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2016-0765. A phase II study of ibrutinib, nivolumab and blinatumomab in Richter Transformation.

Contents

1.0 OBJECTIVES AND STUDY ENDPOINTS

Primary endpoint

1. Determine the overall response rate (complete remission plus partial remission) in Richter transformation (RT) after 2 courses of blinatumomab, ibrutinib and nivolumab treatment.

Secondary endpoints

1. Assess the safety and feasibility of administering blinatumomab combined with ibrutinib and nivolumab to patients with RT.
2. Determine the complete remission rate for RT after 1 and 2 courses of therapy.
3. Determine the progression-free survival rate for RT at 1 year.
4. Determine the overall survival rate for RT at 1 year.
5. Determine the proportion of patients who proceed to allogeneic stem cell transplantation as next treatment.

Exploratory objectives

1. Pre- and post-treatment (progression) tumor biopsies for immunologic analysis, including immune checkpoint expression by tumor and by infiltrating T cells, flow cytometry and RNA-sequencing analysis (including the potential to perform single cell RNA-seq) or array-based analysis of immune cell subsets.

1. Immune checkpoint expression by circulating T cells and T cell subset analysis.
2. "Liquid biopsy" using circulating tumor DNA analysis and comparison with mutational profile identified in concurrent CLL specimen and tumor biopsy. This will also be used as an MRD analysis tool.

Correlation of RT microRNA profile with response to treatment and outcomes.

2.0 BACKGROUND AND RATIONALE

2.1 Richter Transformation

RT is defined as the transformation of CLL into a more aggressive lymphoma; while this is most commonly diffuse large B cell lymphoma (DLBCL) histology, rare cases of transformation to Hodgkin Lymphoma (HL)[1] histology are recognized. A large series, comprising all newly diagnosed CLL patients seen at the Mayo Clinic over 12 years, demonstrated that 2.3% of patients subsequently

developed biopsy-proven RT, at a rate of 0.5% per year; almost half had never required treatment for CLL prior to the diagnosis of RT.[2] Clinicopathologic features suggestive of the diagnosis include high fever, weight loss, rapidly enlarging lymph nodes, hypercalcemia and elevated LDH.[3] There is an ongoing incidence of RT seen in patients treated with highly effective, novel, targeted therapies for CLL, such as ibrutinib[4] and venetoclax.[5]

Prognosis is determined by both genetic and clinical features. Approximately 80% of DLBCL transformations are clonally related to the underlying CLL; the 20% with clonally unrelated DLBCL have a significantly better prognosis. Clonal relationship can be determined by comparing the sequences of the *IGHV* gene of the lymphoma to that of untransformed CLL cells. Two clinical prognostic models have been developed,[6, 7] the latter of which also demonstrated the importance of *TP53* disruption as a negative prognostic feature.

Treatment is generally unsatisfactory. Moderate to high-intensity chemoimmunotherapy regimens have produced CR rates of 5-38%, with median survival in most series of <1 year.[8-12] *TP53* disruption likely plays a major role in chemotherapy resistance. A minority of patients achieved long-term survival after allogeneic stem cell transplantation (alloSCT),[6] but most patients are not eligible for this treatment due to age, co-morbidities, lack of appropriate donor, and/or failure to achieve a response to initial treatment. Nonetheless, long-term survival after alloSCT in a subgroup of patients suggests that immunologic control is possible. More effective therapy is urgently needed in order to increase the proportion of patients able to undergo alloSCT and to achieve more durable disease control in those patients who are not candidates for alloSCT.

2.2 Blinatumomab

Blinatumomab (BLINCYTO®) is a murine recombinant single-chain antibody construct combining both the binding specificity for the pan B cell antigen CD19 and the epsilon chain of the T cell receptor/CD3 complex on one polypeptide chain. It is monomeric, non-glycosylated, with a molecular weight of 55 kilo-Daltons (kDa). It belongs to a new class of bispecific antibody constructs called bispecific T cell engagers (BITE). Bispecific T cell engagers were designed to direct T-effector memory cells against target cells. The proximity induced by the BITE triggers target cell-specific cytotoxicity, which resembles typical cytotoxic T lymphocyte (CTL) activation. This T cell–mediated target-specific killing is the therapeutic mechanism of action of blinatumomab.[13, 14]

Blinatumomab specifically targets cells that express CD19, a B cell-restricted surface antigen. Blinatumomab recruits and activates T cells via a lower affinity interaction with CD3 (8.7 x 10-8 M). The activated T cells then induce a half-maximal target cell lysis ranging *in vitro* between 10 to 100 pg/mL showing blinatumomab to be an extremely potent molecule.[15]

During the course of tumor cell elimination, activated T cells synthesize and secrete pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin (IL)-6, and IL-2, which can induce symptoms such as fever or decreases of blood pressure. *In vitro* data demonstrate cytokine release as a result of blinatumomab-mediated activation, which can be attenuated by corticosteroids without impairing the cytotoxic activity. *In vivo* data indicate cytokine release to be most prominent following the first dose of blinatumomab.

2.2.1 Blinatumomab in Precursor B-cell Acute Lymphoblastic Leukemia

A large, 189 patient phase II study in precursor B cell acute lymphoblastic leukemia (B-ALL), confirmed the safety and efficacy of blinatumomab and was the basis for FDA approval in that disease. Blinatumomab was given as a continuous IV infusion (4 weeks on followed by 2 weeks off) for up to 5 cycles (cycle 1 only: 9 µg/d days 1-7; then 28 µg/d). Regardless of causality, the most common adverse events (AEs) were pyrexia (59%), headache (35%) and febrile neutropenia (29%). The most common grade ≥3 AEs were febrile neutropenia (26%), anemia (15%) and neutropenia (15%); 2% had grade ≥3 cytokine release syndrome. The most common grade ≥3 nervous system disorders were headache (4%), encephalopathy (3%) and ataxia (2%). Three (2%) pts had grade 5 AEs considered treatment-related (sepsis, n=2; candida infection, n=1).[16]

2.2.2 Blinatumomab in Diffuse Large B-cell Lymphoma (DLBCL)

An ongoing phase 2 study in patients with heavily pre-treated relapsed/refractory diffuse large B cell lymphoma (DLBCL) showed that blinatumomab, delivered by continuous infusion for 8 weeks, has an acceptable safety profile.[17] After closure of one cohort, where blinatumomab was dosed at 112mcg/day from day 1, a stepwise dose escalation (9mcg/day for 1 week, 28mcg/day for 1 week then 112mcg/day for the remaining 6 weeks) was used for the remaining 23 patients. Serious AEs occurred in 22 (95%) of the patients, regardless of causality; the most common were pneumonia (13%), device-related infection (13%), and cytopenias (34%). Six of 23 (26%) had grade ≥3 neurologic AEs; there were no grade 4 or 5 neurologic events thought to relate to the study drug.[18]

The drug demonstrated considerable efficacy in this high-risk population, with an overall response rate of 43% (4 CRs and 5 PRs in 21 evaluable patients). The study permitted a 4 week consolidation period after a 4 week treatment-free period in patients achieving an objective response after the 8 week induction period. All patients who responded did so within the first 8 weeks. All patients received prophylactic dexamethasone (2 × 20 mg before infusion start and at infusion start; 3 × 8 mg/day for the first 2 days after infusion start and at each dose increase).

Given the importance of *TP53* mutation in the pathogenesis of RT, the use of a treatment that acts in a *TP53*-independent manner, such as blinatumomab, is attractive.

2.2.3 Blinatumomab in Richter Transformation.

9 patients have been treated at MD Anderson with blinatumomab in an ongoing phase II study, using a high-dose regimen (112mcg/d) that was used in DLBCL.[7] One patient, who was refractory to 3 prior therapies, had a durable CR lasting >1y. Of note, this patient had received ibrutinib and nivolumab as his most recent prior therapy, without response. Several notable, but transient, responses were also seen:

1. One patient had a 40% nodal reduction during C1 before progressing after C2.
2. One patient had complete resolution of all nodal disease, but progressed in bone marrow.
3. One patient had a packed bone marrow, with 40% circulating DLBCL cells, and initially cleared her circulating DLBCL, before developing disease progression.

Our impression, from in this patient cohort, is that there was less toxicity than was seen in the study by Viardot et al. in DLBCL, where the same high-dose blinatumomab regimen was used. We saw only 1 case of significant neurotoxicity (grade 3). This occurred in a patient who had escalated to full dose blinatumomab (patient #3, above), but had a fall in the hospital, resulting in a fractured neck of femur that required surgical repair. As a result, blinatumomab was interrupted and, despite appropriate pre-medication, neurotoxicity developed on re-initiation of therapy. Otherwise there were no cases of ≥grade 1 CRS or neurotoxicity. None of the other 7 patients required dose interruption or reduction of blinatumomab due to toxicity).

During the study, patients had blood samples taken pre-treatment and at day 1, 7, 14, 28 and 84 during blinatumomab therapy for analysis of T cell subsets and immune checkpoint molecule expression. All patients were lymphopenic and there was a skewing of T cell subsets toward effector and effector-memory subtypes, with very few naïve and central memory T cells present. Additionally, most patients expressed high levels of multiple immune checkpoint molecules, particularly TIGIT, PD1 and, to a lesser extent, TIM3. (see Figure 1).

Immune checkpoint molecule expression and individual patient-level data suggests a complementary and potentially synergistic role for ibrutinib + nivolumab and blinatumomab in RT.

There was significant inter-patient variability in immune checkpoint molecule expression in patients analyzed in the blinatumomab trial, both in terms of the expression levels and specific immune checkpoint molecules expressed. However, the most highly expressed molecules were TIGIT, PD1 and TIM3, which were all expressed at much higher levels than in normal controls in most patients. The consistent expression of PD1, which often increased during therapy, suggests that PD1 inhibition may be synergistic with blinatumomab in RT. Eventually, the heterogeneity of immune checkpoint expression may lead to a personalized approach to targeting specific immune checkpoint molecules. However, currently, the most practical path to drug development would be to combine approaches that have demonstrated safety and response in the clinic in RT.

At the individual patient level, two patients received sequential therapy with ibrutinib + nivolumab and blinatumomab on separate clinical trials and are therefore very informative when developing potential combination approaches:

1. Patient #1 (T cell immune checkpoint profile shown in Figure 1 and PETCT shown in Figure 2) received ibrutinib + nivolumab, without response. He had multi-focal, bulky, extra-nodal disease and achieved CR lasting >1 year with blinatumomab therapy. This patient had the lowest level of immune checkpoint molecule expression (particularly of PD1) of all patients tested. The fact that his was the most favorable response to blinatumomab is suggestive of the importance of immune checkpoint molecule expression on T cells in mediating blinatumomab resistance.
2. Patient #2 (T cell immune checkpoint profile shown in figure 3) received blinatumomab, with transient response (clearance of circulating DLBCL cells from the blood) followed by an MRD-

negative CR lasting >1y with ibrutinib + nivolumab. This patient had very high levels of PD1 on her T cells, which increased during blinatumomab therapy.

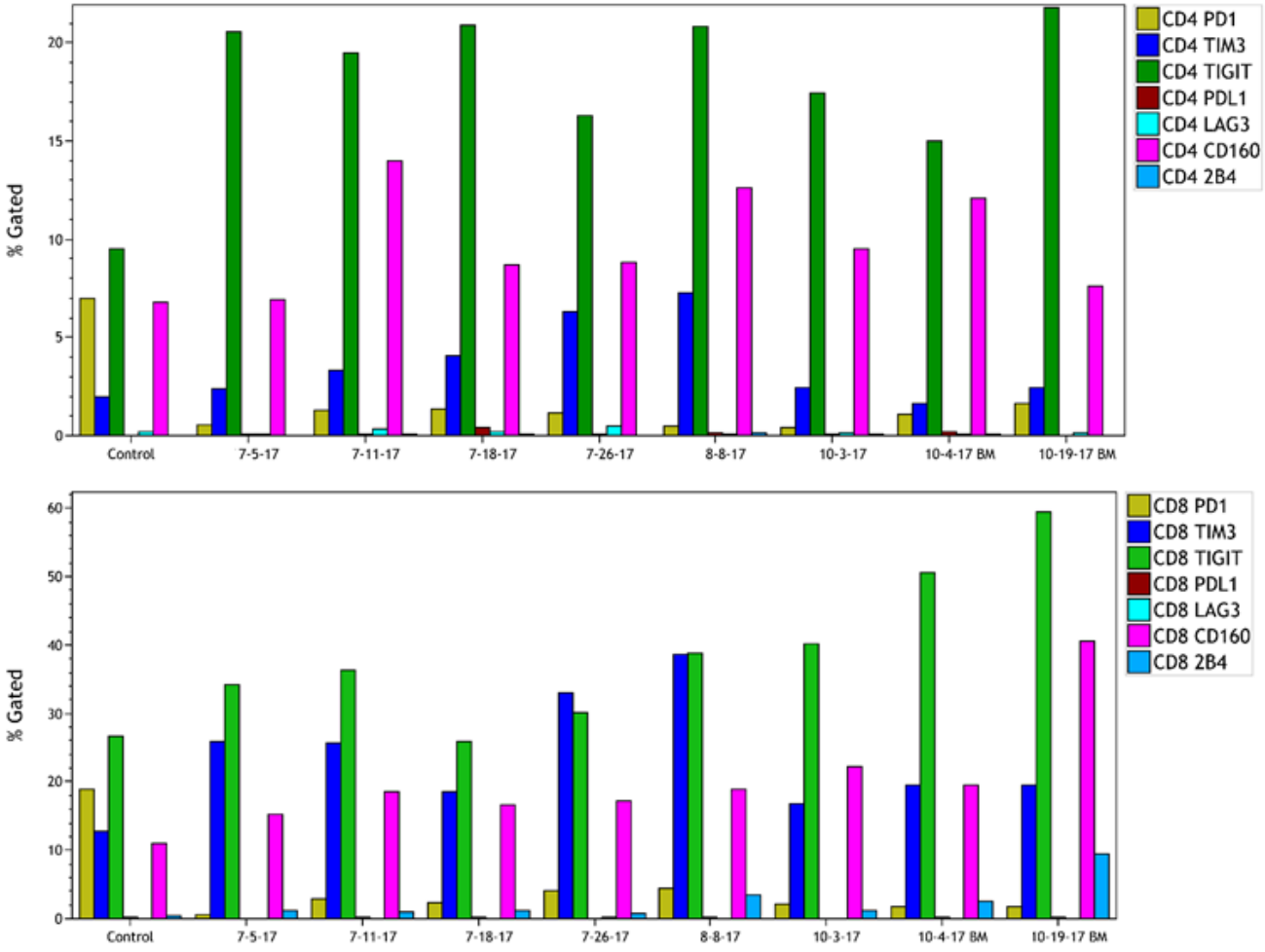

Figure 1. Sequential Immune checkpoint expression profiling pre-treatment and during therapy on patient #1 treated with blinatumomab. This patient had recently received ibrutinib and nivolumab, without response. His CD4 and CD8 T cells showed the lowest PD1 expression of all the patients profiled in the study. He achieved CR with blinatumomab (PETCT shown in Figure 2)

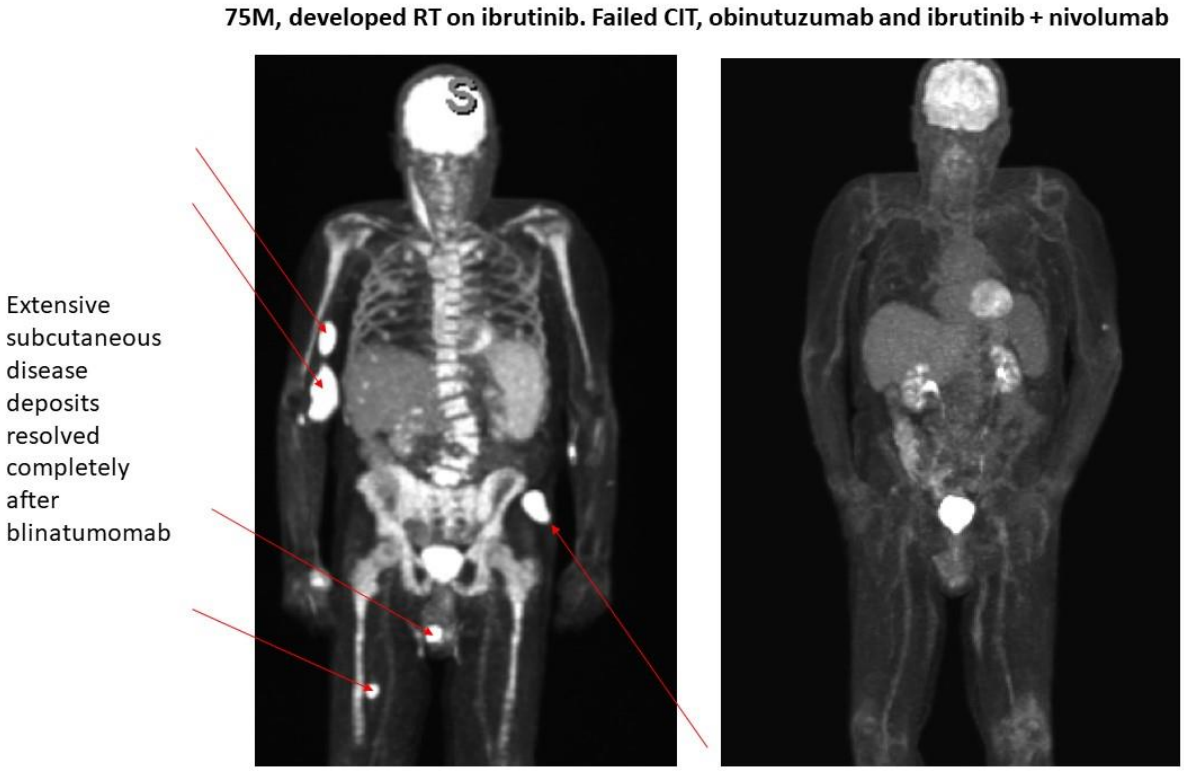

Figure 2. PETCT prior to blinatumomab (left) and post-cycle 2 of blinatumomab (right) in a patient who achieved CR with treatment.

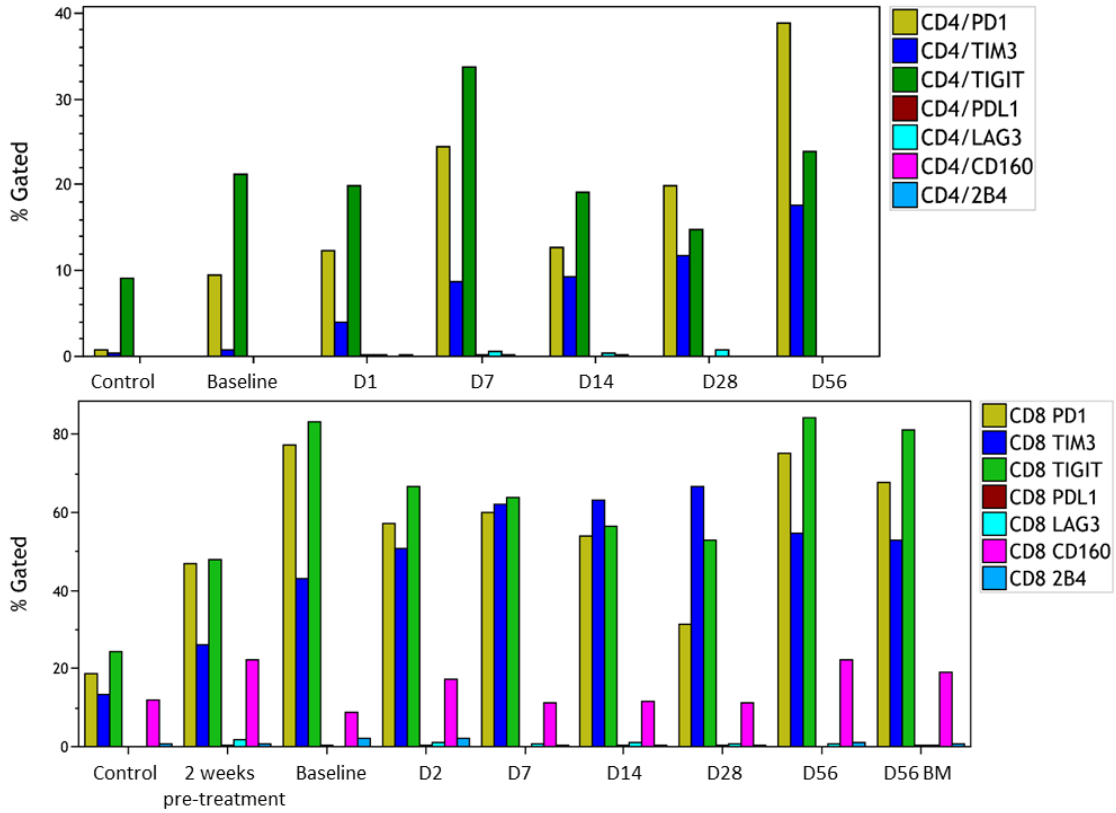

Figure 3. Sequential Immune checkpoint expression profiling pre-treatment and during therapy on two patients treated with blinatumomab. In each panel, the control specimen from a healthy donor is left-most, followed by baseline specimen from the patient and then serial on-treatment specimens for the same patient. The top panel shows patientprofiling showed high levels of expression of PD1, TIM3 and TIGIT on CD4 and CD8 cells pre-treatment, with a notable increased expression during therapy on CD4+ and CD8+ T cells of both PD1 and TIGIT. This patient had a transient response to blinatumomab, with clearance of circulating DLBCL cells, before progressing. She subsequently had a durable MRD-negative CR (lasting ~1y) with ibrutinib + nivolumab, before progressing with CNS disease.

2.3 Ibrutinib + nivolumab in RT:

- This regimen is a major advance in RT treatment. In a phase II, single center study at M.D. Anderson, there was an overall response rate of 43% and a complete remission rate of 35% in 23 heavily pre-treated patients.[6]
- In addition to the high CR rate achieved in this difficult-to-treat population patients with RT (median 3 prior therapies), this regimen was delivered entirely as an outpatient and was very well tolerated, even by older patients (median age was 65, with patients as old as 88

successfully enrolled). There were only two grade 3-4 immune-related toxicities: 1 patient had grade 3 transaminitis and one patient had grade 4 lipase/amylase elevation. One patient developed grade 2 pneumonitis, and one patient had grade 2 uveitis. These toxicities were manageable with corticosteroids and continued therapy was possible in all patients. Only one patient eventually stopped treatment due to toxicity, which was the development of psoriasis after 20 cycles of therapy.

- Although encouraging, responses are seen in <50% of patients and there are relapses after initial response, suggesting that the addition of other potentially synergistic agents to this treatment backbone is needed.

3.0 STUDY POPULATION

30 patients will be enrolled in this phase II study, 9 in the blinatumomab monotherapy phase and 21 in the combination phase.

3.1 Inclusion Criteria

1. Patients with previously treated CLL and biopsy-proven Richter's transformation with DLBCL histology according to IWCLL criteria (Richter Transformation – RT) AND CD19 positive by flow cytometry OR immunohistochemistry.
2. Eastern Co-operative Oncology Group (ECOG) performance status ≤2.
3. Age ≥18 years at the time of informed consent.
4. Able to provide informed consent and be willing to participate in study schedule and events.

3.2 Exclusion Criteria

1. Other active malignancy receiving systemic therapy.
2. History or presence of clinically relevant disorder affecting the CNS such as epilepsy, childhood or adult seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis, with the exception of a history of CNS lymphoma that is controlled with intrathecal therapy.
3. Known active DLBCL in the CNS (confirmed by CSF analysis).
4. Current autoimmune disease requiring >/= 20mg/day of prednisone or systemic immunosuppressive therapy (eg. With cyclosporine or azathioprine).
5. Allogeneic HSCT within 24 weeks before the start of protocol-specified therapy.

6. Active Graft-versus-Host Disease (GvHD), grade 2-4 according to the Glucksberg criteria, active chronic GvHD requiring systemic treatment or requirement for systemic GvHD prophylaxis with cyclosporine or tacrolimus.
7. Cancer chemotherapy within 2 weeks before start of protocol-specified therapy, with the exception of intrathecal chemotherapy, dexamethasone, and oral small molecule inhibitors such as BTK-inhibitor, PI3K-inhibitor, or Bcl-2-inhibitor, which are allowed until the start of protocol-specified therapy). In addition, any subject whose organ toxicity (excluding hematologic) from prior treatment has not resolved to no more than CTCAE grade 1
8. Radiotherapy within 2 weeks before the start of protocol-specified therapy
9. Abnormal screening laboratory values as defined below:
   - ALT (SGOT) and/or ALT (SGPT) and/or ALP ≥5 x upper limit of normal (ULN)
   - Total bilirubin ≥ 1.5 x ULN, unless due to Gilbert's disease
   - Creatinine ≥ 2.0 x ULN or creatinine clearance <50 mL/min (calculated)
10. Known infection with human immunodeficiency virus (HIV) or chronic infection with hepatitis B virus (HBsAg positive) or hepatitis C virus (anti-HCV positive)
11. Patient is pregnant or breast feeding
12. Woman of childbearing potential and is not willing to use 2 highly effective methods of contraception while receiving protocol-specified therapy and for an additional **5 months** after the last dose of protocol-specified therapy
13. Male who has a female partner of childbearing potential or a pregnant partner, and is not willing to use a condom during sexual activity while receiving protocol-specified therapy and for **7** months after the last dose of protocol-specified therapy
14. Currently receiving treatment in another investigational device or drug study
15. Subject previously treated with blinatumomab
16. History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the Principal Investigator would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.
17. Previously received nivolumab or other PD1 inhibitor.

4.0 TREATMENT PLAN

This is a single arm, open label, phase II study of ibrutinib, nivolumab and blinatumomab in patients with RT.

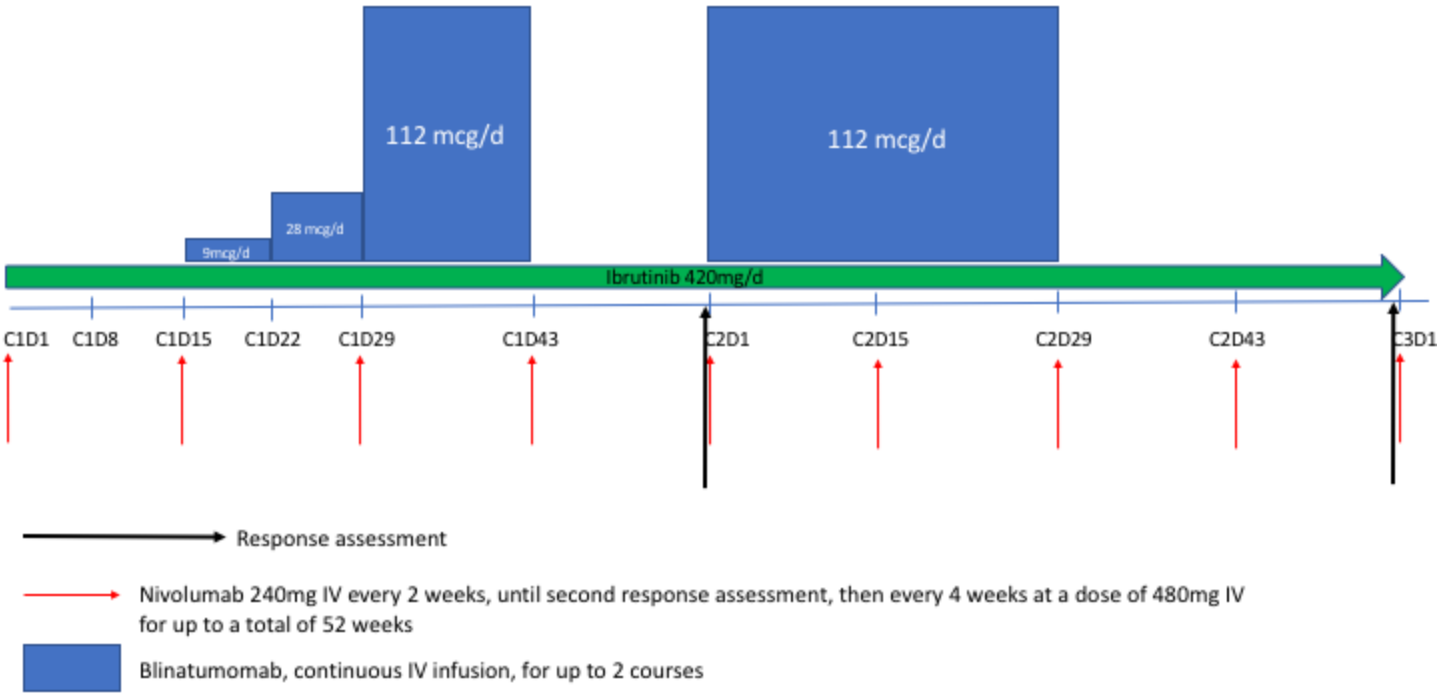

Figure 4. Schematic of treatment plan

Patients will receive treatment as follows:

1. 2 cycles of 3 drug combination (ibrutinib, nivolumab and blinatumomab). These cycles will be 8 weeks each.
2. 9 cycles of 2 drug combination (ibrutinib and nivolumab). These cycles will be 4 weeks each.
3. Maintenance treatment with ibrutinib monotherapy until disease progression following completion of nivolumab.

4.1 Ibrutinib therapy.

Ibrutinib treatment will commence on cycle 1, day 1 at 420mg/d. Dose reductions to 280mg/d or 140mg/d are allowed per treating physician discretion, but the reason must be documented in the medical record. Ibrutinib will be given continuously until disease progression or toxicity.

4.2 Nivolumab therapy.

Patients will receive nivolumab for up to a total of 52 weeks. Dosing will be 240mg IV every 2 weeks, commencing on day 1 until 2nd response assessment, then 480mg IV every 4 weeks.

4.3 Blinatumomab therapy

Patients will receive blinatumomab as a continuous IV infusion, commencing on day 15 of cycle 1 and day 1 of cycle 2, for 2 courses of 4 weeks each separated by a 2 week blinatumomab treatment-free interval.

In cycle 1 and cycle 2 of blinatumomab, dexamethasone pre-medication will be given as outlined in table 1, below.

Table 1. Dexamethasone treatment during the study

Treatment phase	Target patient	Dexamethasone dose
Screening	Patients with bulky or rapidly-progressive disease	Dose and duration at the discretion of the investigator
Pre-dose dexamethasone before cycle 1 and 2 of blinatumomab and before dose-escalation	All patients (before each blinatumomab cycle and dose increase)	Dexamethasone 20 mg IV/PO 12-24 hours prior to and within 1 hour before start of blinatumomab treatment in each treatment cycle, and before dose increase
During cycle 1 and 2 for the first 48 hours of blinatumomab and after each dose escalation	All patients, for the first 48 hours of each treatment cycle	Dexamethasone 8mg IV/PO Q8 hours for 48 hours.
Infusion interruption/dose modification due to adverse event	Patients who interrupt treatment > 4 hours	Dexamethasone 20 mg IV/PO 12-24 hours prior to and within 1 hour before re-start of blinatumomab treatment
In case of signs of cytokine release (CRS) of grade ≥2 (see Appendix C for grading of CRS and Appendix D for definition of high dose vasopressors)*	Patients with signs of CRS	Principal Investigator must be notified. Dexamethasone IV/PO at a dose of at least 24mg per day. The dose should then be reduced step-wise over approximately 4 days, provided signs of CRS have

		improved/resolved.
In case of CNS event grade ≥2 (See Appendix E for grading)*	Patients with CNS-related AE	Principal Investigator must be notified. Dexamethasone should be administered at a dose of at least 24mg/day. Dexamethasone should be reduced step-wise over approximately 4 days, provided neurological toxicity has improved/resolved.

*Please note that when dexamethasone is given for the management of toxicity, the above dexamethasone doses are a guideline. Management of dexamethasone dosing should be individualized according to the severity of toxicity and the patient's response. This management should be at the investigator's discretion.

In cycle 1 of blinatumomab, patients will be hospitalized on day 15-31 (for the first 17 days of blinatumomab therapy). To mitigate for potential CRS and CNS events associated with introduction of blinatumomab, in cycle 1, blinatumomab will be initiated at 9mcg/day from day 15-21, followed by 28 mcg/day from day 22-28. This will be followed by 112 mcg/day from day 29-42. In cycle 2, patients will be admitted for the first 3 days. Blinatumomab in cycle 2 will be administered at a dose of 112 mcg/day from day 1-28.

4.4 Response assessment

Formal response assessment will take place 2weeks (+/- 1 week) following completion of the first course of blinatumomab.. Response assessment will comprise laboratory evaluation (CBC), bone marrow examination and PETCT scan. Responses in RT for the primary study endpoint will be assessed according to the Lugano criteria[19] and, as an exploratory endpoint, in co-existing CLL, according to 2018 IWCLL response criteria. Responses in RT will be assessed separately from responses in CLL. Any nodal or extranodal lesion with SUV ≥5.0 on PETCT will be considered indicative of RT, for the purposes of response assessment. Lesions with SUV <5.0 pre-treatment will be considered to be due to CLL, rather than RT; residual PET avidity in such lesions post-treatment will not be considered evidence of failure of control of RT, provided SUV remains <5.0. In order for CR to be attained, all lesions with SUV ≥5.0 pre-treatment must be PET negative post-treatment and there must be no new PET avid lesions, unless these are proven by biopsy not to be due to Richter

Transformation. PET characterization of target lesions as due to CLL or RT pre-treatment will allow separate response assessment for RT (the primary end point) and CLL (an exploratory endpoint), without discrepancies arising due to the differences in response criteria. When possible, biopsy of residual RT sites will be requested to evaluate for residual disease.

Please note that there may be instances where PETCT is not able to be performed. In these instances, CT scan will be performed instead (see section 8.0 and 9.0)

A second response assessment will be undertaken 4 weeks (+/-1 week) after completion of the consolidation cycle.

4.5 Allogeneic stem cell transplantation.

In patients where a suitable donor is identified and who are considered eligible, allogeneic stem cell transplantation may be offered any time after completion of the first cycle of blinatumomab and initial response assessment. Patients will be considered "off study" on the date they commence pre-transplant conditioning chemotherapy. If the patient agrees, they will be enrolled on a departmental umbrella protocol (DR09-0223) to continue to follow them for overall survival.

4.6 Surveillance after completion of blinatumomab.

After completing blinatumomab, patients will have PETCT every 3 months until completion of nivolumab therapy. If PETCT cannot be performed, for whatever reason, CT with oral and IV contrast (unless contraindicated) will be performed instead.

5.0 STUDY MEDICATIONS

5.1 Blinatumomab

5.1.1. Blinatumomab formulation, reconstitution and administration

Blinatumomab will be supplied as 4 mL single-use glass injection vials containing a sterile, preservative-free, white to off-white, lyophilized powder for intravenous (IV) administration following reconstitution with sterile water for injection (sWFI). Each vial contains a target of 38.5 µg

blinatumomab (nominal) formulated with 3.68 mg citric acid monohydrate, 105.0 mg trehalose dihydrate, 25.55 mg lysine hydrochloride, and 0.70 mg polysorbate 80, pH of 7. Following reconstitution with 3 mL sterile water for injection the final concentration of blinatumomab will be 12.5 µg/mL.

Since blinatumomab will be administered via continuous intravenous route, it needs to be stabilized at low concentrations to prevent absorption to surfaces. Therefore, the IV bag must be conditioned by prior addition of a product-specific diluent (IV solution stabilizer - IVSS), resulting in a final diluent concentration of 0.5 mM citrate, 25 mM lysine hydrochloride and 0.002% (w/v) polysorbate 80. IVSS is supplied in 10 mL single-use glass injection vials as a sterile, preservative-free, clear, colorless-to-slightly-yellow liquid concentrate. It consists of 25 mM citric acid monohydrate, 1.25 M L-lysine hydrochloride, and 0.1% (w/v) polysorbate 80, pH of 7. Following dilution in 0.9% NaCl, the ingredient concentrations are 25 mM L-lysine hydrochloride, 0.002% (w/v) polysorbate 80, and 0.5 mM citric acid monohydrate. Sterile water for injection and supplies required for reconstitution and injection of blinatumomab will not be provided to clinical sites.

The drug administration should not be interrupted, if possible. In case of infusion interruption, due to any technical or logistic reason, the interruption should be as short as possible and the infusion continued at the earliest time possible. Every interruption longer than 1 hour should be documented. If the interruption is longer than 4 hours, re-start of the infusion should be performed in the hospital. The subject should be observed overnight for possible side effects after the re-start. Administration of dexamethasone premedication as described in Table 1 is required. If possible, the infusion duration before and after an interruption should total 28 days per treatment cycle (i.e. if interruptions occur, the missed days should be “made up” after re-commencement so a total of 28 days is given). This will not be considered a protocol violation if interruptions occurred for documented medical reasons.

5.1.2 Adverse events associated with blinatumomab

5.1.2.1 General Infusion Reactions

Infusion reactions may be clinically indistinguishable from manifestations of cytokine release syndrome (CRS). Patients should be observed closely for infusion reactions, especially during the

first infusion of the first and second cycles. Management of infusion reactions may require either temporary interruption or discontinuation of blinatumomab.

5.1.2.2 Hepatic/Biliary/Pancreatic

Treatment with blinatumomab was associated with transient elevations in liver enzymes. The majority of these events were observed within the first week of blinatumomab initiation and did not require blinatumomab interruption or discontinuation.

Pancreatitis, life threatening or fatal, has been reported in patients receiving blinatumomab in clinical trials and the post-marketing setting. High-dose steroid therapy may have contributed, in some cases, to the pancreatitis.

5.1.2.3 Immune Cytokine Release Syndrome Cytokine Release Syndrome (CRS)

This may be severe, life-threatening or fatal and was reported in patients receiving blinatumomab. Serious adverse events that may be associated with CRS included pyrexia, asthenia, headache, hypotension, total bilirubin increased, elevation of liver enzymes (AST and ALT). The median time to onset was 2 days. Disseminated intravascular coagulation (DIC) and Capillary leak syndrome (CLS) have been commonly associated with CRS. Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) has been uncommonly reported in the setting of CRS.

5.1.2.4 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), which may be severe, life-threatening or fatal, has been observed in patients receiving blinatumomab. Appropriate prophylactic measures include aggressive hydration and antihyperuricemic therapies (such as allopurinol or rasburicase).

5.1.2.5 Infections

Pneumonia, bacteremia, opportunistic infections, and catheter site infections have been observed, some of which were life-threatening or fatal.

5.1.2.6 Hematologic abnormalities

Neutropenia and febrile neutropenia, including life threatening cases, have been observed in patients receiving blinatumomab.

5.1.2.7 Neurologic abnormalities

General Neurologic events (any grade) were observed in approximately half of patients receiving blinatumomab. Grade 3 or higher (severe, life-threatening and fatal) neurologic events that occurred following the initiation of blinatumomab included: encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, coordination and balance disorders. Encephalopathy was the most frequently reported serious neurological event in the pivotal study and two cases resulted in death. Neurologic events, that may be associated with encephalopathy, include tremor, muscular weakness, confusion, stupor, coma, seizures, altered consciousness and personality changes. The median time to onset of a neurologic event was 9 days, and the majority of events resolved and infrequently led to blinatumomab treatment discontinuation. There is limited experience with blinatumomab in patients with active malignant involvement of the central nervous system (CNS) or a history of neurologic events. Patients with a history or presence of clinically relevant CNS pathology were excluded from clinical trials.

5.1.2.8 Leukoencephalopathy

Cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving blinatumomab, especially in patients with prior treatment with cranial irradiation and anti-leukemic chemotherapy (including systemic high dose methotrexate or intrathecal cytarabine). The clinical significance of these imaging changes is unknown.

5.1.3 Inpatient admission

As described above, patients receiving blinatumomab may experience a spectrum of neurologic and psychiatric events, such as seizure, encephalopathy, tremor, apraxia, speech disorders (dysarthria, aphasia) and disorientation. The incidence of patients experiencing neurologic and psychiatric events is greatest within the first few days of initiating blinatumomab therapy and on dose escalation. Reversible, grade 3 neurotoxicity was seen in 6 of 21 patients (26%) receiving blinatumomab for DLBCL, given at the same dose and schedule as will be used in this study. As such, patients will be hospitalized for the first 17 days of cycle 1 and 3 days of cycle 2 as outlined in section 5.1.6 and if dose interruption of >4 hours occurs during outpatient therapy. In addition, cytokine release syndrome (CRS) and/or tumor lysis syndrome (TLS) may occur on initiation of therapy, particularly in patients with high tumor load. Patients will receive IV hydration and allopurinol for tumor lysis syndrome

prophylaxis. Rasburicase will be given if indicated, according to institutional guidelines. Allopurinol (or equivalent, in the case of allergy) will be continued for the duration of hospitalization. Patients will be discharged after 17 days, provided no significant AEs requiring blinatumomab interruption and/or dose reduction have occurred.

5.1.4 Dexamethasone during pre-phase and as pre-medication before blinatumomab

Dexamethasone will be given during the study as outlined in table 1.

5.15.1.5 Blinatumomab dosage, administration, and schedule

Blinatumomab will be administered as a continuous intravenous infusion (CIVI), through a peripherally inserted central catheter (PICC) line or tunneled central venous catheter (CVC). Preparation and administration of blinatumomab will comply with the instructions in the US Prescribing Information or with institutional standards (outlined in the pharmacy manual). Schedule of administration is outlined in section 4.3.

5.15.1.6 Blinatumomab inpatient dosing

Patients will be hospitalized for the first 17 days of the cycle 1 and first 3 days of cycle 2. Patients will be re-admitted after dose interruptions of >4 hours as described in section 5.3.

5.1.7 Blinatumomab outpatient dosing

After a subject meets the minimum criteria for outpatient administration, as described in section 5.1.3, and if a subject is deemed stable by the investigator, continuation of blinatumomab infusion may continue as an outpatient. 24-hour emergency on-call service must be ensured in the outpatient setting.

In the outpatient setting, the subject will return to the study site for changes of infusion bags.

5.2 Nivolumab.

Nivolumab is a fully human, IgG4 (kappa) isotype, monoclonal antibody that binds PD-1. Nivolumab will be supplied in vials of 100 mg (10 mg/mL), 5 vials per container, and packaged in an open-label fashion. See Pharmacy Reference Material.

5.2.1 Preparation and Dispensing of Nivolumab

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

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

Nivolumab vials must be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves. For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the Investigator Brochure section for “Recommended Storage and Use Conditions”. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.

Nivolumab is to be administered as an IV infusion over approximately 30 minutes, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 1 mg/ml. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Unused or expired nivolumab vials will be disposed per MDACC guidelines.

5.2.2 Administration of Nivolumab

Patients will receive nivolumab as an IV infusion over approximately 30 minutes. No doses of nivolumab may be given within 11 days of another.

5.2.3 Patient Monitoring During Infusion

For first dose, patient vital signs should be monitored prior to dosing, about 15 minutes after initiation of the infusion (then every 15-20 minutes as indicated) and at 30 minutes after completion of the infusion, or longer if indicated, until the vital signs normalize or return to baseline. For subsequent infusions, vital signs should be collected prior to dosing and every 30 minutes during dosing.

5.2.4 Treatment of Nivolumab Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Infusion reactions should be graded according to NCI CTCAE (version 5.0) guidelines.

Treatment recommendations for nivolumab related infusion reactions are provided below and may be modified based on MD Anderson treatment standards and guidelines, as appropriate:

For Grade 1 symptoms (Mild reaction; infusion interruption not indicated; intervention not indicated): Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g. antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours): Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat The subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic

premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms [Severe reaction, Grade 3: prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms followinginitial improvement; hospitalization indicated for other clinical sequelae (e.g. renal impairment, pulmonary infiltrates), Grade 4: life- threatening; pressor or ventilatory support indicated]: Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Institutional guidelines will be followed for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g. appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g. oral antihistamine or corticosteroids).

5.2.5. AEs associated with nivolumab:

5.2.5.1 Pulmonary Adverse Events:

Pulmonary AEs have been observed following treatment with nivolumab. The frequency of pulmonary AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. The majority of cases reported were Grade 1 or 2, and subjects presented with either asymptomatic radiographic changes (eg, focal ground glass opacities and patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Subjects with reported Grade 3 or 4 pulmonary AEs were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia.

Pulmonary AEs have been reported in subjects with a variety of tumor types; however, there have been numerically more cases in subjects with NSCLC. It is not clear whether the underlying NSCLC

is a distinct risk factor, or if subjects with NSCLC are more likely to develop radiographic changes and symptoms for which it is difficult to distinguish between nivolumab-related and unrelated causes. At this time, no other underlying risk factor, including prior radiotherapy, presence of lung metastases, or underlying pulmonary medical history, has yet to be identified.

Asymptomatic subjects were typically managed with dose delay. Subjects with Grade 2 pneumonitis were managed with dose delay, treated with corticosteroids, and had resolution of pneumonitis within days to weeks. In cases where nivolumab treatment was restarted, recurrence of pneumonitis was infrequently reported across the nivolumab program. Subjects with more severe cases of pneumonitis can be difficult to treat. In a few cases, subjects who did not initially respond to corticosteroids were administered anti-tumor necrosis factor therapy (infliximab) and/or cyclophosphamide. In some of these cases, pneumonitis began to resolve following the use of these additional therapies.

Guidelines on the recommended management of pneumonitis and other pulmonary AEs are found in Appendix K. Early recognition and treatment of pneumonitis is critical to its management. Subjects should be advised to seek medical evaluation promptly if they develop new-onset dyspnea, cough, or fever or if they have worsening of these baseline symptoms. As respiratory symptoms are common in subjects with cancer (eg, NSCLC), it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, infection or progression of disease) and a possible drug-related pulmonary toxicity as the management of these events can be quite different. For symptomatic nivolumab-related pneumonitis, the principal treatment is corticosteroids (Appendix K). All subjects with Grade 3-4 pneumonitis should discontinue nivolumab and initiate treatment with high doses of corticosteroids. Consultation with the PI or designee should be sought for all suspected cases of pneumonitis.

5.2.5.2 Gastrointestinal adverse events.

Gastrointestinal AEs have been observed following treatment with nivolumab (Section 5.5). Most cases of diarrhea were of low grade (Grade 1-2). Colitis occurred less frequently than diarrhea. High-grade cases of diarrhea and colitis were managed with corticosteroids and, in all cases, the events resolved.

The recommended management of GI AEs is provided in Appendix K. Early recognition and treatment of diarrhea and colitis are critical to their management. Subjects should be advised to seek medical evaluation if they develop new-onset diarrhea, blood in stool, or severe abdominal pain or if they have worsening of baseline diarrhea. As GI symptoms are common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, infection or progression of disease) and a possible drug-related AE as the management can be quite different. The principal treatment for high-grade GI AEs is corticosteroids (Appendix K). Caution should be taken in the use of narcotics in subjects with diarrhea, colitis, or abdominal pain as pain medicines may mask the signs of colonic perforation. Consultation with the PI or designee should be sought for all moderate- and high-grade cases of GI AEs.

5.2.5.3 Diverticular Perforation

The prevalence of diverticulosis in the general population is common and increases with age from 10% under 40 years of age to approximately 50% over 60 years of age. Approximately 10% to 25% of subjects with diverticulosis develop diverticulitis. Perforation occurs in 50% to 70% of instances of complicated diverticulitis. Corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and opioid analgesics are known risk factors for diverticular perforation. Given the high prevalence of diverticulosis and diverticulitis in the general population, it is expected that some nivolumab-treated subjects will have these conditions concurrently with their malignancy. Cases of diverticular perforation while on concomitant corticosteroids (6 cases) or NSAID (1 case) were observed in nivolumab program. While there is insufficient evidence to suggest that diverticulosis or diverticulitis is a predisposing factor for GI perforation following nivolumab administration, clinical caution should be exercised, as appropriate, for subjects on concomitant medications of corticosteroids, NSAID, or opioid analgesics. In addition, be vigilant for signs and symptoms of potential perforation, especially in subjects with known diverticular disease.

5.2.5.4 Hepatic Adverse Events

Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, DILI, have been observed following treatment with nivolumab and nivolumab in combination with ipilimumab. Most cases were of low or moderate grade. Higher-grade hepatic AEs, including DILI, were managed with corticosteroids (with or without mycophenolate mofetil) and, in almost all cases, the events resolved. The recommended management of hepatic AEs is provided in Appendix K. Early recognition and

treatment of elevated LFTs and DILI are critical to their management. Subjects should be advised to seek medical evaluation if they notice jaundice (yellow appearance of skin or sclera) or if they develop bruising, bleeding, or right-sided abdominal pain. Physicians should monitor LFTs prior to each nivolumab treatment. As LFT abnormalities are common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, infection, progression of disease, concomitant medications, or alcohol) and a possible drug-related AE as the management can be quite different. The principal treatment for high-grade hepatic AEs is corticosteroids (Appendix K). Consultation with the PI or designee should be sought for all moderate- and high-grade hepatic AEs.

5.2.5.5. Endocrinopathies

Endocrinopathies have been observed following treatment with nivolumab (Section 5.5). Most cases were of low or moderate grade. The events have typically been identified through either routine periodic monitoring of specific laboratories (eg, TSH) or as part of a work-up for associated symptoms (eg, fatigue). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (eg, hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Moderate- to high-grade cases were managed with hormone replacement therapy and, in some cases, with the addition of corticosteroids. In some cases, nivolumab treatment was held until adequate hormone replacement was provided.

Guidelines on the recommended management of endocrinopathies are provided in Appendix K. Early recognition and treatment of endocrinopathies are critical to its management. Subjects should be advised to seek medical evaluation if they notice new-onset fatigue, lightheadedness, or difficulty with vision or if baseline fatigue worsens. As fatigue is common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, progression of disease, anemia, concomitant medications, or depression) and a possible drug-related AE as the management can be quite different. The principal management of endocrinopathies is hormone replacement therapy. For subjects with moderate- or high-grade events, corticosteroids may also be used (Appendix K). Consultation with the PI or designee should be sought for all moderate- and high-grade cases of endocrinopathies.

5.2.5.6. Skin Adverse Events

Rash and pruritus were the most common skin AEs observed following treatment with nivolumab (Section 5.5). The rash was typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. Most cases have been of low or moderate grade. In some cases, rash and pruritus resolved without intervention. Topical corticosteroids have been used for some cases of rash. Anti-histamines have been used for some cases of pruritus. More severe cases responded to systemic corticosteroids.

Subjects should be advised to seek medical evaluation if they notice new-onset rash. Early consultation with a dermatology specialist and a biopsy should be considered if there is uncertainty as to the cause of the rash, or if there is any unusual appearance or clinical feature associated with it. Other drugs that may cause rash should be considered in the differential and, if possible, discontinued. In addition, careful evaluation of potential benefit-risk is necessary when considering the use of nivolumab or ipilimumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on a prior immune-stimulating therapy.

Guidelines on the recommended management of skin AEs are provided in Appendix K. The principal treatment for skin AEs, such as rash and pruritus, consists of symptomatic management. Topical corticosteroids can be used for low- to moderate-grade focal rash. Systemic corticosteroids should be used for diffuse and high-grade rash. Consultation with the PI or designee should be sought for all moderate- and high-grade cases of skin AEs.

Rare cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been observed. If symptoms or signs of SJS or TEN appear, nivolumab or nivolumab in combination with ipilimumab should be withheld and the patient referred for specialized care for assessment and treatment. If the patient has confirmed SJS or TEN, permanent discontinuation of nivolumab or nivolumab in combination with ipilimumab is recommended.

5.2.5.7 Renal Adverse events

Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with nivolumab. The frequency of renal AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. Most cases were

Grade 2 or 3 and based on creatinine elevation. Subjects with a history of RCC or prior nephrectomy did not appear to be at higher risk. Events were managed with corticosteroids and, in all cases, renal function partially or fully improved.

The recommended management of renal AEs is provided in Appendix K. Physicians should monitor creatinine regularly. As creatinine abnormalities are common in subjects with cancer and other comorbidities, it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, dehydration, concomitant medications, hypotension, or progression of disease) and a possible drug-related AE as the management can be quite different. The principal treatment for renal AEs is corticosteroids (Appendix K). Consultation with the PI or designee should be sought for all moderate- and high-grade cases of renal AEs.

5.2.5.8 Neurologic Adverse events

Neurologic AEs have been uncommonly observed following treatment with nivolumab (Section 5.5). The frequency of neurologic AEs may be greater with nivolumab + ipilimumab combination therapies than with nivolumab monotherapy or other nivolumab combinations. Neurologic AEs can manifest as central abnormalities (eg, aseptic meningitis, encephalopathy, or encephalitis) or peripheral sensory/motor neuropathies (eg, Guillain-Barre Syndrome, myasthenia gravis complicated with sepsis and fatality). The onset has been observed as early as after a single treatment with the nivolumab + ipilimumab combination.

The recommended management of neurologic AEs is provided in Appendix K. Early recognition and treatment of neurologic AEs is critical to its management. Subjects should be advised to seek medical evaluation if they notice impairment in motor function (eg, weakness), changes in sensation (eg, numbness), or symptoms suggestive of possible central nervous system abnormalities such as new headache or mental status changes. As neurologic symptoms can be common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, progression of disease, concomitant medications, or infection) and a possible drug-related AE as the management can be quite different. The principal treatments for neurologic toxicity are dose delay, corticosteroids, and IV immunoglobulin as outlined in the safety algorithm (Appendix K). For high-grade related neurological AEs, nivolumab should be discontinued. Consultation with the PI or designee should be sought for all moderate- and high-grade cases of neurologic AEs.

5.2.5.9 Infusion Reactions

Infusion reactions, including high-grade hypersensitivity reactions, following administration of nivolumab are uncommon. Investigators are advised to monitor for fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty in breathing during and immediately after administration of nivolumab. Study protocols provide explicit guidance on the management of infusion-related reactions.

5.2.5.10 Lipase/Amylase Elevations

Asymptomatic elevations in lipase and amylase have been reported. In monotherapy studies, lipase and amylase levels were not systematically monitored, so an estimate of the frequency of asymptomatic lipase/amylase elevations is unknown. In studies evaluating the safety of the nivolumab + ipilimumab combination in multiple tumor types, lipase and amylase levels were systematically monitored, and elevations in any grade of lipase/amylase were consistently noted in approximately 10% to 30% of subjects. Very few subjects reported associated symptoms (eg, abdominal pain) or radiographic findings (eg, stranding) consistent with pancreatitis. Thus, there does not seem to be clinical significance to the elevated laboratory values.

As lipase/amylase abnormalities are not uncommon in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, progression of disease, concomitant medications, or alcohol) and a possible drug-related cause as the management can be quite different. The recommended management of nivolumab-related elevated lipase/amylase values centers around close observation. Physicians should ensure that subjects have no associated symptoms consistent with pancreatitis, such as abdominal pain. Corticosteroids do not seem to alter the natural history of lipase/amylase elevations. Laboratory values tend to fluctuate on a day-to-day basis and eventually return to baseline or low grade over the course of weeks, whether or not subjects receive corticosteroids. Asymptomatic elevations should be monitored approximately on a weekly basis, and nivolumab should be held per protocol **instructions**. For subjects with elevated lipase/amylase and symptoms consistent with possible pancreatitis, nivolumab should be discontinued, and consultation with a gastroenterologist should be considered. Consultation with the PI or designee should be sought for all high-grade cases of elevated lipase/amylase.

5.2.5.11 Uveitis and visual complaints.

Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (eg, uveitis) is an uncommon, but clinically important, event. Uveitis may occur more frequently with nivolumab + ipilimumab combination therapy than with nivolumab monotherapy or nivolumab in combination with other therapies. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Topical corticosteroids may be used to manage low-grade events. Low-grade events that do not resolve and high-grade events should be managed with systemic corticosteroids. Consultation with the PI or designee for all cases of ocular inflammatory events. Complaints of double vision should also prompt medical evaluation. In addition to ocular inflammatory events, a work-up should also consider pituitary inflammation as a cause (Section 5.2.2.4).

Vogt-Koyanagi-Harada syndrome (VKH) is a T-cell mediated autoimmune attack on melanocytes. VKH manifests as a multi-system disorder characterized by granulomatous panuveitis with exudative retinal detachments, often associated with neurologic and cutaneous manifestations. Rare cases have been observed in post-marketing use of nivolumab. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued, and corticosteroids administered accordingly.

5.2.5.12 Other Immune-mediated Adverse Events

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab should be withheld or discontinued, and corticosteroids administered accordingly. Upon improvement, nivolumab may be resumed after corticosteroid taper. If there is recurrence of any Grade 3 or 4 immune-related adverse reactions or life-threatening immune-related adverse reactions, nivolumab or nivolumab must be permanently discontinued.

Cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab. Diagnosis of myocarditis requires a high index of suspicion and in some cases can be asymptomatic. Therefore, any cases with cardiac or cardio-pulmonary symptoms should undergo prompt diagnostic work- up to evaluate for myocarditis with close monitoring. Troponin is a sensitive but not diagnostic marker of myocarditis. If suspected, prompt initiation of

high dose of steroids (prednisone 1 to 2 mg/kg/d or methylprednisolone 1 to 2 mg/kg/d) and cardiology consultation with diagnostic workup with ECG, troponin and echocardiogram. Additional testing as guided by the cardiologist and may include cardiac MRI. Once a diagnosis is confirmed, nivolumab should be withheld. For grade 3 myocarditis, nivolumab should be permanently discontinued. The recommended management of myocarditis is provided in Appendix K.

The following events have been identified during post approval use of nivolumab. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

- Solid organ and tissue transplant rejection has been reported in patients who have previously undergone transplantation and who were subsequently treated with programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) inhibitors, including nivolumab. Treatment with nivolumab may increase the risk of rejection in solid organ or tissue transplant recipients.
- Rapid-onset and severe GVHD, some with fatal outcome, has been reported in patients who had undergone prior allogeneic HSCT and subsequently received PD-1/PD-L1 inhibitors. Subjects should be screened to determine whether they have undergone a prior allogeneic HSCT prior to participating in nivolumab clinical trials.
- Complications of allogeneic HSCT after treatment with PD-1/PD-L1 inhibitors including nivolumab, administered before allogeneic HSCT, may be associated with an increased risk of transplant-related complications, including GVHD. Fatal cases have been reported in clinical studies. Patients should be monitored closely for early evidence of transplant-related complications

5.2.5.13 Overdose, Warnings, and Precautions

There is no available information concerning overdose with nivolumab. Depending on the symptoms and/or signs leading to the suspicion of overdose, supportive medical management should be provided. There is no specific antidote.

The nonclinical findings of increased late-stage pregnancy loss and early infant deaths/euthanasia in nivolumab-exposed pregnant monkeys (additional details in Section 4.3.8) suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy. However, cases

of human in-utero exposure to nivolumab (involving the fetuses of female subjects receiving nivolumab and female partners of male subjects receiving nivolumab) were reported. Given the potential risk suggested by preliminary data from nonclinical and clinical data, dosing during pregnancy will continue to be prohibited. In addition, women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of nivolumab.

These durations have been calculated using the upper limit of the half-life for nivolumab (~25 days) and are based on the recommendation that WOCBP use contraception for 5 half-lives plus 30 days, and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days after the last dose of nivolumab. Females should not breastfeed while receiving nivolumab and for any subsequent protocol-specified period.

5.3 Ibrutinib.

Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. Ibrutinib 420 mg will be administered orally once daily. Ibrutinib should be administered at the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water. If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules of ibrutinib should not be taken to make up for the missed dose.

Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g. ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is prohibited. Concomitant use of strong CYP3A inducers (e.g. rifampin, rifabutin, phenytoin, carbamazepine, and St. John's Wort) is prohibited. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

5.3.1 Ibrutinib - How Supplied

Supplied as 140mg capsules or as tablets of 3 different strengths: 140mg, 280mg and 420mg. Ibrutinib will be obtained commercially through the patient's insurance.

5.3.2 Stability

Store bottles at room temperature 20°C to 25°C.

5.3.3 Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the Btk. *In vitro*, ibrutinib is a potent inhibitor of Btk activity (IC50 = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of Btk results in sustained inhibition of Btk catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation (IC50 = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression.

5.3.4 Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 6 hours, with a median time to maximum plasma concentration (T_{max}) of 1 to 2 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by CYP 3A4-mediated metabolic pathways. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. About 8% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

5.3.5 Summary of Clinical Safety

For monotherapy studies:

Integrated safety data for a total of 1,523 subjects treated with ibrutinib monotherapy from 17 studies in B-cell malignancies, which includes subjects from 2 randomized-control studies who crossed over from comparator treatment or placebo to receive ibrutinib monotherapy, are summarized below.

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1,523):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Diarrhea	Neutropenia	Pneumonia
Fatigue		Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	
Anemia		Diarrhea
Pyrexia		Fatigue
Neutropenia Upper respiratory tract infection Oedema peripheral Thrombocytopenia Muscle spasms Constipation Arthralgia Vomiting Decreased Appetite Dyspnoea Headache Pneumonia Rash Hypertension Abdominal Pain Back Pain Contusion Dizziness	Diarrhea Fatigue Nausea Cough Pyrexia Muscle spasms Arthralgia Vomiting Decreased Appetite Rash	Anemia Neutropenia Thrombocytopenia Pneumonia Hypertension Hypokalaemia Hyponatraemia

For more detailed information refer to the current version of the IB.

5.3.5.1 Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and

petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria.

In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Use of either anticoagulant or antiplatelet agents comcomitantly with ibrutinib increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. Monitor for signs or symptoms of bleeding.

Supplements such as fish oil and vitamin E preparations should be avoided.

Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Subjects with congenital bleeding diathesis have not been studied.

5.3.5.2 Cardiac arrhythmias

Atrial fibrillation, atrial flutter and cases of ventricular tachyarrhythmia, including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor subjects clinically for atrial fibrillation. Subjects who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, sycope, new onset of dyspnea or chest pain) should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias which persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines.

5.3.5.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Subjects should be monitored for fever, weakness, or easy bruising and/or bleeding, and blood counts should be monitored as outlined in the protocol.

5.3.5.4 Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as Clostridium difficile or other infectious agents. Should symptoms be severe or prolonged follow the protocol dose modification guidelines.

5.3.5.5 Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with mantle cell lymphoma (MCL) and 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib.

5.3.5.6 Non-Melanoma Skin Cancer

Non-melanoma skin cancers have occurred in patients treated with ibrutinib. Monitor patients for the appearance of non-melanoma skin cancer.

5.3.5.7 Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity. One case of Stevens-Johnson Syndrome (SJS), with a fatal outcome, was reported in a subject with CLL. The subject received ibrutinib (420 mg/day) and was also receiving various antibiotics and anti-gout medication (allopurinol) known to be associated with SJS.

5.3.5.8 Lymphocytosis and Leukostasis

Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/μL) may confer increased risk.

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/ small lymphocytic lymphoma (SLL) treated with ibrutinib as single agent. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first month of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in subjects with MCL and 18.7 weeks in subjects with CLL/SLL.

A large increase in the number of circulating lymphocytes (eg, >400,000/μL) has been observed in some subjects. Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in subjects with CLL/SLL receiving ibrutinib in combination with chemoimmunotherapy.

5.3.9 Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of tumor lysis syndrome are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated lactate dehydrogenase (LDH), bulky disease at baseline, and pre-existing kidney abnormalities.

5.3.10 Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. Should symptoms develop follow the protocol dose modification guidelines.

5.3.11 Aspergillosis

Preliminary information from a Phase 1b, single US-center CTEP study (ClinicalTrials.gov Identifier NCT02203526) of primary central nervous system lymphoma (PCNSL) using a novel immune-

chemotherapy regimen of dose-adjusted temozolomide, etoposide, DOXIL®, dexamethasone, ibrutinib, and rituximab (DA-TEDDI-R) confirmed 4 cases of invasive aspergillosis in the first 18 patients that initiated treated. Three of the 4 confirmed cases had a fatal outcome. Additionally, 3 clinically suspected cases were reported in the same study, in which all 3 patients experienced Grade 3 lung infections; however, aspergillosis could not be diagnostically confirmed (bronchoalvelolar lavage and blood cultures in 2 patients were negative for fungi). Two additional ISTs in subjects with relapsed/refractory CNS lymphoma are currently ongoing with single agent ibrutinib, and both allow the concomitant use of systemic steroids to control symptomatic disease. One case of invasive aspergillosis was reported for each of these studies, with incidences of 5.0% and 2.6%, respectively, for an overall incidence of 7.8% across all three IST/CTEP studies.

There are currently no company sponsored clinical trials ongoing in PCNSL or CNS lymphoma. In a recent analysis of completed and ongoing sponsored ibrutinib clinical trials (N=3038), the reported incidence of aspergillosis was 0.49%, which was similar to the reported pooled incidence in 4 active comparator studies (0.5%) across the ibrutinib clinical development. Based on the existing clinical experience with ibrutinib in subjects with B-cell malignancies under approved indications, an association between ibrutinib and invasive aspergillosis could not be established at this time.

5.3.12 Febrile Neutropenia / Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

5.3.13 Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset of hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

5.3.14 Overdose

There is no specific experience in the management of ibrutinib overdose in patients. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

6.0 DOSE DELAYS, MODIFICATIONS AND MANAGEMENT OF TOXICITY

Adverse events that are clearly attributable to one medication (eg. atrial fibrillation due to ibrutinib or hypophysitis due to nivolumab) may be managed by dose interruption, reduction or permanent cessation of the offending medication, depending on the severity of the adverse event (see specific information for each drug, below). Provided the patient is clinically stable, in the opinion of the investigator, the other medication(s) may be continued per protocol. Where a severe adverse event occurs that is thought to be therapy-related, but it is unclear which of the study medications is responsible (eg. abnormal liver function tests), all study drugs should be held until severity has reduced to grade ≤1. If a severe adverse event occurs that leads to permanent cessation of either nivolumab or blinatumomab, but the patient continues to derive benefit from receiving the remaining study medications, the patient may remain on study. However, if both nivolumab and blinatumomab are ceased due to AEs, the patient will come off study. Ibrutinib discontinuation for AEs will not mandate that the patient be removed from the study

If a decision is made to permanently discontinue a study medication due to an adverse event, this must be discussed with the PI or designee.

6.1 Blinatumomab Infusion interruption/dose modification due to adverse events

Dose modifications (interruptions, withholdings, and criteria for restarting treatment) are summarized in table 2.

Table 2. Dose interruptions, modifications and criteria for discontinuation and recommencement of therapy

Toxicity	Grade	Action
Cytokine Release Syndrome (CRS) +/- DIC/coagulopathy	Grade 2	Continue blinatumomab. Give IV fluid bolus (500-1000mL normal saline); repeat as necessary to keep systolic BP >90mmHg. If systolic BP ≤90mmHg after 2L IV normal saline, withhold blinatumomab and consider ICU transfer and inotropic support. Manage blinatumomab re-commencement as per grade 3 AE, below.
	Grade 3	Withhold blinatumomab until resolved to < or = grade 1, then restart blinatumomab at the next lowest dose* after dexamethasone pre-medication (see table 1). Re-escalate to the next highest dose level after 7 days and to the highest dose level after a further 7 days if toxicity does not recur.
	Grade 4	Discontinue blinatumomab permanently.
Neurological Toxicity	Seizure	Discontinue blinatumomab permanently if more than one seizure occurs.
	Grade 3*	Withhold blinatumomab for at least 3 days and until no more than Grade 1 (mild) and, then restart blinatumomab at the next lowest dose level†, after dexamethasone pre-medication. Re-escalate to the next highest level after 7 days and to the highest dose level after a further 7 days if the toxicity does not recur. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently.
	Grade 4	Discontinue blinatumomab permanently.
Other Clinically Relevant Adverse Reactions at least possibly related to blinatumomab	Grade 3	Withhold blinatumomab until no more than Grade 1 (mild) toxicity, then restart blinatumomab at the next lowest dose level†, after dexamethasone pre-medication. Re-escalate to the next highest level after 7 days and to the highest dose level after a further 7 days if the toxicity does not recur. If the

		toxicity occurred at 9 mcg/day If the toxicity takes more than 14 days to resolve, discontinue blinatumomab permanently.
	Grade 4	Discontinue blinatumomab permanently.
Unrelated AEs	All grades	If blinatumomab was interrupted due to an AE that was ultimately deemed by the investigator to be unrelated to blinatumomab (eg. Infection resulting in febrile neutropenia), blinatumomab can be resumed at the same dose as prior to dose interruption, when the patient is deemed by the investigator to be clinically stable. Pre-medication with dexamethasone as per Table 1 should be given prior-to and after recommencement of blinatumomab.

* **NB.** Grade 3 neurotoxicity due to >1 generalized seizure will mandate permanent cessation of blinatumomab. †The next lowest dose is 28mcg/day if the toxicity occurred at 112mcg/day or 9mcg/day if the toxicity occurred at 28mcg/day. If the toxicity occurred at 9mcg/day, re-challenge after resolution to grade 1 or less may be attempted after appropriate pre-medication. Dose modifications other than those described in the table may be made, if deemed, after discussion with the PI, to be in the patient's best interests.

Common Terminology Criteria for Adverse Events (CTCAE) clinical grade 4 adverse events (AEs) that are characteristic of blinatumomab (i.e. CNS events and cytokine release syndrome (CRS), described in more detail below), will require permanent discontinuation of blinatumomab. For all other grade 4 AEs, the Principal Investigator or designee should be notified; an assessment should be made to determine causality and the risk:benefit for each individual patient to continue or discontinue blinatumomab treatment. CTCAE version 5.0 will be used for grading of AEs, with the exception of CRS (graded according to appendix C) and neurotoxicity (graded according to appendix E). Please see Appendix F for the CTCAE grading of common organ-associated AEs.

6.1.1 Infusion interruption/dose modification due to CNS events

Please see Appendix E for the grading of CNS-related AEs. In case of CNS-related AEs, dexamethasone should be administered at a dose of at least 24 mg/day. The dexamethasone dose

will then be reduced step-wise over approximately 4 days. The following investigations should be performed:

If the CNS-related adverse event is CTCAE grade 3 or higher, blinatumomab will be stopped immediately and a physical exam, vital signs and safety laboratory tests will be performed. Additional measures can be taken at the discretion of the investigator, depending on the nature of the adverse event. The following diagnostic investigations are recommended:

1. A non-contrast CT scan of the head to exclude CNS hemorrhage.
2. Assessment of cerebrospinal fluid should be performed for cytology, cell count, B- and T-cell measurement (by flow cytometry), and viral studies (HSV 1/2, HSV6, JC virus and adenovirus).
3. Additional investigations of the CSF should be performed as clinically appropriate.
4. A contrast-enhanced magnetic resonance imaging (MRI) of the head should be performed for subjects who had to interrupt treatment because of a CNS event grade 3, before treatment is resumed.

Please note that there may be circumstances in which some of the above investigations will not be able to be performed (for example, CSF assessment may not be possible in patients with low platelet counts or abnormal coagulation parameters, for safety reasons, and MRI may not be possible if patients are unable to lie still for the duration required to perform this examination). Therefore, not performing these tests will not be considered protocol deviations.

For subjects who experience a CTCAE grade 3 CNS adverse event or serious adverse event leading to treatment interruption, if the event has decreased to at least CTCAE grade 1 within 1 week, treatment may be restarted within 2 weeks, but not earlier than 72 hours (3 days) after the infusion was stopped. When recommenced, treatment will begin at the next lowest dose.

However, a grade 3 CNS event leading to treatment interruption at the dose of 9 µg/day or a CNS event needing more than 1 week to resolve to grade less than or equal to 1 will result in permanent treatment discontinuation.

In case of CNS-related events CTCAE grade 4, or in case of occurrence of more than one generalized seizure (considered grade 3 CNS toxicity), the infusion of blinatumomab will be stopped immediately and treatment will be permanently discontinued.

For patients in whom the criteria for recommencement of blinatumomab, as described above, are met, blinatumomab can be recommenced, following dexamethasone premedication as described in Table 1, at the next lowest dose. Blinatumomab will be escalated to the next highest dose after 7 days, if the toxicity does not recur. The subject should remain hospitalized until at least 2 days after re-escalation to the dose at which the toxicity first occurred.

If the CNS event was a generalized seizure (CTCAE grade 2 or above), appropriate prophylactic anticonvulsant treatment will be administered prior to recommencing therapy.

6.1.2 Dose interruption and modification for cytokine release syndrome (CRS) and/or DIC/coagulopathy

For CTCAE grade 2 CRS which requires inotropes, grade 3 CRS and CTCAE grade 3 DIC/coagulopathy, blinatumomab can then be restarted at the next lowest dose (see table 2), once the event has returned to grade ≤1 severity. If the event occurred at a dose of 9 mcg/day and no neurological toxicity of greater than or equal to grade 3 occurred, treatment with blinatumomab will be interrupted until the event resolves to less than or equal to grade 1 and then resumed at 9 mcg/d, after dexamethasone pre-medication as described in Table 1. However, if the AE lasts for ≥2 weeks, then blinatumomab will be permanently discontinued.

In CRS of ≥grade 2, dexamethasone should be administered orally or IV at an initial dose of at least 3 x 8 mg/day. The dose can then be reduced step-wise over approximately 4 days according to clinical response.

6.1.3 Dose interruption and modification for all other events

For all other CTCAE grade 3 events and clinically significant laboratory value changes, investigator assessment should be used to determine causation. If considered to be at least possibly related to blinatumomab, the blinatumomab must be interrupted. Blinatumomab can be recommenced after resolution of the AE to grade 1 or less, after dexamethasone pre-medication as described in Table 1.

6.1.4 Resumption of dosing and dose escalation after dose interruption

Patients who have had their dose interrupted, who meet the safety criteria outlined above, will have an option to resume dosing, once the event has resolved to grade ≤1, after the time periods outlined for the specific AEs above and in table 2. Please note that, in the event of grade 3 neurological toxicity, the blinatumomab must not be resumed for at least 72 hours after interruption, in addition to waiting for the event to resolve to grade ≤1. After all other reasons for interruption, blinatumomab may be resumed when the toxicity has resolved to grade ≤1.

Pre-medication will be given with 20mg of PO/IV dexamethasone 12-24 hours prior and 20mg dexamethasone 1 hour prior to recommencement of the infusion, as per table 1.

Dosing should be resumed at the next lowest dose level (i.e. 9 µg/day if the AE occurred at 28 µg/day or 28 µg/day if the AE occurred at 112 µg/day). After 7 days of dosing, provided the patient is clinically stable, dose escalation may resume per protocol, with appropriate dexamethasone pre-medication (as outlined in table 1). Alternatively, treatment may be continued at the reduced dose after discussion with the principal investigator, if it is felt that the risks of further dose escalation outweigh the benefits. Re-start of the infusion and all subsequent dose escalations should be performed in the hospital.

The patient should be observed in hospital for the remainder of the dose re-escalation period and for 3 days after reaching the highest dose that will be administered in that cycle.

The total duration of blinatumomab in cycle 1 and 2 should total 28 days If dose interruptions occur, the missed days should be added to the end of the cycle. The total number of days of blinatumomab administration will not exceed 28 days, even if dose reductions occurred. An infusion interruption of more than 2 weeks due to an adverse event related to blinatumomab will lead to permanent discontinuation of treatment. In case of logistical difficulties, restart of treatment can be postponed for up to 7 additional days without resulting in permanent treatment discontinuation. Treatment may be also interrupted or permanently discontinued at the discretion of the investigator if any clinical/laboratory adverse event is considered to be medically relevant.

If there is recurrence of grade ≥3 toxicity, determined as at least possibly related to blinatumomab, after reinstitution of blinatumomab, blinatumomab will be permanently discontinued.

For the sake of clarity, if blinatumomab is interrupted and subsequently recommenced, the days when blinatumomab was not given will not be counted as treatment days. e.g. If treatment was interrupted on day 7 for 3 days and then recommenced, the day that blinatumomab was recommenced will be numbered as day 8, not day 11.

Nivolumab (in the absence of nivolumab-related adverse events requiring treatment interruption) will always be given on day 1 and day 15 of blinatumomab treatment. For this reason, if there are delays in blinatumomab administration due to adverse events, there will be an identical delay in administration of the next nivolumab dose. This is important both for reasons of clarity and also because nivolumab could potentiate blinatumomab-related adverse events.

6.2 Recommendations for management of nivolumab-associated toxicity.

Please see appendix K.

6.3 - management of ibrutinib-associated toxicity and dose modifications

Section 6.3 outlines recommendations for management of ibrutinib-associated toxicity. However, dose adjustments outside these guidelines can be made by the investigator if considered to be in the patient's best interests.

6.3.1 Recommended dose modifications:

Recommended dose modifications of ibrutinib are described below:

Toxicity Occurrence	**Dose modification** **Starting Dose = 420 mg daily**
First	Restart at 420 mg daily
Second	Restart at 280 mg daily
Third	Restart at 140 mg daily
Fourth	Discontinue ibrutinib

6.3.2 Hematologic toxicity:

Interrupt ibrutinib for any Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the toxicity has resolved to Grade ≤1 or baseline, reinitiate ibrutinib as

per the table above.

6.3.3 Non-hematologic toxicity:

Interrupt treatment for any grade 3 or greater non-hematological toxicity. Once the toxicity has resolved to grade ≤1 or baseline, restart the study drugs as per the guidelines for the hematologic toxicity as above.

If the dose of ibrutinib is reduced, at the investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction if the toxicity that led to the reduction has resolved to Grade ≤1 or baseline. Dose changes will be recorded in the medical record.

6.3.4 Leukocytosis/Leukostasis:

A high number of circulating malignant cells (>400000/mcL) may confer increased risk of leukostasis; these subjects should be closely monitored. Administer supportive care such as hydration and/or leukophoresis as indicated. Ibrutinib may be temporarily held, and investigator should be contacted.

6.3.5 Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of screening (Child- Pugh class B or C) are excluded from study participation. For patients with mild liver impairment (Child-Pugh class A), recommended dose is 140mg per day. See Appendix L for Child-Pugh grading system.

6.3.6 Dose Modification of Ibrutinib in patients receiving CYP3A4 enzyme inhibitors and inducers:

Co-administration with strong or moderate CYP3A inhibitors should be avoided, where possible and alternative agents with less CYP3A inhibition considered.

Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended. For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g., antifungals and antibiotics) consider interrupting ibrutinib therapy until the CYP3A inhibitor is no longer needed.

Reduce ibrutinib dose to 140 mg if a moderate CYP3A inhibitor must be used (e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, and ciprofloxacin).

Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of ibrutinib toxicity.

Use of strong CYP3A4 enzyme inducers (eg. rifampicin) should be avoided.

7.0 CONCOMITANT THERAPY

7.1 Allowed concomitant therapy

Patients should receive full supportive care during study participation, including hematopoietic growth factors, transfusion of blood products, fluid and electrolyte replacement, and antibiotics when appropriate.

7.2 Excluded concomitant therapy

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Immunotherapy (outside of this study)
- Radiotherapy (Note: Localized radiotherapy to an area not compromising bone marrow function is allowed), provided this is being performed for treatment of another malignancy. If radiotherapy is performed for progressive Richter Transformation, the patient should be removed from the study.
- Any therapies intended for the treatment of lymphoma/leukemia whether FDA-approved or experimental (outside of this study)
- Steroid therapy for anti-neoplastic intent, after initiation of blinatumomab. Inhaled steroids for asthma, topical steroids, steroids as part of premedication for blinatumomab or management of blinatumomab toxicity, or replacement/stress corticosteroids are permitted.

7.3 Recommended anti-infective prophylaxis

- Pneumocystis pneumonia prophylaxis with co-trimoxazole 160/800mg twice daily on Mondays, Wednesdays and Fridays. Patients with hypersensitivity to co-trimoxazole may receive alternative prophylaxis, per investigator discretion.
- Varicella Zoster prophylaxis with valacyclovir 500mg daily, or equivalent.
- Anti-fungal prophylaxis may be given, per investigator discretion.

7.4 Tumor lysis syndrome prophylaxis

- All patients will receive allopurinol 300mg per day for the first 16 days of cycle 1, unless contraindicated. If the patient has a contraindication to allopurinol, a suitable alternative will be chosen.
- Rasburicase may be given in high risk patients, per institutional guidelines.

8.0 PRE-TREATMENT EVALUATION

Pre-treatment evaluation is outlined in table 3.

Table 3. Pre-treatment evaluation

Pre-treatment evaluation is outlined in table 3, below. Further explanation for the specific tests ordered is provided in table 4, contained within section 9.

Procedure	Schedule
Informed consent	Within 30 days of therapy
Medical history	Within 14 days of therapy
Complete physical examination including vital signs	Within 14 days of therapy
Complete neurologic exam	Within 14 days of therapy
Document concomitant medications	Within 14 days of therapy
Hematology	Within 14 days of therapy
Biochemistry	Within 14 days of therapy
Bone marrow aspirate and biopsy	Within 60 days of therapy
CLL prognostic marker evaluation on bone marrow (FISH, using probes for ATM (11q22.3), D12Z3 (12cen), D13S319 (13q14.3), LAMP1 (13q34), p53 (17p13.1); stimulated metaphase cytogenetics; next generation sequencing (NGS) panel for CLL-associated mutations, including *TP53* (see below for details); *IGHV* mutational status and VH utilization (this does not need to be repeated if previously performed at M.D. Anderson); flow cytometry, including CD38. Please note tests can be done on peripheral blood if a bone marrow sample is not available. Additionally, some patients with Richter Transformation may not have sufficient CLL cells in bone marrow or blood to perform this testing. Not performing these tests will therefore not be considered as deviations.	Within 60 days of therapy
PETCT scan. If PETCT cannot be done for logistic reasons, CT scan of the neck, chest, abdomen and pelvis will be performed instead.	Within 28 days of therapy
Lymph node biopsy (or pathology review of recent biopsy material). If a lymph node biopsy consistent with Richter Transformation was performed outside this window and PETCT shows changes consistent with Richter Transformation, biopsy does not need to be repeated. Pathology review for out-of-window biopsies does not need to be performed if the diagnosis was made originally at M.D. Anderson.	Within 28 days of therapy
Prognostic marker evaluation on lymph node biopsy material. Where possible, this will include CLL FISH panel or array cGH, unstimulated and stimulated metaphase cytogenetics, *IGHV* mutational status and VH utilization and NGS panel	
Pregnancy test	Within 7 days of therapy
Immunologic evaluation, if patient consents to correlative studies	Within 14 days of therapy

Tissue banking	Within 28 days of therapy

9.0 EVALUATION DURING TREATMENT

Table 4: evaluation which will take place pre-treatment and during the study

Assessment	**Base-line(1)**	**Cycle 1**				**Response assess**	**Cycle 2**						**Response assess**	**Ibrutinib + nivolumab consolidation (q4w for 36 weeks from 2nd response assessment**	**Survei-llance (2)**	**At progress-sion/ End-of-study**
Day within cycle(3)	**-28 to 1**	**1**	**15-31**	**36**	**43**	**57 (+/- 1 week)**	**1-3**	**8**	**15**	**22**	**29**	**43**	**57 (+/- 1 week)**			
Informed consent(4)	**X**															
Medical history(5)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**q12w**	**X**
Physical examination(6)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**q12w**	**X**
Neurological examination(7)	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**					
Concomitant medications(8)	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**		**X**	**q12w**	**X**
CBC with differential(9)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**q12w**	**X**
Bio-chemistry(10)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**q12w**	**X**
Thyroid function(11)	**X**	**q4 w**														
Bone marrow(12)	**X**					**X**							**X**			**X**
PETCT scan(13)	**X**					**X**							**X**	**q12 weeks**	**q24w**	**X**
Lymph node biopsy(14)	**X**															**X**
Pregnancy test(15)	**X**															**X**
NGS panel(16)	**X**															**X**
Immunologic evaluation(17)	**X**															**X**
Tissue banking(18)	**X**															**X**
ctDNA(19)	**X**					**X**							**X**	**At completion of nivolumab**		**X**
Saliva (20)	**X**															

[1]Baseline/screening testing. This must be performed within the timeframes outlined in table 3.

[2]Surveillance. Patients will have routine history and physical examination, CBC, routine biochemistry approximately every 12 weeks and a PETCT scan or CT scan with and without IV contrast approximately every 24 weeks (+/- 4 weeks) after completing ibrutinib + nivolumab consolidation, until 2 years after initiation of therapy, until relapse,allogeneic stem cell transplantation, or initiation of salvage therapy, whichever occurs first. Patients who have not proceeded to allogeneic

transplantation and who remain in remission at the end of the study, and those who proceed to transplant, will be enrolled on a departmental umbrella protocol (DR09-0223) to follow them for overall survival.

[3]Evaluations during the inpatient stay (planned for day 15-31) must take place on the scheduled day. Please note that many patients will have treatment delays, as a result of toxicity. This is expected. After hospital discharge, evaluations during cycle 1 occur weekly and can occur within +/- 4 days of the scheduled time. Response assessment must take place between 2 and 4 weeks after the completion of cycle 1 of therapy. Cycle 2 should commence 4-8 weeks after completion of cycle 1. Evaluation during cycle 2 days 1-3 (given as an inpatient) should occur on the scheduled day. Subsequent evaluations during cycle 2 can occur within +/- 4 days of the scheduled time. Subsequent response assessment must take place between 2 and 4 weeks after the completion of cycle 2 of therapy. Please note that response assessments should take place on day 57 of cycle 1 and cycle 2 (+/- 1 week). Cycle 2 will not commence, until after completion of the first response assessment.

[4]Informed consent. All patients must take part in the informed consent process. During the consent process, the person obtaining consent must inform the patient of all elements of informed consent. Adequate time must be allowed for questions and for the patient to make a voluntary decision. No protocol-specific procedures are to be performed until the patient has signed and dated an Institutional Review Board (IRB)/Ethics Committee (EC)-approved informed consent form. Each patient's participation in the trial begins with the signing and dating of the informed consent form.

[5]Medical history. Medical and surgical history and demographic information will be recorded at baseline. Medical and surgical history includes diagnoses, therapies, and medical and surgical treatments. Particular attention should be paid to any pre-existing neurological symptoms. At subsequent assessments, focused history/AE assessment will be performed.

[6]Physical examination, including vital signs. Vital signs are temperature, pulse, respiratory rate, and blood pressure. A complete physical examination, including measurement of weight, must be performed at screening; at Cycle 1, Day 1 prior to the first administration of study drug and at the end-of-treatment Visit. Height need only be recorded at the initial visit. Following the physical examination for Cycle 1, Day 1 — with the exception of the end-of-treatment Visit, where a full physical

examination must also be performed — all subsequent physical examinations, can be focused to the individual needs of the individual patient.

[7]A neurological examination must be performed during the screening period. Neurological examination at the screening assessment should include examination of the peripheral nervous system, cranial nerves and cognitive function. The latter must be determined using The M.D. Anderson simplified 10 point neurologic examination. Subsequent to the screening exam, the neurological assessment can be tailored, according to the patient's symptoms. Whenever there is a change in neurological status suggestive of blinatumomab-related neurotoxicity, the M.D. Anderson 10 point neurological examination score will be documented, to assist toxicity grading (see Appendix E and G).

[8]Concomitant medications. These will be captured in the medical record.

[9]Complete blood count with differential.

[10]Biochemistry. At screening, at a minimum this should include the following: sodium, potassium, chloride, bicarbonate (or total carbon dioxide [CO2]), blood urea nitrogen (BUN, or urea), random glucose, albumin, creatinine, total bilirubin (direct and indirect), ALT +/- AST, alkaline phosphatase, phosphorous, calcium, uric acid and LDH. At subsequent timepoints, this should include, at a minimum, creatinine, potassium and ALT. On the day of and for two days after dose initiation or dose escalation, uric acid, calcium and phosphorous should be measured at least daily.

[11]Thyroid function (at least TSH and T4) is required at baseline and approximately every 4 weeks during the study to monitor for nivolumab-induced hypothyroidism, until the completion of nivolumab therapy.

[12]Bone marrow examination Bone marrow aspiration and trephine biopsy will be performed pre-treatment for cytological and histological assessment during the screening period. The following additional studies will be performed on the pre-treatment bone marrow and on bone marrow evaluation performed at disease progression: CLL prognostic marker evaluation on bone marrow (or blood if bone marrow not available): FISH, using probes for ATM (11q22.3), D12Z3 (12cen), D13S319 (13q14.3), LAMP1 (13q34), p53 (17p13.1); stimulated metaphase cytogenetics; next

generation sequencing (NGS) panel for CLL-associated mutations, including *TP53* (see below for details); *IGHV* mutational status and VH utilization (this does not need to be repeated if previously performed at M.D. Anderson); flow cytometry. Some patients with Richter Transformation may not have sufficient CLL cells in bone marrow or blood to perform this testing. Not performing the CLL prognostic factor evaluations outlined above will therefore not be considered as protocol deviations, Bone marrow evaluation for response assessment will include aspirate and biopsy for cytological and histological assessment and a standard 4-color flow cytometry panel for evaluation of minimal residual disease (MRD) in the co-existing CLL.

[13]18-FDG PETCT scan, from the head to mid-thigh, will be performed during the screening period, for response assessment, during surveillance and at disease progression. Target lesions will be evaluated by a trained radiologist: bi-directional lymph node measurements will be performed and quantitation of 18-FDG uptake in target lesions, using standardized uptake values (SUV). If PETCT cannot be done for any reason, CT will be performed instead. If CT scan was done for initial staging purposes rather than PETCT, CT scan will also be performed for restaging and surveillance.

[14]Lymph node biopsy may be performed. This is at treating physician discretion. The site for biopsy will be chosen according to the PETCT. The target lymph node for biopsy should have a maximal diameter of ≥1.5cm and a SUV of at least 5. An SUV of ≥10 is preferred for the biopsy. The investigator, in consultation with the proceduralist, who will perform the biopsy, will determine the optimal lymph node for biopsy. A surgical excisional biopsy is preferred, but if not feasible for technical or logistic reasons, a core biopsy, performed in interventional radiology, will be performed instead. If a diagnosis of RT has already been made from lymph node or bone marrow biopsy, patients need not have a repeat biopsy – however, the pathology will be reviewed at MD Anderson for diagnostic accuracy prior to the patient being considered eligible for the study. Patients will be asked for consent to store lymph node tissue for research purposes, on a separate protocol, prior to a diagnostic biopsy being performed. Lymph node biopsy will be performed during the pre-treatment screening period and at relapse.

[15]Pregnancy test. The pregnancy test must be a beta-human chorionic gonadotropin (β-HCG) test, using either urine or serum. Women who are not of childbearing potential (status post-hysterectomy, status post-bilateral oophorectomy, or postmenopausal [defined as amenorrhea for at least 12

months]) do not need to have the test performed. If the test is deemed necessary, it must be performed within 7 days of treatment initiation and known to be negative prior to treatment initiation. Women of childbearing potential at study commencement must also complete the pregnancy test at the End-of-Treatment Visit.

[16]A targeted next generation sequencing panel will be performed to identify important driver mutations in CLL and RT. The panel will be performed during the pre-treatment screening period and at relapse.

[17]Exploratory immunologic investigation will be performed. This will be optional and patients consented separately on protocol PA16-0360.

[18]Patients will be asked to have tumor tissue stored in a sample bank for later exploratory genomic analyses, on a separate IRB protocol (PA15-0965). This is optional and a separate informed consent process will be undertaken for these studies. These will be performed on the diagnostic specimen and relapse specimen.

[19]Blood samples will be taken pre-treatment, at each response assessment, at 1 year, 2 years and at disease progression for plasma and cell banking. These samples will be used to perform serial NGS (including potentially NGS and WGS), to identify gene mutations and copy number alterations in ctDNA and circulating mononuclear cells, if the patient agrees to participate in protocol PA16-0919.

[20]Saliva collection will be done at baseline if the patient is participating in protocol PA16-0919.

10.0 CRITERIA FOR RESPONSE

10.1 Richter's Transformation

Response assessment in RT will be performed according to the Lugano criteria for diffuse large B-cell lymphoma, as outlined in Appendix H.

10.2 Response Criteria in Chronic Lymphocytic Leukemia

The response of the co-existing CLL will be assessed according to the 2018 IWCLL criteria, which are re-produced in appendix I Overall response is defined as a CR or PR. Patients with missing or no response assessment will be classified as non-responders. The full criteria are re-produced below. The co-existence of RT may result in difficulty determining whether residual nodal, splenic or hepatic enlargement is due to persistent RT or CLL. For the purposes of response assessment, PET criteria

will be used to distinguish the two. However, if diagnostic difficulty exists, biopsy may be required.

11.0 ADVERSE EVENT REPORTING

Toxicities will be graded according to the NCI Expanded Common Toxicity Criteria.[21]

11.1 Leukemia-specific Adverse Event Recording and Reporting Guidelines

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

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

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe. The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all patients enrolled on the trial.

11.1.1 Electronic case report (eCRF)

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

11.1.2 Guidelines for recording and reporting of adverse and serious adverse events

These guidelines will be followed for the recording and reporting of adverse (AEs) and serious adverse events (SAEs).

1. Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event. The medical history

section of the case report form will serve as the source document for baseline events once signed and dated by the principal investigator.

a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before initiation of treatment:
    i. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
    ii. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.

2. The maximum grade of the adverse event will be captured per course or protocol defined visit date.
3. These adverse events will be recorded in the case report form:
    a. Any grade adverse event that is possibly, probably, or definitely related to the study drug(s).
    b. All serious adverse events regardless of attribution to the study drug(s).
    c. Any grade adverse event regardless of attribution to the study drug(s) that results in any dose modification.
    a. Hematologic adverse events will be recorded and reported according to IWCLL guidelines, as outlined in Appendix J.
4. Serious adverse events will be reported according to institutional policy.
5. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

11.1.3 Abnormal hematologic and chemical values

Abnormal hematologic and chemical values, the apogee or nadir (whichever is appropriate) will be reported per course on the case report form.

11.1.4 Attribution of AEs

All events will be collected for the purpose of

grading, and determining attribution to study drugs by the PI using the following scale:

- Unrelated: The AE is clearly NOT related to the intervention.
- Unlikely: The AE is doubtfully related to the intervention.
- Possible: The AE may be related to the intervention.
- Probable: The AE is likely related to the intervention.
- Definite: The AE is clearly related to the intervention.

11.1.5 Documentation of grade 3 and greater non-hematologic adverse events

All grade 3 and greater non-hematological events that are felt to be related to protocol treatment drugs will be documented on the toxicity log and entered into the case report form. The toxicity log and case report form data must reflect the relationship to the drug the event is felt to be related to.

11.1.6 Serious Adverse Event Reporting (SAE)

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

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

11.1.7 Serious adverse reaction (SAR)

An SAE where a causal relationship between a medicinal product and the SAE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

11.1.8 Suspected Unexpected Serious Adverse Reaction (SUSAR)

An SAR, the nature or severity of which is not consistent with the applicable product information i.e. Investigator’s Brochure for an unauthorized medicinal product or summary of product characteristics for an authorized product).

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

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 100 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 100 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

11.3 Reporting to FDA

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32). Pregnancy, drug overdose, and secondary malignancy will be handled as SAE.

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The

University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

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

11.4 Investigator Communication with Amgen

- Suspected unexpected serious adverse reactions (SUSARs). When PI/Research staff receives a SUSAR, it shall transmit the final report of that event to Amgen within **twenty four (24) hours** of submitting that report to the applicable regulatory authority.
- Any pregnancy occurring during the study must be reported to Amgen within 10 days.
- SAEs will be reported to Amgen as a cumulative report, every 6 months.
- All adverse events recorded during the study will be forwarded to Amgen at the completion of the study for reconciliation. However, expedited reporting is not required for AEs not classified as serious.
- Investigational pharmacy will communicate with Amgen regarding how expired on unused drug will be handled.

All SAEs and SUSARs should be reported via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:

Fax: 888-814-8653 (toll-free, US)
805-480-9205 (toll) OR
E-mail: svc-ags-in-us@amgen.com.

11.5 Investigator Communication with BMS

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS

Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- An SAE report should be completed for any event where doubt exists regarding its seriousness;
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- Institutional eSAE form will be used to submit SAE data to BMS. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.
- The Sponsor will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).
    - The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
    - GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
    - The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).
- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).
- In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious

Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.

- ✓ Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.
- ✓ Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS. BMS will perform due diligence follow-up using the BMS Pregnancy Form which the investigator must complete.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:
Related: There is a reasonable causal relationship between study drug administration and the AE.
Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.
Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

NONSERIOUS ADVERSE EVENT

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from following the subject's written consent to participate in the study.

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin following the subject's written consent to participate in the study. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.
The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

12.0 CRITERIA FOR REMOVAL FROM STUDY.

Criteria for removal from study include, but are not restricted to, the following:

- Clinically significant progressive disease.
- Recurrent non-compliance by the patient with protocol requirements.
- Patient's request to be removed from the study.
- Investigator’s decision that a subject does not benefit from treatment anymore, e.g., non-response or development of progressive disease
- Transition to an alternative therapy, including allogeneic stem cell transplantation.
- Permanent cessation of nivolumab **and** blinatumomab: if a patient permanently discontinues either nivolumab or blinatumomab (but not both) due to adverse events, they may remain on study, if they continue to derive treatment benefit and benefit outweighs risk, in the opinion of the investigator. Patients who permanently discontinue both nivolumab and blinatumomab due to adverse events will be removed from the study.
- Permanent discontinuation of ibrutinib for any reason will not be an indication to remove a patient from study, if, in the opinion of the investigator, the patient is deriving benefit from treatment and it is safe to continue the other agent(s).

13.0 CORRELATIVE STUDIES

All correlative studies are optional and failure to collect these studies at any of the specified time-points is not a protocol deviation. Patients will consent separately to having these studies taken.

13.1 Immunologic analyses

The purpose of these analyses is to determine pre-treatment immunologic parameters predictive of response to blinatumomab treatment and to evaluate treatment-induced immunologic changes within the blood and tumor tissue during treatment and their correlation with response:

13.1.1 Studies on tumor tissue

Patients will have surgical excisional biopsy or interventional radiology-guided core biopsies performed at baseline if required for diagnostic purposes. If patients consent to a separate IRB-approved protocol (PA15-0965), excess tumor tissue will be cryopreserved and used for exploratory immunohistochemical characterization of tumor infiltrating lymphocyte (TIL) populations, including expression of immune checkpoint molecules (PD1 and PDL1). In addition, tissue will be cryopreserved for later genomic investigation (see section 13.2, below)

13.1.2 Studies on peripheral blood T-cell population

In addition, if patients consent, circulating T-cell numbers and function will be analyzed at the following time points: i) baseline; ii) 24-48 hours after initiation of cycle 1; iii) 1 week after initiation of cycle 1; iv) 4 weeks after initiation of cycle 1; v) prior to initiation of cycle 5; vi) at the completion of cycle 2. This comprehensive analysis will include both phenotypic and functional characterization of T-cells, as well as the expression levels of immune checkpoint molecules. We hypothesize that T-cell numbers and function will be predictive of response to blinatumomab and that up-regulation of PD1 on T-cells will be a potential resistance mechanism. This testing will be performed on protocol PA16-0360.

13.2 Tumor banking.

Patient tumor tissue, DNA, RNA and plasma will be stored pre-treatment and at relapse on a separate IRB-approved research protocols (PA15-0965). This will be optional and patients will sign separate consent forms for this. At a later date, this tissue may be used in genomic and proteomic studies to determine drivers of disease biology and resistance mechanisms to therapy.

13.3 Evaluation of plasma circulating tumor DNA (ctDNA)

If patients consent, peripheral blood samples will be collected, processed and banked at baseline, 1st and 2nd response assessments, 12 and 24 months and at the time of relapse. We will bank saliva from patients at baseline; sequencing from saliva will serve as a normal control. In patients where there is a clinical need to perform a lymph node biopsy for diagnostic purposes (eg. suspicion of Richter Transformation), we will use leftover tissue for sequencing. Targeted next-generation sequencing will be performed on ctDNA and compared to bone marrow, peripheral blood mononuclear cells and lymph node tissue, where available. At disease progression, we will perform whole exome and low coverage whole genome sequencing, where appropriate, from the cellular component of peripheral blood, plasma and/or bone marrow at baseline and relapse and from nodal tissue where available, to identify mutations and copy number alterations which have emerged during therapy and may be responsible for resistance. This testing will be performed at Peter MacCallum Cancer Centre in Melbourne, Australia. If new, somatic mutations are identified at progression, targeted deep sequencing and/or digital PCR testing for these mutations will be performed from stored, serial plasma samples to identify and quantitate their presence in plasma over time. This testing will be performed on protocol PA16-0919 as an optional procedure.

14.0. STATISTICAL CONSIDERATIONS

The cohort of 9 patients already treated demonstrates the feasibility and safety of blinatumomab as a single agent for the treatment of RT. The overall toxicity profile of blinatumomab in RT was very favorable and this cohort of patients can be used as a “safety cohort,” prior to proceeding with a phase II study evaluating the combination with ibrutinib + nivolumab. As discussed above, the combination of ibrutinib and nivolumab was also very well tolerated.

We have completed a phase II study of ibrutinib + nivolumab, and achieved an ORR of 43%. This will serve as our “base case” estimation of the response rate that we would see with the combination of ibrutinib + nivolumab. If blinatumomab (ORR 1/8 = 12.5%) provides additive benefit only, this will result in an ORR of 50-55% with the combination of ibrutinib + nivolumab and blinatumomab. However, we expect synergy between the two regimens. We have therefore designed our statistical analysis around achieving an ORR of approximately 60%, which would suggest some synergy

between the two regimens. Higher response rates would suggest a greater degree of synergy between blinatumomab and ibrutinib + nivolumab, which we hope to achieve.

We propose to enroll an additional 21 patients, with the goal of evaluating the efficacy and safety of the proposed combination therapy. A sample size of 21 patients ensures that, if the trial is not terminated early, a posterior 90% credibility interval for overall response rate will have width of 0.33, under the assumption of a 60% of overall response rate (13/21 responses) and beta prior as described below. Under this scenario, the lower boundary of the 90% credibility interval matches the 43% ORR that was seen with ibrutinib + nivolumab therapy.

The primary outcome will be overall response (ORR), assessed after completion of 2 courses of blinatumomab.

We will utilize a Bayesian trial design to enable simultaneous monitoring of efficacy and toxicity using the approach of Thall, Simon, and Estey (1995, 1996). After an initial 6 patient safety cohort, subsequent patients will be enrolled in cohorts of size 3.

The existing trial of blinatumomab as a single agent assumes that a toxicity rate greater than 31% would be excessive. Since we propose combining blinatumomab with two additional agents, we aim to achieve a higher ORR, and allow for acceptable toxicity no higher than 40%. For the purposes of toxicity monitoring, toxicity will be defined as follows: grade 4-5 neurotoxicity or CRS; grade 3 neurotoxicity or CRS that fails to resolve within 1 week or recurs at grade ≥3 severity on re-challenge; grade 3-5 therapy-related immune-related toxicity at least possibly related to nivolumab.

For the Bayesian design, the following parameter settings will be used:

- For the standard treatment response and toxicity rates, constant rates of 0.4 are assumed.
- For the response and toxicity rates under the proposed treatment, a beta(0.8, 1.2) prior is assumed for each rate, which has the same mean as the rates under the standard treatment, and an effective sample size of 2.
- The maximum number of patients if no early stopping is applied will be 21, and a minimum of 6 patients will be treated before stopping.
- The planned cohort size is 3.

- The trial will be stopped early based on response if the posterior probability that the response rate of the experimental treatment is less than the current standard rate is greater than 0.9.
- The trial will be stopped early based on toxicity if the posterior probability that the toxicity rate of the experimental treatment is greater than the current standard rate is greater than 0.8.
- Toxicity will be monitored continuously for the first year of treatment.

Response Stopping Boundaries

# Patients (in complete cohorts of 3) (inclusive)	Stop the trial if there are this many responses total:
	# Responses (inclusive)
3	Never stop with this many patients
6	0
9	0-1
12	0-2
15	0-3
18	0-4
21	Always stop with this many patients

Stopping boundaries for toxicity

# Patients (in complete cohorts of 3) (inclusive)	Stop the trial if there are this many toxicities total:
	# Toxicities (inclusive)
3	Never stop with this many patients
6	4-6
9	5-9
12	7-12
15	8-15
18	10-18
21	Always stop with this many patients

Summary of operating characteristics

The operating characteristics are summarized in the table below. The probabilities of stopping the trial early are exact calculations from MultcLean Desktop under the assumption that response is independent of toxicity.

True Toxicity Rate	True OR Rate	Prob(stop the trial early)	Avg # patients enrolled (25^{th} – 75^{th} percentile)
0.2	0.6	0.04	20.5 (21 – 21)
	0.5	0.07	20.1 (21 – 21)
	0.4	0.19	19.0 (21 – 21)
	0.3	0.45	16.4 (12 – 21)
0.3	0.6	0.14	19.2 (21 – 21)
	0.5	0.17	18.8 (21 – 21)
	0.4	0.28	17.8 (15 – 21)
	0.3	0.51	15.5 (9 – 21)
0.4	0.6	0.36	16.4 (9 – 21)
	0.5	0.39	16.2 (9 – 21)
	0.4	0.46	15.4 (9 – 21)
	0.3	0.63	13.6 (6 – 21)
0.5	0.6	0.64	12.9 (6 – 21)
	0.5	0.66	12.7 (6 – 15)
	0.4	0.70	12.2 (6 – 21)
	0.3	0.79	11.1 (6 – 15)

Analysis Plan

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. Logistic regression will be utilized to assess the effect of patient prognostic factors on the response rate and the toxicity rate. The distribution of time-to-event endpoints will be estimated using the method of Kaplan and Meier. Cox proportional hazard regression will be employed for multivariate analysis on time-to-event outcomes.

An Efficacy/Safety Summary will be submitted to the IND Office Medical Monitor, after the first 6 evaluable patients complete 8 weeks of study treatment, and every 3 evaluable patients thereafter. Toxicity information of previously submitted patients will be updated during every submission.

Trial Conduct

Conducting a trial designed by this method does not require software since the stopping conditions have been tabulated before the trial begins.

15.0 REFERENCES

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Appendix C. Grading of Cytokine Release Syndrome (CRS)

CRS Parameter		CRS grade 1	CRS grade 2	CRS grade 3	CRS Grade 4
Fever*	Temperature >/= 38°C	Temperature >/= 38°C	Temperature >/= 38°C	Temperature >/= 38°C	
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin	
				and/or†	
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by		Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg. CPAP, BiPAP, intubation and mechanical ventilation)

*Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6L/minute

Appendix D: Definition of high-dose vasopressors

Vasopressor	Definition of high-dose vasopressor
Norepinephrine monotherapy	Greater than or equal to 20 mcg/minute
Dopamine monotherapy	Greater than or equal to 10 mcg/kg/minute
Phenylephrine monotherapy	Greater than or equal to 200 mcg/minute
Epinephrine monotherapy	Greater than or equal to 10 mcg/minute
Vasopressin	Vasopressin + norepinephrine equivalent of greater than or equal to 10mcg/minute
Combination vasopressors (not including vasopressin)	Norepinephrine equivalent of greater than or equal to 20 mcg/minute

[5]VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (mcg/minute)] + [dopamine (mcg/kg/minute)/2] + [epinephrine (mcg/minute)] + [phenylephrine (mcg/minute)/10].

Appendix E: ASTCT INCANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.
Seizure	N/A	N/A	Any clinical seizure, focal or generalized, that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention	Life -threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

*A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Appendix F. CTCAE v5.0 grading of common adverse events

Category	Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac	Sinus tachycardia	Asymptomatic, no intervention needed	Symptomatic, non-urgent intervention indicated	Urgent intervention indicated	
	Arrhythmia or heart block	Asymptomatic, no intervention needed	Symptomatic, non-urgent intervention indicated	Urgent intervention indicated	Life threatening consequences
	Ejection fraction		EF 40-50% or 10-19% drop from baseline	EF 20-39% or >/=20% drop from baseline	EF <20%
Respiratory	Pleural effusion	Asymptomatic, no intervention needed	Symptomatic, intervention indicated (diuretics or thoracentesis)	Symptomatic with respiratory distress; needs surgical intervention (chest tube or pleurodesis)	Life-threatning respiratory or hemodynamic compromise; intubation or urgent intervention indicated
	Pulmonary edema	Radiologic findings only; Minimal dyspnea on exertion	Moderate dyspnea on exertion; medical intervention indicated; limits instrumental ADL	Severe dyspnea or Dyspnea at rest; oxygen indicated; limits self-care ADL	Life-threatening urgent intervention or intubation with ventilatory support indicated
Gastro-intestinal	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant dehydration, malnutrition or weight loss	Inadequate oral caloric or fluid intake; receiving tube feeding, TPN or hospitalization indicated	
	Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	tube feeding,TPN or hospitalization indicated	Life-threatening
	Diarrhea	Increase of 1-3 stools/day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >6 stools/day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limits self-care ADL	Life-threatening consequentes; urgent intervention indicated
Hepatic	AST or ALT	>ULN to 3xULN if	>3xULN to 5x ULN	>5xULN to 20xULN if	>20xULN if

	increased	baseline was normal; 1.5 – 3.0 x baseline if baseline was abnormal	if baseline was normal; >3.0-5.0 x baseline if baseline was abnormal	baseline was normal; >5.0-20.0 x baseline if baseline was abnormal	baseline was normal; >20.0 x baseline if baseline was abnormal
	Total bilirubin increased	>ULN to 1.5xULN if baseline was normal; >1.0-1.5 x baseline if baseline was abnormal	>1.5xULN to 3xULN if baseline was normal; >1.5-3.0 x baseline if baseline was abnormal	>3xULN to 10xULN if baseline was normal; >3.0 – 10.0 x baseline if baseline was abnormal	>10xULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Renal	Urine output decreased			Oliguria (<80mL/8 hours)	Anuria (<240mL/24 hours)
	Acute kidney injury	=		Hospitalization indicated	Life-threatening; dialysis indicated
	Creatinine increased	>ULN – 1.5 x ULN	>1.5 – 3.0 x baseline; >1.5 – 3.0 x ULN	>3.0 x baseline; >3.0-6.0 x ULN	>6.0 x ULN
Coagulopathy	Disseminated intravascular coagulation (DIC)		Laboratory findings with no bleeding	Laboratory findings with bleeding	Life-threatening; urgent intervention indicated

Appendix G. Simplified 10-point neurologic examination

- Orientation to year, month, city, hospital,: 4 points.
- Ability to write a standard sentence (eg. The national bird is the bald eagle): 1 point.
- Name 3 objects (eg. clock, pen, button): 3 points.
- Count backwards from 100 by 10s: 1 point.
- Can the patient follow commands? 1 point for yes.

Appendix H. Lugano Response Criteria for Malignant Lymphoma

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	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	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	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 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	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	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

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
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 undertreatment). 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 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.

Appendix I – response criteria in CLL.

Table 4. Response definition after treatment of CLL patients

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline)*	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Liver and/or spleen size†	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of −49% to +49%
B	Platelet count	≥100 × 10^9/L	≥100 × 10^9/L or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL	Change of −49 to +49%
	Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥50% over baseline	Decrease of ≥2 g/dL from baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or decrease <2 g/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

For a detailed description of the response parameters, see section 5.

*Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).

†Spleen size is considered normal if <13 cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.

CR, complete remission (all of the criteria have to be met); PD, progressive disease (at least 1 of the criteria of group A or group B has to be met); PR, partial remission (for a PR, at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); SD, stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD).

Appendix J – Grading of hematologic toxicity in CLL trials.

Table 5. Grading scale for hematological toxicity in CLL studies

Grade*	Decrease in platelets† or Hb‡ (nadir) from baseline value, %	Absolute neutrophil count (nadir)§ × 10^9/L
0	No change to 10	≥2
1	11-24	≥1 and <2
2	25-49	≥1 and <1
3	50-74	≥0.5 and <1
4	≥75	<0.5

*Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from baseline will be recorded as grade 5.

†Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is <20 × 10^9/L, this will be considered grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (eg, 20 × 10^9/L) was present at baseline, in which case the patient is not evaluable for toxicity referable to platelet counts.

‡Hb levels must be below normal levels for grades 1-4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.

§If the absolute neutrophil count (ANC) reaches <1 × 10^9/L, it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count or in circulating granulocytes are not to be considered because a decrease in the white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was <1 × 10^9/L before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of G-CSF is irrelevant for the grading of toxicity, but should be documented.

Appendix K – Management Algorithms.

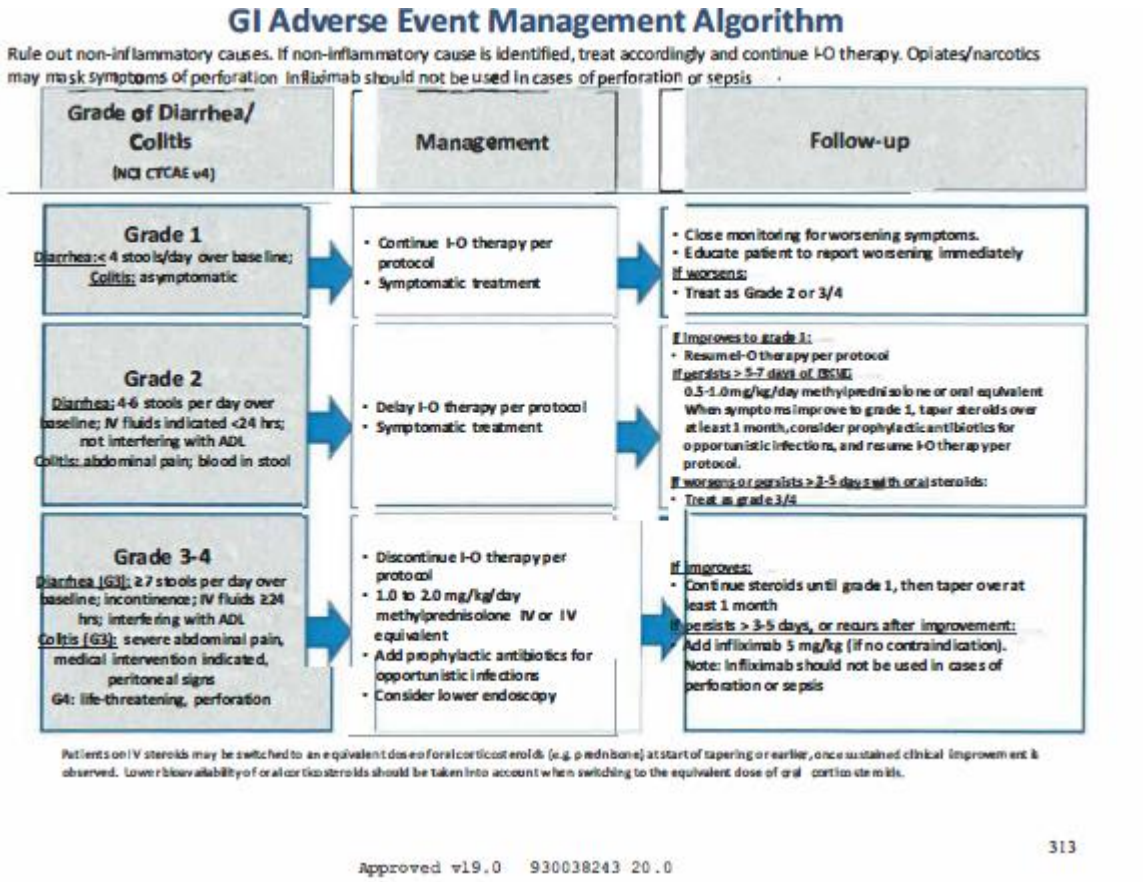
These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

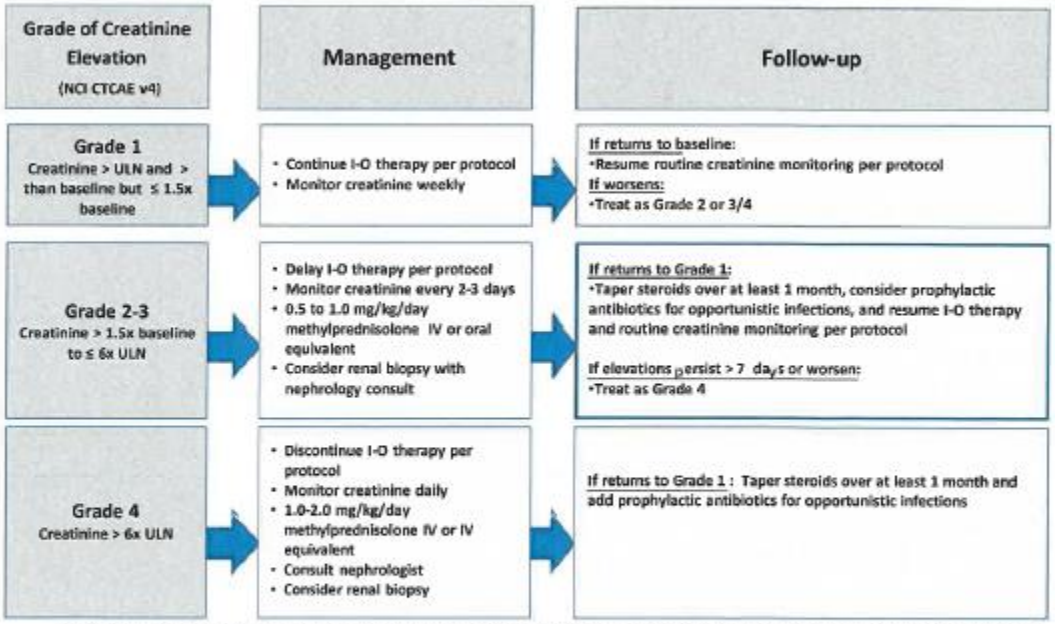
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.



Renal Adverse Event Management Algorithm

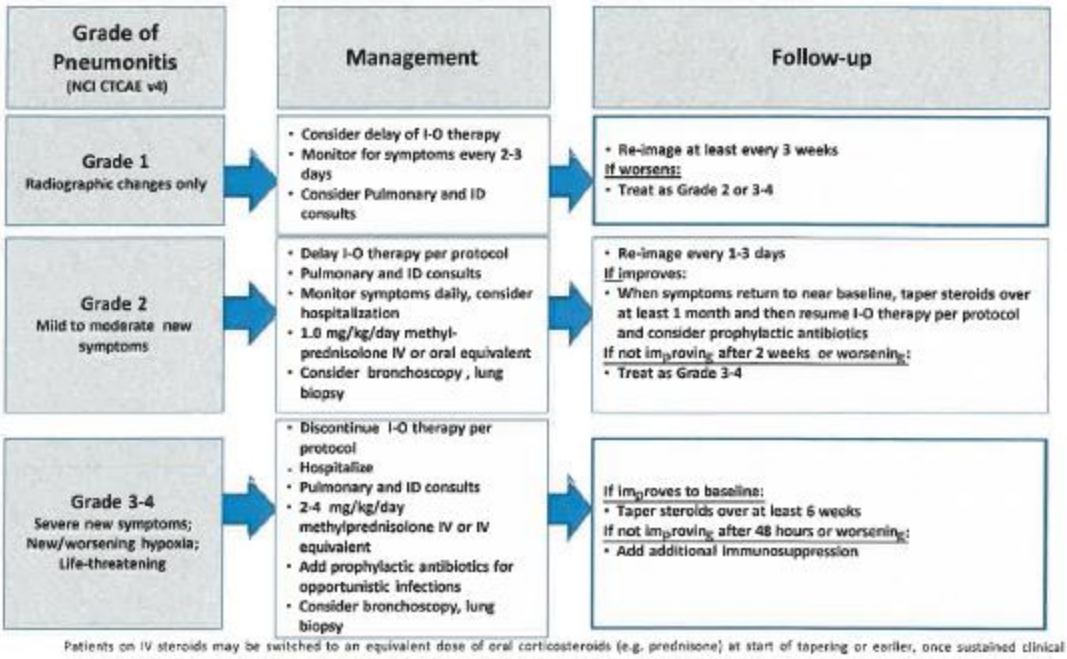
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

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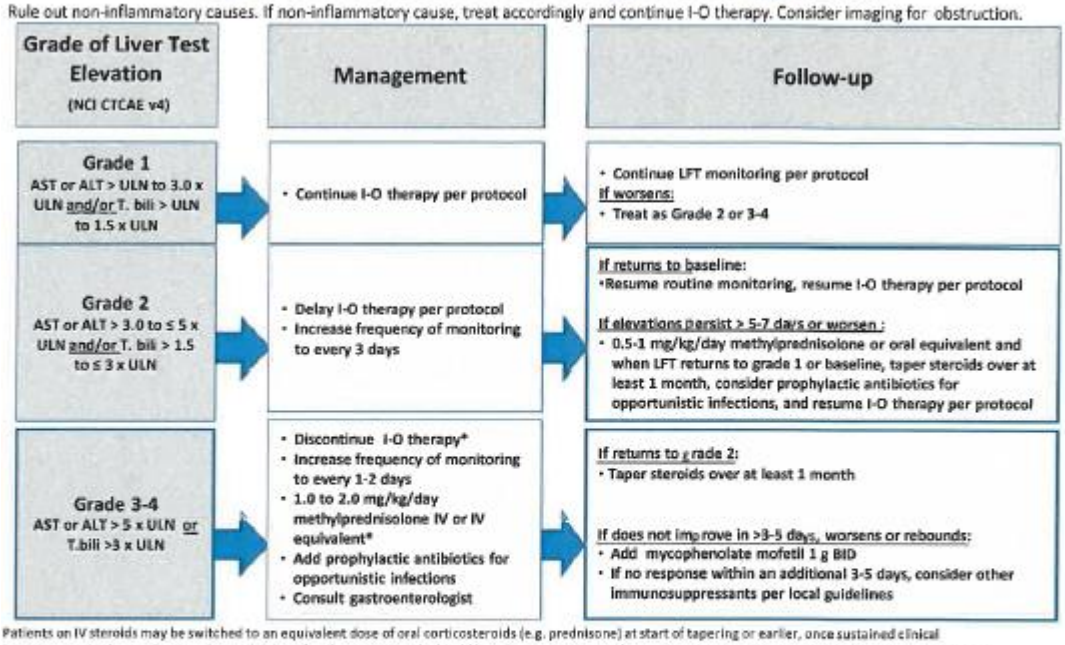
Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

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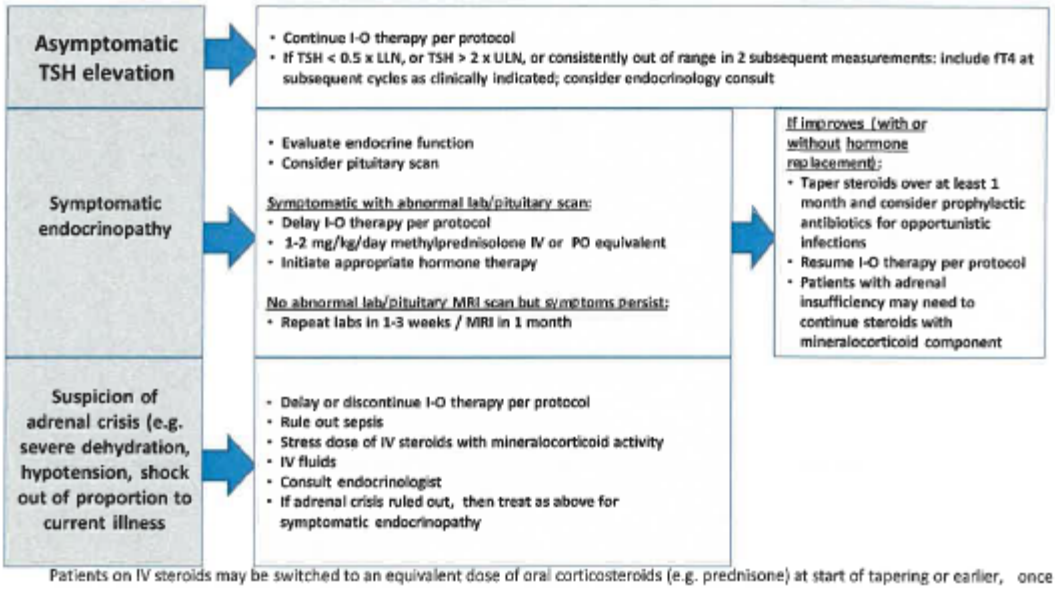
Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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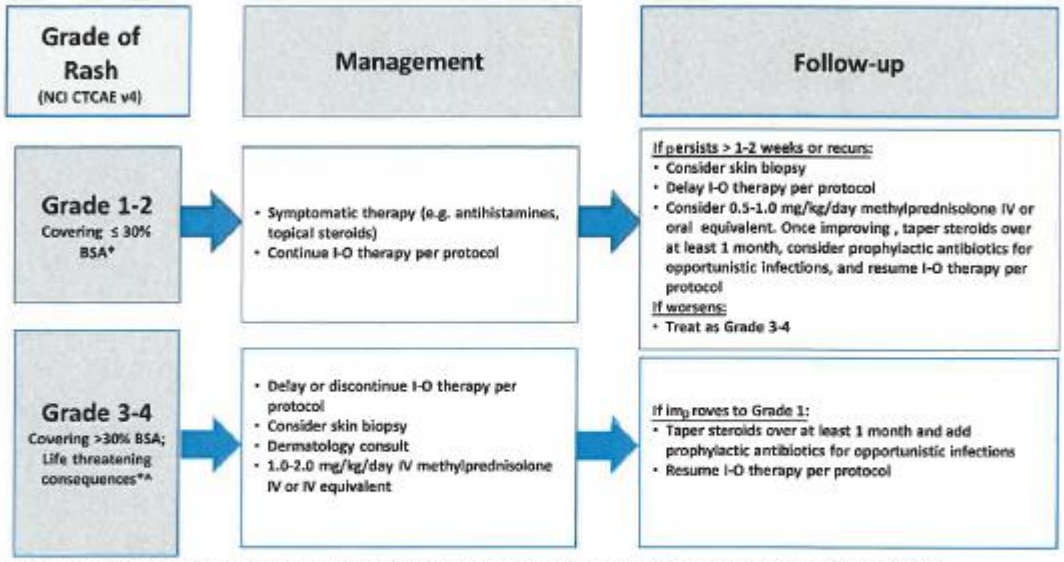
Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



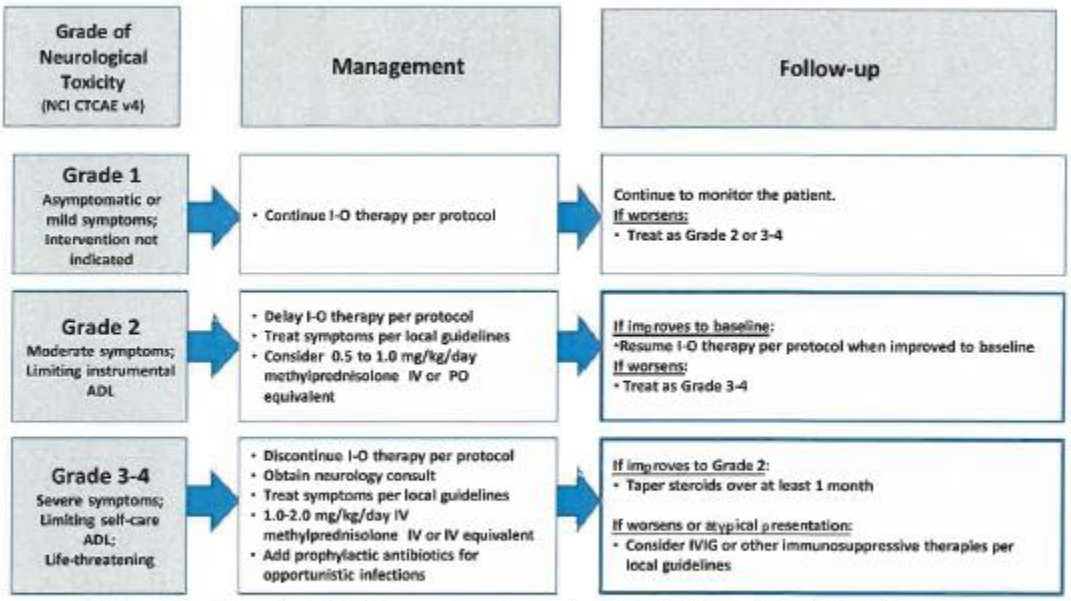
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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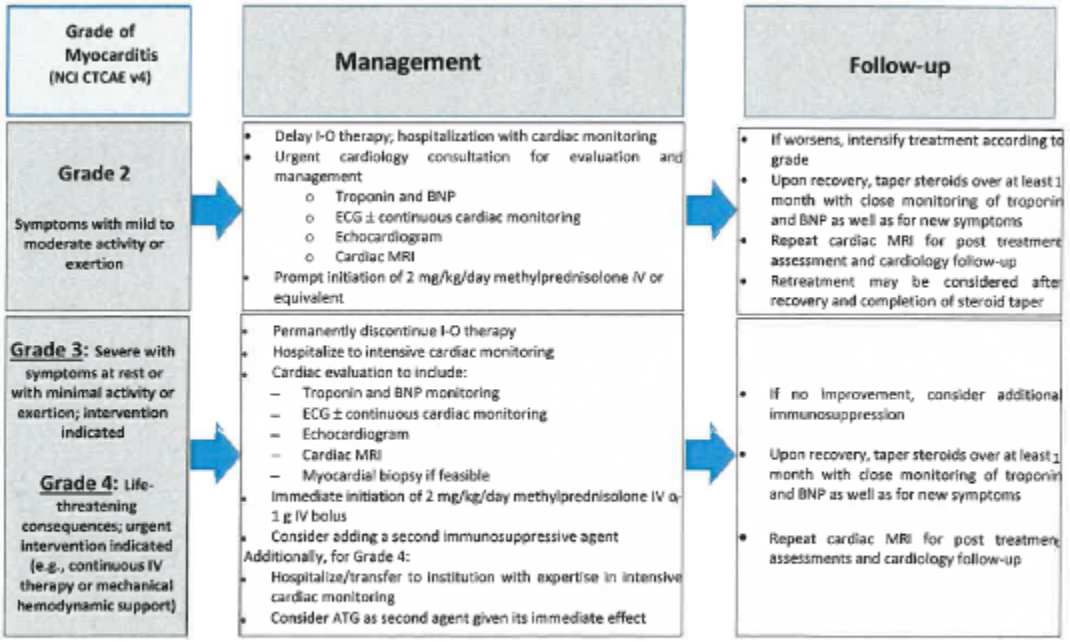
Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

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Appendix L. Child-Pugh Grading System for Cirrhosis.

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	**Points***		
	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
or			
International normalized ratio	<1.7	1.7-2.3	>2.3
***Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)**			
Class A = 5 to 6 points			
Class B = 7 to 9 points			
Class C = 10 to 15 points			