronidase human in patients with relapsed or refractory mantle cell lymphoma (MCL). The relapsed/refractory MCL patient population will include both ibrutinib-naive and ibrutinib-pretreated patients. An early safety analysis will be conducted in patients with B cell NHL who have relapsed or progressed after at least one line of therapy prior to continuing accrual in this phase II study.

16.11 Primary Endpoint: The primary endpoint of this trial is the complete response rate at the end of induction by PET-CT scans according to Lugano 2014. A complete response will be considered synonymous with "success", unless specified otherwise. All patients meeting the eligibility criteria, who have signed a consent form and have begun treatment, will be evaluable for response, unless they are determined to be a major violation.

16.2 Statistical Design

16.21 Decision Rule: The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 15%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 35%. The following one-stage design with an interim analysis is based on a two-stage Simon optimum design[2] and requires 46 evaluable patients to test the null hypothesis that the true success proportion in this patient population is at most 15%.

16.211 Interim Analysis: Enter 16 evaluable patients into the study. If 3 or fewer successes are observed in the first 16 evaluable patients, we will consider this regimen ineffective in this patient population and terminate the study. Otherwise, if the number of successes is at least 4, we will continue accrual.

16.212 Final Decision Rule: Enter an additional 30 evaluable patients into the study. If 10 or fewer successes are observed in the first 46 evaluable patients, we will consider this regimen ineffective in this patient population and terminate the study. Otherwise, if the number of success is at least 11, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies in this population.

16.213 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision-making process. Analysis involving over accrued patients is discussed in section 16.313.

NOTE: We will not suspend accrual at the interim analysis to allow the first 16 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an AE stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety data on these patients before re-opening accrual to further patients.

16.214 Dose de-escalation in safety analysis: A safety analysis will be performed in the first 6 evaluable patients per Section 16.4. In the case of unacceptable toxicity, the dose will be de-escalated. If this occurs, the first 6 patients will be evaluated separately and will not be included in any decision-making criteria.

16.22 Sample Size: The one stage design with an interim analysis to be utilized is fully described above. A minimum of 16 and a maximum of 46 evaluable patients with MCL will be accrued onto this phase II study unless undue toxicity is encountered. Patients with MCL treated at the final dose level in the early safety analysis will be included in phase II. If dose de-escalation is required during the safety analysis, an additional 6 evaluable patients will be accrued per section 16.4. We anticipate accruing an additional 5 (10%) patients to account for ineligibility, cancellation, major treatment violation, or other reasons for a total of up to 57 patients. If none of the six patients with B cell NHL enrolled in safety portion are MCL, the total sample size will be 63 patients.

16.23 Accrual Rate and Study Duration: The anticipated accrual rate is 2-3 evaluable MCL patients per month. At this rate, it will likely take about 2 years to enroll the patients. The maximum total study duration is expected to be approximately 5 years, or until the last patient accrued has been observed for at least 3 years. The earliest date anticipated for presentation of results is at approximately 2.5 years for the primary endpoint, or when the last patient accrued has been observed for at least 6 months.

16.24 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .05, i.e. there is a 5% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) and the probability of stopping at the interim analysis under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is…	0.15	0.20	0.25	0.30	0.35
Then the probability of declaring that the regimen warrants further studies is…	0.049	0.212	0.467	0.700	0.851
And the probability of stopping at the interim analysis is…	0.790	0.598	0.405	0.246	0.134

16.25 Other Considerations: AEs, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan

The analysis for this trial will commence at planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. The Statistician and Study Chair will make the decision, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of

data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when last patient has been followed for at least 6 months.

16.31 Primary Outcome Analysis

16.311 Definition: The primary endpoint of this trial is the complete response rate at the end of induction as determined by investigator on the basis of PET-CT scans according to Lugano 2014. A complete response is defined as an objective status of CR at the end of induction. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation. Only MCL patients treated at the final dose level will be included when evaluating the decision rules in Sections 16.211 and 16.212. Patients without MCL and patients treated at other dose levels will be summarized separately.

16.312 Estimation: The proportion of success will be estimated by the number of success divided by the total number of evaluable patients. 95% confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner[3].

16.313 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision-making process; however, they will be included in final point estimates and confidence intervals.

16.32 Secondary Outcome Analysis

16.321 The overall response rate (ORR) at the end of induction will be estimated by the total number of patients who achieve a CR or PR by PET-CT scans according to Lugano 2014 divided by the total number of evaluable patients. All evaluable patients will be used for this analysis. Exact binomial 95% confidence intervals for the true overall response rate will be calculated. The ORR between ibrutinib-naive and ibrutinib-pretreated patients will be compared using Fisher's exact test.

16.322 The Best Response Rate to maintenance therapy will be evaluated. CR, PR and SD rates for patients who continue to maintenance will be estimated by number of patients who continue on maintenance therapy and achieve CR, PR or SD, respectively, at the end of maintenance divided by the total number of evaluable patients who continue to maintenance. Conversion rate from PR to CR will be evaluated by the number of patients achieving CR at EOM divided by the total number of patients who continue to maintenance in PR. Conversion rate from SD to PR or SD to CR will be evaluated by the number of patients achieving PR or CR, respectively at EOM divided by the total number of patients who continue to maintenance in SD.

16.323 Progression free survival (PFS) is defined as the time from registration to the earliest date of documentation of disease progression by CT or

PET/CT or death due to any cause. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier[4]. The PFS between ibrutinib-naive and ibrutinib-pretreated patients will be compared using log-rank test.

16.324 Overall survival (OS) is defined as the time from registration to death due to any cause. The distribution of OS will be estimated using method of Kaplan-Meier. The OS between ibrutinib-naive and ibrutinib-pretreated patients will be compared using log-rank test.

16.325 AEs: All eligible patients that have initiated treatment will be considered evaluable for assessing AE rate(s). The maximum grade for each type of AE from each patient will be used for analysis, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the AE(s) to the study treatment will be taken into consideration.

16.326 Correlative Analysis: Due to the small overall sample size, the results of these analyses will be considered exploratory and hypothesis- generating in nature.

16.327 MRD Analysis: MRD will be assessed on whole blood using the Roche panel at pre-treatment, end of induction, and end of maintenance. MRD status for both responders and non-responders at each time point will be reported descriptively and explored for correlation with clinical factors and patient outcomes such as PFS and OS. Changes in MRD status from baseline to end of induction and end of maintenance will also be summarized.

16.328 T cell and cytokine subsets: Systemic immune profiles and T cell activation will be investigated using multi-parameter flow cytometry, and cytokine analysis in the peripheral blood of patients at the following timepoints: a) pre-treatment, b) early in treatment (cycle 3), c) end of induction (cycle 7), d) end of maintenance year 1 (cycle 18), f) end of maintenance year 2. The results from T cell and Cytokine subsets analysis will be reported descriptively by median, min, max, and interquartile range.

16.329 High risk cytogenetic alterations and other risk stratification scores will be summarized using frequency and percentages.

16.4 Early Safety Analysis

The first cohort of three patients will be treated at the starting dose level of Venetoclax (400 mg days 1-21) and observed for at least 63 days (3 cycles) from the start of treatment to assess toxicity. If significant toxicity as defined in section 7.7 is observed in 0 or 1 of these 3 patients, 3 new patients will be accrued and treated at same dose level of Venetoclax (400 mg days 1- 21) and observed for 3 cycles. After enrolling 6 patients on Venetoclax dose level of 400 mg days 1-21, if ≤1 patient experience significant toxicity, then this dose will be considered safe and rest of the patients in expansion cohort will be treated at this dose level of Venetoclax.

However, if 2 or more out of the first 3 or 6 patients experience significant toxicity, then the dose of venetoclax may be de-escalated to 300 mg days 1-21 (Dose Level -1, Table 8.21). In this case, another safety analysis using similar 3+3 design approach will be conducted at the reduced dose level of venetoclax.

Safety will be assessed through summaries of adverse events and changes from baseline laboratory results. All adverse events occurring on or after first study treatment will be summarized by NCI CTCAE v5.0 grade. Deaths reported during the treatment period and during post-treatment follow-up will be listed and summarized.

16.5 Data & Safety Monitoring

16.51 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, AE, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. We note that the AE Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the AE profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected AE profiles that have not crossed the specified rule below.

16.521 Safety Cohort: By the nature of the "cohorts of three" safety portion, stopping rules are in place for dose level of Venetoclax. Specifically, if 2 or more significant toxicities are observed during cycle 3 at the given dose level, accrual to that dose level will be stopped, and patients will be accrued to the next lower dose level until a maximum of 6 patients are treated at the lower level. Note that significant toxicities that affects dose de-escalation is only that which is observed in the first three cycles of treatment. However, all cycles will be reviewed, and the study team will determine whether the dose level needs to be adjusted for future patients if patients experience a Grade 4 or higher non- hematologic adverse event over all cycles at any given dose level unless it is considered definitely unrelated to treatment.

16.522 Expansion Cohort: Accrual will be temporarily suspended to this study as documented below in both the safety run in and the full study population if at any time, we observe events considered at least possibly related to study treatment (i.e. an AE with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- If 4 or more patients in the first 12 treated patients experience a grade 4 non-hematologic AE at least possibly related to treatment
- If after the first 12 patients have been treated, 30% of all patients experience a grade 4 non-hematologic AE at least possibly related to treatment.
- If 4 or more patients in the first 12 patients require discontinuation of therapy due to grade 3-4 hematologic AE of at least possibly related to

treatment
- If after the first 12 patients are treated 30% of all patients require discontinuation of therapy due to grade 3-4 hematologic AE
- If 2 patients experienced a grade 5 AE, at least possibly related to treatment.

We note that we will review grade 4 and 5 AEs deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related AE.

Note: If safety analysis fails in first 6 patients, those patients will not be used to evaluate the stopping rule. in expansion cohort.

16.6 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on [redacted] For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 2.5 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time all patients registered have achieved a confirmed complete response during induction or have completed induction treatment without achieving a confirmed complete response.

16.7 Subset Analysis for Minorities

16.71 Study availability: This study will be available to all eligible patients, regardless of gender, race or ethnic origin.

16.72 Statistical analysis by subset: There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.73 Regional population: The geographical region served by MCCC has a population which includes approximately 5% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 5-7% of patients will be classified as minorities by race and about 25% of patients will be women.

Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	1	3	0	4
Not Hispanic or Latino	15	44	0	59
Ethnic Category: Total of all Patients *	16	47	0	63
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0

Black or African American	1	4	0	5
Native Hawaiian or other Pacific Islander	0	0	0	0
White	15	43	0	58
Racial Category: Total of all Patients*	16	47	0	63

Ethnic Categories:
Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
Not Hispanic or Latino Racial Categories:
American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission

NOTE: Patients must have consented to submission of the optional tissue(s) listed in the following table.

17.11 Summary Table of Tissue Biospecimens for This Protocol

Type of tissue biospecimen to submit	Mandatory or optional	When to submit
Formalin-fixed paraffin- embedded (FFPE) tissue blocks with corresponding H&E (OR unstained slides with corresponding H&E)	Mandatory	Within 30 days of registration
Viably cryopreserved core needle biopsy	Optional	Within 30 days of registration
Formalin-fixed paraffin- embedded (FFPE) tissue blocks with corresponding H&E (OR unstained slides with corresponding H&E)	Optional	End of cycle 1
Viably cryopreserved core needle biopsy	Optional	End of cycle 1
Formalin-fixed paraffin- embedded (FFPE) tissue blocks with corresponding H&E (OR unstained slides with corresponding H&E)	Optional	Progression

Viably cryopreserved core needle biopsy	Optional	Progression

NOTE: Viably cryopreserved core needle biopsy is preferred when possible. However, FFPE and/or viably cryopreserved core needle biopsies will be accepted.

17.2 All Diagnostic Slides from initial and relapse confirmatory biopsy original and/or recurrent tissue

17.2.1 Paraffin Embedded Tissue Blocks/Slides

17.2.1.1 Submit one formalin fixed paraffin embedded (FFPE) tumor tissue block with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection) (from original and recurrent) surgery. Please submit biopsy material from each surgery if available. Submission of materials from at least one biopsy is required.

17.2.1.2 The FFPE tissue block is preferred; however, **if an institution is unable to provide a tissue block**, cut 15 five-micron sections and mount on charged glass slides. **Label the slides with ACCRU patient ID number, accession number, and order of sections.** The unstained slides will be processed as described in 17. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. **Do not bake or place covers slips on the slides.**

17.2.1.3 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- Paraffin embedded tissue blocks OR 15 unstained slides
- Research Tissue Specimen Submission Form
- Surgical Pathology Report

Note: Please include the ACCRU patient ID number on all materials listed above. Please do not place sticky labels on slides.

17.2.1.4 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials.

17.2.1.5 Tissue specimens must be shipped ≤ 30 days after registration.

17.2.1.6 Verify that the appropriate sections of the Tissue Specimen Submission Form are completed and filled in correctly. Enter information from the Tissue Specimen Submission Form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).

17.2.1.7 Ship all **block/slide tissue specimens** and accompanying materials to the ACCRU Research Base (**no frozen tissue**):

ACCRU Operations Office

[redacted]

17.2.1.8 Assessment of tissue quality will occur at the time the translational studies are performed.

17.2.1.9 After the pathologist assesses the tissue quality, the block and appropriate paperwork will be returned to the ACCRU Operations Office.

17.2.1.10 When an appropriate request is submitted, the ACCRU Operations Office will forward the block/slides to the ACCRU Research Base PRC Shared Resource, Stabile 13-10B, Mayo Clinic Rochester (Attn: PRC Supervisor) for processing as outlined in Section 17.

17.3 Frozen Tumor tissue

17.31 Submit one core from optional biopsies for viable cryopreservation.

17.32 Viably cryopreserved one core in fetal bovine serum with 10% dimethyl sulfoxide (DMSO) in a screw cap cryovial. Store in vapor phase of liquid nitrogen.

17.33 Ship all **frozen tissue specimens** and accompanying materials to the Mayo Clinic BAP Freezer:

[redacted]

17.4 Study Methodology and Storage Information

17.41 Submitted tissue samples will be analyzed as follows: Tissue will be stored for future analysis.

17.42 At the completion of the study, any unused/remaining material will be stored in the ACCRU Central Operations Office (Attn.: Pathology Coordinator) for future research according to the patient consent permission. Potential future research may include immunohistochemistry (IHC) analyses to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval.

17.43 Banking of tumor tissue, according to the patient consent permission is for future research. As protocols are developed, they will be presented for ACCRU and IRB review and approval.

17.44 The institutional pathologist will be notified by the Pathology Coordinator if the block may be depleted.

17.45 Blocks requested to accommodate individual patient management will be returned promptly upon request.

17.46 Return of Genetic Testing Research Results: No genetic specimens will be collected from tissue biospecimens for this study. If future genetic testing is being requested for stored tissue, patient reconsent is required.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Survival Follow-up

See Section 4.

18.3 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on the organization roster at the enrolling site.

18.4 Site responsibilities

Each site will be responsible for ensuring that all materials contain the patient's initials, ACCRU registration number, and ACCRU protocol number. All PHI must be redacted from any documentation.

18.5 Supporting documentation

Upload a copy of documentation of response or progression in RAVE on the Supporting Documentation Form.

Baseline: The following documents are required for diagnosis and eligibility verification: Imaging report, Pathology report, and Lab report. These documents should be submitted within 14 days of registration.

At patient progression or restaging for evidence of response: Imaging report, Pathology report, Operative report, Lab report, Clinic note, etc.

18.6 Labeling of materials

Each site will be responsible for ensuring that all materials contain the patient's initials, ACCRU registration number, and ACCRU protocol number. Patient's name must be

removed.

18.7 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition to this, the Overdue Materials report is available on the ACCRU website. Only site staff rostered with the Rave CRA role will have access to these reports.

All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. Access the RAVE RDE system through the iMedidata portal at [redacted] All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions [redacted]

19.0 Budget

Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

20.0 References

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Appendix I: Sample List of Excluded and Cautionary Medications for Patients treated with of polatuzumab vedotin, venetoclax, and rituximab and hyaluronidase human

Type	Medication
Excluded during the venetoclax ramp-up period and cautionary after patients are on 400 mg/day of venetoclax	
Strong CYP3A inducers	Avasimibe, carbamazepine (Tegretol), phenobarbital, phenytoin (Dilantin), rifampin (Rifadin), and St. John's wort
Moderate CYP3A inducers	Bosentan, efavirenz, etravirine, modafinil, and nafcillin
Strong CYP3A inhibitors [a]	Boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole
Moderate CYP3A inhibitors [a]	Amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib[b], darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib [b], and verapamil
Cautionary throughout the study	
Warfarin	
Weak CYP3A inducers	Amprenavir, aprepitant, armodafinil, clobazamechinacea, pioglitazone, prednisone, rufinamide, and vemurafenib [b]
Weak CYP3A inhibitors	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide[b], cilostazol, cimetidine, cyclosporine [b], fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib[b], oral contraceptives, pazopanib[b], ranitidine, ranolazine, tipranavir/ritonavir, ticagrelor, and zileuton
P-gp substrates	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus[b], fexofenadine, lapatinib[b], loperamide, maraviroc, nilotinib[b], ranolazine, saxagliptin, sirolimus[b], sitagliptin, talinolol, tolvaptan, and topotecan [b]
BCRP substrates	Methotrexate[b], mitoxantrone[b], irrinotecan[b], lapatinib[b], rosuvastatin, sulfasalazine, and topotecan[b]
OATP1B1/1B3 substrates	Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, and olmesartan
P-gp inhibitors	Amiodarone, azithromycin, captopril, carvedilol, dronedarone, felodipine, quercetin, ronalzine, and ticagrelor

Appendix II: Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

FIRST DOSE OF VENETOCLAX OR DOSE ESCALATION

- Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- Intravenous (IV) fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150−200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of tumor lysis syndrome (TLS) (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.
- Vital signs should be taken at time of all blood draws or any intervention.
- 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.

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

- For potassium increase ≥ 0.5 mmol/L from baseline, or any value > 5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT and follow first guideline.
- 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 within 1 hour STAT.

Appendix III: Prophylaxis and Management of Tumor Lysis Syndrome for Patients Being Treated with venetoclax

TLS is a risk for patients with CLL who are treated with high cell-killing agents like venetoclax. . Clinical data from patients with CLL treated to date with venetoclax suggest that patients with baseline lymph nodes ≥ 5 cm diameter are at a greater risk for TLS than those with baseline lymph nodes < 5 cm. In addition, the data showed that CrCl of ≤ 80 mL/min at screening was a secondary risk factor for TLS. A detailed description of risk factors for developing TLS following treatment with venetoclax is available in the venetoclax Investigator's Brochure.

Based on the data review performed by the Sponsors, the following three risk categories for developing TLS after treatment with venetoclax were defined (see Table 8). These risk groups were developed using assessments of nodal disease burden obtained from imaging tests performed at screening in several other studies of venetoclax in CLL. Therefore, assigning a patient's TLS risk MUST be made based on an imaging test performed at screening. Assessments of TLS risk categorization and monitoring/prophylaxis guidance is being continuously assessed throughout the venetoclax program, and future updates to these guidelines are possible.

Table 8 Risk Categories for Developing Tumor Lysis Syndrome

TLS Risk Category	Definition
Low	All measurable lymph nodes with the largest diameter < 5 cm and < 25×10^9/L ALC. Lymph node size will be determined by radiologic assessment.
Medium	Any measurable lymph node with the largest diameter ≥ 5 cm but < 10 cm OR ≥ 25×10^9/L ALC. Lymph node size will be determined by radiologic assessment.
High	Any measurable lymph node with the largest diameter ≥ 10 cm or the presence of both ≥ 25×10^9/L ALC AND any measurable lymph node with the largest diameter ≥5 cm but <10 cm. Lymph node size will be determined by radiologic assessment.

ALC=absolute lymphocyte count; CT=computed tomography; MRI=magnetic resonance imaging; TLS= tumor lysis syndrome.

TLS Risk Assessment MUST be made based on measurements of nodal disease burden based on radiologic assessments (CT scan or MRI) performed during the screening period.

All patients enrolling in the study will be assessed at screening and categorized in a risk category as described above. Investigators may reassess patient's TLS risk after they start treatment and may assign them to a lower risk group. For example, patients classified as TLS high-risk at screening because of an ALC of ≥ 25×10^9 AND a measurable lymph node with the largest diameter ≥ 5 cm but < 10 cm by radiologic assessment may have a re-evaluation of their TLS risk category based on their most recent ALC after initiating study treatment. If the patient's ALC decreases to < 25×10^9/L, the patient may be categorized as TLS medium-risk and may follow the management guidelines for the TLS medium-risk category at subsequent visits and during the venetoclax ramp-up period. Re-assessment of the patient's TLS risk category can occur continuously during Cycle 1 and the venetoclax dose ramp-up period. If a patient is re-assigned to a lower risk group, the investigator may follow the prophylaxis guidance for the lower risk group to which they are assigned.

However, patients who are classified as high-risk because they have a lymph node with largest diameter ≥ 10 cm MAY NOT have their TLS risk re-assessed and should follow the prophylaxis plan for high-risk patients throughout the venetoclax ramp-up period.

Patients who develop signs or symptoms of TLS regardless of the risk group to which they were assigned may have additional monitoring at subsequent visits at the investigator's discretion.

This section describes the management of patients throughout dosing given their risk factors for developing TLS identified upon study entry.

Table 9 Summary of Tumor Lysis Syndrome Prophylaxis for venetoclax and Monitoring Measures

TLS Risk Category	**Day 1 of Dose Level**	**Prophylaxis Medication**	**Hospitalization**	**Hydration [a]**	**Laboratory Assessments [b, e]**
TLS low-risk	20, 50, 100, 200, 400 mg	Oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the end of the ramp-up period with venetoclax is completed (C3D1).	No	Oral hydration of 1.5-2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose.	Hematology and chemistry samples will be taken predose and 8 and 24 hours after dosing. Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0 4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS at the 8 and 24 hours after dosing timepoints. The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day. The investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

Table 9 Summary of Tumor Lysis Syndrome Prophylaxis for venetoclax and Monitoring Measures (cont.)

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hospitalization	Hydration [a]	Laboratory Assessments [b, e]
TLS medium- risk	20 and 50 mg	Oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the end of the ramp up period with venetoclax is completed (C3D1).	No [c,d]	Oral hydration of 1.5-2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose. In addition to oral hydration, IV hydration (1.5-2 L) will be given in the outpatient setting during the clinic stay.	Hematology and chemistry samples will be taken predose and 8, and 24 hours after dosing timepoints. Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0-4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS at the 8 and 24 hours after dosing timepoints. The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day. The investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.
	100, 200, 400 mg	Continue oral uric-acid reducer as above.		Oral hydration of 1.5-2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose.	

Table 9 Summary of Tumor Lysis Syndrome Prophylaxis for venetoclax and Monitoring Measures (cont.)

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hospitalization	Hydration [a]	Laboratory Assessments [b, e]
TLS high-risk	20 and 50 mg	Oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the first week of combination therapy with venetoclax is completed. Rasburicase must be administered per regional standards/institutional guidelines as prophylaxis prior to the first dose of venetoclax for high-risk patients with high uric acid levels at pre-dose (above the local laboratory ULN or the Howard et al. [2011] threshold of 8 mg/dL (475.8 mol/L). For patients with a contraindication to rasburicase (i.e., glucose 6 phosphate dehydrogenase deficiency), the TLS risk-mitigation plan must be reviewed with the Medical Monitor. Uric acid levels following treatment with rasburicase must be analyzed using specific guidelines	Yes [d]	Oral hydration of 1.5-2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose. Upon hospital admission, IV hydration should be started with a target of approximately 2-3 L per day or as clinically appropriate.	Hematology and chemistry samples will be taken predose and 8, 12, and 24 hours after dosing. Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0-4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS. The investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

Table 9 Summary of Tumor Lysis Syndrome Prophylaxis for venetoclax and Monitoring Measures (cont.)

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hospitalization	Hydration [a]	Laboratory Assessments [b, e]
TLS high-risk	100, 200, 400 mg	Continue oral uric acid reducer as above	No [c,d]	Oral hydration of 1.5-2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose. In addition to oral hydration, IV hydration (1.5-2L) will be given in the outpatient setting during the clinic stay.	Patients who are not hospitalized at these timepoints will have hematology and chemistry samples taken predose and 8 and 24 hours after dosing. Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0-4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS. The investigator or subinvestigator must review the 24- hour laboratory results prior to dosing on the next day. Patients who are hospitalized at these timepoints will have chemistry and hematology samples obtained predose, 8, 12, and 24 hours postdose. These results must be reviewed promptly by the investigator or subinvestigator. The 24 hour postdose laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug.

Table 9 Summary of Tumor Lysis Syndrome Prophylaxis for venetoclax and Monitoring Measures (cont.)

C = cycle; CrCl = creatinine clearance; D = day; IV = intravenous; TLS = tumor lysis syndrome; ULN = upper limit of normal.

[a] For patients unable to maintain oral hydration at 1.5-2 L/day starting at least 48 hours prior to the start of treatment, IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended (unless being hospitalized) in order to assure that this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

[b] For laboratory samples drawn on days of study treatment, "predose" laboratory samples should be drawn within 0-4 hours before the dose. Other laboratory samples occurring on the same day should be obtained within a ± 15-minute window of any exact scheduled time. Any laboratory tests occurring at time intervals greater than or equal to 24 hours after dose should be obtained within a ± 2-hour window of the scheduled time. If it is not possible to review a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0-4 hours prior to dosing) laboratory samples should still be drawn, and these will serve a baseline for later laboratory values when assessing for laboratory evidence of TLS.

[c] Patients with CrCl < 80 mL/min and/or who have a higher tumor burden (defined per the discretion of the investigator) may be handled as TLS high-risk patients.

Currently, limited clinical experience has been gained with venetoclax in patients with CrCl 30-50mL/min. Therefore, these patients should receive additional consideration by the investigator with regard to their management, including the decision on whether to administer IV hydration and to hospitalize the patient to facilitate monitoring and expedite response to electrolyte changes at initial dosing as well as at each first dose during the ramp-up period.

[d] Nephrology (or acute dialysis service) consultation should be considered on admission (per institutional standards or based on investigator discretion) for hospitalized patients to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.

[e] Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have subsequent venetoclax dose withheld until the electrolyte abnormalities resolve.

Patients who develop electrolyte abnormalities should undergo aggressive management and further monitoring per Appendix 4. Any time during the ramp-up period, if venetoclax was withheld for 7 days or less, the patient may resume venetoclax at the same dose level or at one lower dose-level as determined by the investigator based on a risk assessment (including tumor burden status). The dose must be resumed at one lower dose-level if dose was withheld more than 7 days, with the exception of initial

► ► ► ►

Initial Doses: venetoclax 20 and 50 mg

All patients, irrespective of their TLS risk category at the first dose of venetoclax, must receive the following TLS prophylaxis measures prior to the initiation of the first doses of venetoclax:

- Administration of an oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued to the end of the venetoclax ramp-up period (Cycle 3, Day 1).
- Oral hydration consisting of fluid intake of approximately 1.5−2 L/day starting at least 48 hours prior to the start of treatment and continued for at least 24 hours after the first dose
- Serum chemistry and hematology laboratory samples must be drawn prior to administering venetoclax (predose). If clinically significant laboratory abnormalities are observed in this baseline laboratory assessment, the first dose of venetoclax must be delayed until resolution and management per the protocol and recommendations for Initial Management of Electrolyte Imbalances and Prevention of TLS must be initiated. If needed, patient should receive additional prophylactic treatment prior to the initiation of dosing.

  Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0−4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS.

Additional TLS prophylaxis and monitoring procedures are tailored to the individual TLS risk category as follows.

TLS Low Risk

- Low-risk patients will receive their initial doses of 20 and 50 mg venetoclax as outpatients.
- For patients unable to maintain oral hydration at 1.5−2 L/day starting at least 48 hours prior to the start of treatment, IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended in order to assure that this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.
- Serum chemistry, hematology, and vital signs will be obtained prior to administering venetoclax (predose) and 8 and 24 hours after dosing. Laboratory samples should be sent and analyzed immediately.

  Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0−4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when

assessing for laboratory evidence of TLS.

The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

Additional laboratory assessments may be performed per investigator discretion.

TLS Medium Risk

- Medium-risk patients who have CrCl ≥ 80 mL/min will receive their initial doses of 20 and 50 mg venetoclax as outpatients. Patients with CrCl < 80 mL/min and/or who have higher tumor burden (defined per the discretion of the investigator) may be handled as High-Risk patients (see the High Risk section for details of hydration, laboratory, etc.).
- In addition to oral hydration stated above, IV hydration (1.5−2 L) will be given in the outpatient setting during the clinic stay. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.
- Serum chemistry, hematology, and vital signs will be obtained prior to administering venetoclax (predose) and 8 and 24 hours after dosing timepoints. Laboratory samples should be sent and analyzed immediately.

  Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0−4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS.

  The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

  Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

  Additional laboratory assessments may be performed per investigator discretion.

TLS High Risk

- High-risk patients will be hospitalized to receive their initial doses of 20 and 50mg venetoclax. Hospitalization will begin the evening prior to each initial dose of venetoclax and continue for 24 hours after each dose.
- Upon admission, serum chemistry and hematology laboratory samples should be drawn, and IV hydration should be started with a target of 2−3 L per day or as clinically appropriate.
- Rasburicase must be administered per regional standards/institutional guidelines as prophylaxis prior to the first dose of venetoclax for high-risk patients with high uric acid levels at pre-dose (above the local laboratory ULN or Howard et al. [2011] threshold of 8 mg/dL [475.8 µmol/L]). For patients with a contraindication to rasburicase (i.e., glucose-6-

phosphate dehydrogenase deficiency), the TLS risk-mitigation plan must be reviewed with the Medical Monitor. Uric acid levels following treatment with rasburicase must be analyzed using specific guidelines described in the following:

Please note that at room temperature, rasburicase causes enzymatic degradation of the uric acid in blood, plasma, and serum samples, which could potentially result in spuriously low plasma uric acid assay readings. The following special sample handling procedure must be followed to avoid ex vivo uric acid degradation:

Uric acid must be analyzed in plasma.

Blood must be collected into prechilled tubes containing heparin anticoagulant. Immediately immerse plasma samples for uric acid measurement in an ice water bath.

Plasma samples must be prepared by centrifugation in a precooled centrifuge (4°C).

The plasma must be maintained in an ice water bath and analyzed for uric acid within 4 hours of collection.

- Nephrology (or acute dialysis service) consultation should be considered on admission (per institutional standards or based on investigator discretion) for hospitalized patients to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.
- Serum chemistry, hematology, and vital signs will be obtained prior to administering venetoclax (predose) and at 8, 12, and 24 hours after dosing. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator.

Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0−4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS.

The 24-hour post-dose laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug.

Additional laboratory assessments may be performed per investigator discretion.

Subsequent Dose Increases during the venetoclax Ramp-Up Period 100, 200, and 400 mg venetoclax

All patients, irrespective of their risk category, must receive the following TLS prophylaxis measures prior to subsequent dose increases of venetoclax:

- Continued administration of an oral uric acid reducer as indicated above.
- Oral hydration consisting of fluid intake of approximately 1.5−2 L/day starting at least 48 hours prior to dosing. IV hydration is encouraged at subsequent dose increases for patients

unable to maintain such oral hydration. IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended in order to assure this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

- Serum chemistry and hematology laboratory samples must be drawn prior to administering venetoclax (predose). If clinically significant laboratory abnormalities are observed in this laboratory assessment, dose of venetoclax must be delayed until resolution, and management per the protocol, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome, must be initiated. If needed, patient should receive additional prophylactic treatment prior to the initiation of dosing.

  Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0 to 4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS.

  Additional TLS prophylaxis and monitoring procedures are tailored to the individual TLS risk category as follows.

TLS Low Risk

- Low-risk patients will receive the subsequent dose increases (100, 200, and 400 mg venetoclax) as outpatients.
- Serum chemistry, hematology, and vital signs will be obtained prior to administering venetoclax (predose) and at 8 and 24 hours after dosing. Laboratory samples should be sent and analyzed immediately.

  Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0 to 4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS.

  The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

  Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

  Additional laboratory assessments may be performed per investigator discretion.

TLS Medium Risk

- Medium-risk patients who have CrCl ≥ 80 mL/min will receive their subsequent dose increases as outpatient. Patients with CrCl < 80 mL/min and/or who have high tumor burden (defined per the discretion of the investigator) may be hospitalized.
- For patients who receive this subsequent dose increases as outpatient, serum chemistry, hematology, and vital signs will be obtained prior to administering venetoclax (predose) and at 8 and 24 hours after dosing. Laboratory samples should be sent and analyzed immediately.

  Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0 to 4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS.

  The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

  Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

  Additional laboratory assessments may be performed per investigator discretion.
- For patients hospitalized during subsequent dose increases, serum chemistry, hematology, and vital signs will be obtained prior to dosing (predose, defined as up to 4 hours before venetoclax dose) and 8, 12, and 24 hours after dosing. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. The 24-hour after dosing laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug.
- IV hydration should be started with a target of approximately 2−3 L per day oras clinically appropriate for patients who are hospitalized.

TLS High Risk

- High-risk patients with CrCl of ≥ 80 mL/min will receive the subsequent dose increases as outpatients. Patients with CrCl < 80 mL/min and/or high tumor burden (defined per the discretion of the investigator) may be hospitalized. Hospitalization will begin the evening prior to the dose of venetoclax and continue for 24 hours after the dose.
- IV hydration (1.5−2 L) will be given in the outpatient setting during the clinic stay. For patients who are hospitalized, IV hydration should be started with a target of approximately 2−3 L per day or as clinically appropriate.
- For patients who are not hospitalized, serum chemistry, hematology, and vital signs will be obtained prior to administering venetoclax and at 8 and 24 hours after dosing timepoints. Laboratory samples should be sent and analyzed immediately.

  Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry

sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0 to 4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS.

The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

- For patients who are hospitalized during subsequent dose increases, serum chemistry, hematology, and vital signs will be obtained prior to dosing (predose, defined as up to 4 hours before venetoclax dose) and 8, 12, and 24 hours after dosing. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. The 24-hour after dosing laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug.

  Additional laboratory assessments may be performed per investigator discretion.

Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have his or her subsequent venetoclax dose withheld until the electrolyte abnormalities resolve. Patients who develop electrolyte abnormalities should undergo aggressive management and further monitoring per Appendix II, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome. Any time during the ramp-up period, if venetoclax was withheld for 7 days or less, the patient may resume venetoclax at the same dose level or at one lower dose level as determined by the investigator based on a risk assessment (including tumor burden status). The dose must be resumed at one lower dose-level if interruption lasted more than 7 days, with the exception of the initial dose level of 20 mg (400 mg → 200 mg, 200 mg → 100 mg, 100 mg → 50 mg, 50 mg → 20 mg). All patients must receive the intended dose for at least 7 days before increasing to the next ramp-up dose.

For patients who are at high risk of TLS:

- Hospitalized patients should receive TLS prophylaxis as described above for initial venetoclax dosing. Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards) to ensure emergency dialysis is available and the appropriate staff are aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.

Appendix IV: Guidelines for Defining Tumor Lysis Syndrome

Howard et al. (2011) defined laboratory tumor lysis syndrome as the presence of two or more electrolyte changes above or below the thresholds described above occurring during the same 24-hour period within 3 days before the start of therapy or 7 days after the start of therapy. For the purposes of this study, this window applies to the initiation of any study therapy and each dose escalation of venetoclax. Furthermore, this assessment assumes that a patient has or will receive adequate hydration (±alkalinization) and a hypouricemic agent(s).

Howard Definition of Laboratory Tumor Lysis Syndrome

Laboratory Assessment	Range
Uric acid	>476 µmol/L (>8.0 mg/dL)
Potassium	>6.0 mmol/L (>6.0 mEq/L)
Phosphorous	>1.5 mmol/L (>4.5 mg/dL)
Corrected calcium	<1.75 mmol/L (<7.0 mg/dL) or ionized calcium <1.12 (0.3 mmol/L) [a]

Note: Howard et al. (2011) defined laboratory tumor lysis syndrome as the presence of two or more electrolyte changes above or below the thresholds described above occurring during the same 24-hour period within 3 days before the start of therapy or 7 days afterward. For the purposes of this study, this window applies to the initiation of any study therapy and each dose escalation of venetoclax. Furthermore, this assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricemic agent(s).
a The corrected calcium level in mg/dL is the measured calcium in mg/dL +(0.8 x[4-albumin in g/dL]).

Appendix V: ACCRU-LY-1806 SUBJECT MEDICATION DIARY

Name:	Subject ID Number:
Cycle:	
You will take:	

ORAL MEDICATION DIARY

Subject Instructions

- Please bring your Medication Diary and any empty or unused medication container(s) with you to every appointment
- Please use an ink pen when completing the Medication Diary as these will be retained in our research record.
- Please contact your physician and study coordinator any time you go into the hospital. Your physician can advise if you should continue or stop taking your medication.
- To correct a mistake, please make a single line through that entry and write your initials and the date next to the mistake.
- Please indicate on the calendar on the next page that you took your study medication by recording the date and dose taken on the line under the date.
- If you miss a dose, place a "0" under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- If you accidentally take more than you are instructed to, contact your doctor or the emergency room immediately.
- If you miss a dose of venetoclax within 8 hours of the time it is usually taken, you should take the missed dose as soon as possible and resume the normal daily dosing schedule. If you miss a dose by more than 8 hours, you should not take the missed dose and should resume the usual dosing schedule the next day.

ACCRU-LY-1806 SUBJECT MEDICATION DIARY

Study Drug/Dose	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Date							
Venetoclax (mg)							

Study Drug/Dose	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date							
Venetoclax (mg)							

Study Drug/Dose	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date							
Venetoclax (mg)							

Days 22-30 Included As Needed for Subjects with Venetoclax Treatment Delays

Study Drug/Dose	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
Date							
Venetoclax (mg)							

Study Drug/Dose	**Day 29**	**Day 30**
Date		
Venetoclax (mg)		

Date:_____Subject's Signature_____

Area Below Only To Be Completed only by Coordinator

Week	1	2	3	4	Discrepancy (Yes or No)
Date of Pill Count					
Number of Pills Returned					
Study Coordinator Initials					