# MSK PROTOCOL COVER SHEET

*Phase 2 Study of Tafasitamab and Lenalidomide in Relapsed or Refractory Mantle Cell Lymphoma*

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| Glossary of Terms | |
|---|---|
| **Term** | **Definition** |
| ADCC | Antibody-dependent cellular cytotoxicity |
| AdjBW | Adjusted body weight |
| AOL | Activities of daily living |
| AE | Adverse event |
| AIDS | Acquired immunodeficiency syndrome |
| ALT | Alanine transaminase |
| ANC | Absolute neutrophil count |
| ASCT | Autologous stem cell transplantation |
| AST | Aspartate transaminase |
| BM | Bone marrow |
| BSA | Body surface area |
| BTKi | Bruton's tyrosine kinase inhibitor |
| CBC | Complete blood count |
| CMP | Comprehensive metabolic panel |
| CR | Complete response |
| CRu | Unconfirmed complete response |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | Circulating tumor DNA |
| OCR | Disease Control Rate |
| DOR | Duration of response |
| ECG | Electrocardiogram |
| EOT | End of treatment |
| FOG | [18F]fluorodeoxyglucose |
| G-CSF | Granulocyte colony stimulating factor |
| GVHD | Graft-versus-host disease |
| HBcAb | Hepatitis B core antibody |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HIV | Human immunodeficiency virus |
| IBW | Ideal body weight |

| | |
|---|---|
| IMiD | Immunomodulatory imide drug |
| IMPACT | Integrated Mutation Profiling of Actionable Cancer Targets |
| IND | Investigational new drug |
| IRR | Infusion-related reaction |
| KPS | Karnofsky performance status |
| LAR | Legally authorized representative |
| LOH | Lactate dehydrogenase |
| MCL | Mantle cell lymphoma |
| MIPI | Mantle cell lymphoma international prognostic index |
| NHL | Non-Hodgkin lymphoma |
| MRD | Minimal residual disease |
| NGS | Next-generation sequencing |
| ORR | Objective response rate |
| OS | Overall survival |
| PBMC | Peripheral blood mononuclear cell |
| PET | Positron emission tomography |
| PFS | Progression-free survival |
| P-gp | P-glycoprotein |
| PI | Principal investigator |
| PR | Partial response |
| REMS | Risk Evaluation and Mitigation Strategy |
| R/R | Relapsed or refractory |
| RSA | Research Study Assistant |
| SAE | Serious adverse event |
| SD | Stable disease |
| **SOC** | Standard of care |
| TBW | Total body weight |
| TTP | Time to progression |
| ULN | Upper limit of normal |
| V(D)J | Variable, diversity, and joining gene segments |

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# 1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a single-center, open-label phase II study of the combination of tafasitamab and lenalidomide in relapsed or refractory (R/R) mantle cell lymphoma (MCL) who have received previous treatment with a Bruton's tyrosine kinase inhibitor (BTKi). The study aims to evaluate the efficacy of the combination therapy. The primary endpoint will be objective response rate (ORR) to tafasitamab and lenalidomide, and will be evaluated when all patients have completed 12 cycles of treatment or at treatment discontinuation, whichever comes first.

Patients will be enrolled to receive tafasitamab via IV infusion and self-administer lenalidomide orally according to the treatment schema below. for a maximum of 36 cycles (3 years) In the first stage of the Simon 2-stage design, a total of 19 patients will accrue. If 6 or fewer have objective response, the trial will close due to a lack of efficacy; otherwise, an additional 20 patients will accrue. If at the end of the study, 17 or more out of 39 have an objective response, the trial will be considered promising for future development.

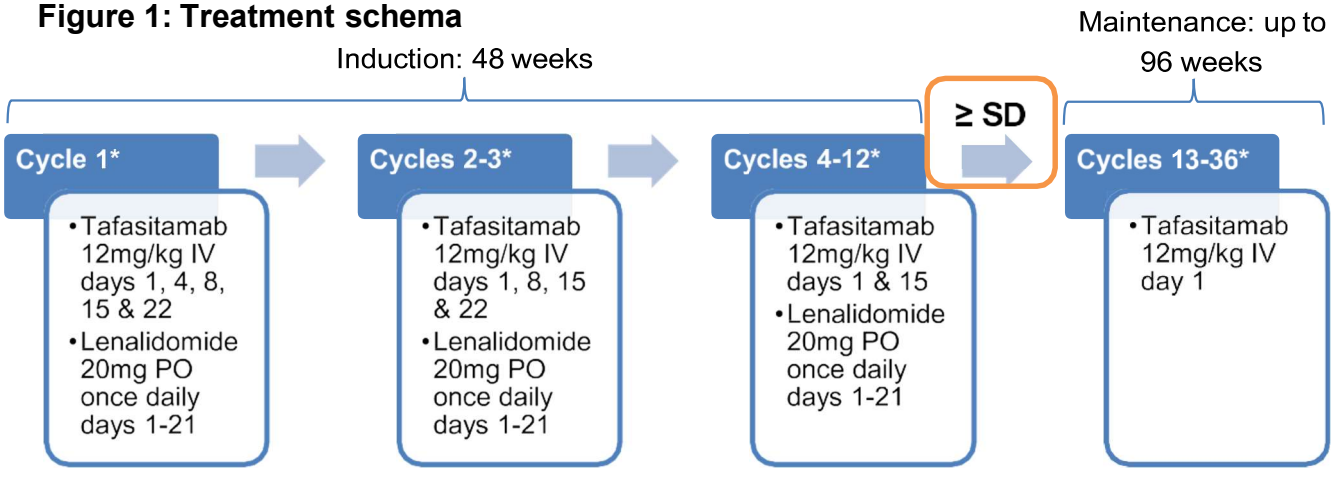
The anticipated accrual rate for this study is 1 to 2 patients per month, and the trial will continue through three years after the last accrued patient.

# 2.0 OBJECTIVES AND SCIENTIFIC AIMS

## 2.1 Primary objective

The primary objective of this study is to assess the ORR, defined as the percent of patients (relative to the total number considered evaluable as in 13.2) who achieve complete response (CR) or partial response (PR) according to the 2014 Lugano response criteria for non-Hodgkin lymphoma (NHL), to the combination of tafasitamab and lenalidomide in patients with R/R MCL who have experienced failure of or intolerance to past treatment with BTKi.[1,2]

**Figure 1: Treatment schema**




*One cycle = 28 days

## 2.2 Secondary objectives

**2.2.1** To determine disease control rate (DCR), defined as the percent of patients (relative to the total number evaluable) who achieve CR, PR, or stable disease (SD) at the time of ORR assessment.

**2.2.2** To estimate DOR, defined as the time from achievement of PR or CR to progression of disease (POD) according to Lugano criteria.[1,2]

**2.2.3** To estimate PFS, defined as the time from initiation of study treatment to the earlier of POD or death from any cause.

**2.2.4** To estimate OS, defined as the time from initiation of study treatment to death from any cause.

**2.2.5** To estimate TTP, defined as the time from initiation of study treatment to POD or death from MCL.

**2.2.6** To describe the safety of the combination of tafasitamab and lenalidomide in patients with R/R MCL, defined as the incidence and severity (according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0).

## 2.3 Exploratory objectives

**2.3.1** To assess the rate of conversion to undetectable minimal residual disease (MRD) by immunoglobulin gene next-generation sequencing (NGS) relative to baseline at 3, 6, and 12 months post initiation of study treatment; MRD will also be assessed at POD.

**2.3.2** To characterize clonal evolution using circulating tumor DNA (ctDNA) in peripheral blood via high-depth targeted genomic sequencing at baseline, at 3, 6, and 12 months post initiation of study treatment, and at POD.

**2.3.3** To evaluate effects of study treatment on:

- Antitumor immune response (via surface protein expression, RNA expression, and variable, diversity, and joining (V(D)J) gene segment recombination of peripheral mononuclear cells (PBMCs)) relative to baseline at 3, 6, and 12 months post initiation of study treatment, and at POD.
  MCL-driven immunosuppression in the tumor microenvironment (via flow cytometry enumeration of lymphocyte subsets in tumor biopsy samples) relative to baseline between days 21-28 of cycle 1, and at POD.

## 3.0 BACKGROUND AND RATIONALE

***R/R MCL***

MCL is an uncommon B-cell NHL comprising approximately 6-8% of all NHL diagnoses.[3,4] MCL is more common in men than women, presents at a median age of 68 years, and is usually in an advanced stage at diagnosis, with bone marrow and the gastrointestinal tract being common extranodal sties of involvement.[5] Despite improvement in overall survival of MCL with intensive frontline chemotherapy, it remains an incurable disease and most patients are destined to relapse after initial therapy.[6] After relapse, MCL is more challenging to treat and is associated with progressively shorter remission durations after each subsequent line of therapy, resistance to traditional cytotoxic chemotherapy, and limited survival.[7] The therapeutic landscape in MCL is rapidly evolving, and a number of biologically targeted therapies, such as lenalidomide, the Bruton's tyrosine kinase inhibitors (BTKis; ibrutinib, acalabrutinib, and zanubrutinib), and venetoclax, have demonstrated promising efficacy in the R/R setting.[8-12] However, after failure of BTKi therapy, outcomes are generally poor for patients with R/R MCL, with median OS of 5.8 months.[13]

Recently, there was a promising therapeutic advance for R/R MCL with the FDA approval of brexucabtagene autoleucel, an anti-CD19 chimeric antigen receptor T-cell (CAR-T) therapy with an associated 93% ORR, including 67% with CR.[14] Unfortunately, some patients may be ineligible for CAR-T, and others may face access constraints and logistical challenges given the need for referral to a specialized treatment center and the complexities associated with leukapheresis and manufacturing of the CAR-T product. In addition, this approach is associated with a high rate of adverse events (AEs), including grade 3 or higher cytokine release syndrome and neurologic events in 15% and 31% of patients, respectively. There remains a need for additional therapeutic options after BTKi failure, particularly in patients with R/R MCL with advanced age and multiple comorbidities.

*Lenalidomide in MCL*

Lenalidomide is an oral immunomodulatory imide drug (IMiD) with multiple immune-mediated and anti-angiogenic antitumor effects. Lenalidomide has been demonstrated to impede angiogenesis through inhibition of bFGF, VEGF, and TNF-a-induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF.[15] Its myriad immunomodulatory effects include stimulation of T-cell proliferation, production of IL-2, IL-10, and IFNy, inhibition of IL-1 and IL6, and modulation of IL-12 production.[16] Lenalidomide produces direct cytotoxicity in some hematologic malignancies through binding of cereblon, a component of the E3 ubiquitin ligase complex and thereby modulating protein ubiquitination and degradation.[17,18] In MCL, lenalidomide's activity appears to be primarily mediated through expansion of CD56+ CD15+ NK cells and increased immune synapse formation, promoting NK cell-mediated cytotoxicity in the tumor microenvironment.[19]

Several studies demonstrated promising activity of single-agent lenalidomide as well as the combination of lenalidomide and the CD20 monoclonal antibody rituximab for treatment of

R/R MCL. In a subset of 57 patients with R/R MCL in the phase II NHL-003 study, lenalidomide 25mg daily was associated with an ORR of 35% with a median duration of response of 16.3 months after median follow-up of approximately 20 months.[20] In the larger international, multicenter phase II EMERGE study in patients with R/R MCL following bortezomib, single-agent lenalidomide produced an ORR of 28% (7.5% CR/unconfirmed CR (CRu)), with a similar median duration of response of 16.6 months.[9] This study led to FDA approval of lenalidomide in patients with R/R MCL after at least two prior therapies, one of which included bortezomib. In a phase 1/11 trial of lenalidomide with rituximab, the combination was well-tolerated and produced an improved ORR of 57% (36% CR/CRu).[21] The maximum tolerated dose of lenalidomide identified in the phase I portion of this trial was 20mg daily. One patient who received lenalidomide 25mg daily developed a grade 4 non-neutropenic infection and died.

After BTKis were established as a standard second-line treatment option for R/R MCL, there was interest in defining outcomes associated with lenalidomide-based therapy after BTKi failure or intolerance. This was evaluated in the retrospective MCL-004 study of a cohort of 58 patients with R/R MCL (13 treated with lenalidomide monotherapy, 11 with lenalidomide and rituximab, and 34 with other lenalidomide combinations).[22] Patients had received median four prior lines of therapy (range 1-13), with an ORR of 29% (14% CR) and median duration of treatment of 8.4 weeks. The median DOR for responders was 20 weeks.

*Tafasitamab in B-ce/1 NHL*

Tafasitamab (MOR00208, previously XmAb5574) is an Fe-engineered, humanized monoclonal antibody that binds to the human B-cell surface antigen CD19.[23] CD19 is broadly expressed across the B-lymphocyte lineage, including in B-cell malignancies, but not by hematological stem cells. Tafasitamab produces significantly higher tumor cytotoxicity compared to the parental, non-engineered, murine 4G7 CD19 antibody. Tafasitamab has increased affinity for Fey receptors through the introduction of two amino acid modifications within the Fe region. Tafasitamab is associated with antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis, and exerts direct cytotoxicity. Preclinial studies indicate potent in vitro and in vivo activity of tafasitamab in lymphoma and leukemia models.[23,24]

Tafasitamab was tested in a phase IIa study in B-cell NHL, including diffuse large B-cell lymphoma (DLBCL, follicular lymphoma (FL), other indolent NHL, and MCL.[25] Patients received tafasitamab 12mg/kg IV once weekly for 8 weeks, with those achieving at least SD eligible to continue treatment for an additional 4 weeks. Patients who achieved PR or CR after 12 weeks could receive further extended treatment every 2 or 4 weeks until POD. The primary endpoint of this study was ORR. Ninety-two patients were enrolled: 35 patients with DLBCL, 34 with FL, 11 with other indolent NHL, and 12 with MCL. Responses were observed among patients with DLBCL, FL, and other indolent NHL (ORR 26%, 29%, and 27%, respectively), including several durable responses. Among patients with MCL, there were no responders; however, six patients (50%) achieved SD, while five (42%) progressed and one

was not evaluable. This experience is in keeping with the poor activity rituximab monotherapy, which functions via similar mechanisms, in patients with untreated or R/R MCL.26

*Tafasitamab and lenalidomide*

It was hypothesized that modulation of immune effector cells by lenalidomide would enhance **NK** cell-mediated ADCC exerted by tafasitamab, thereby resulting in therapeutic synergy when used in combination. Furthermore, given that prior rituximab exposure in patients with R/R DLBCL may result in down-regulated expression and/or internalization of CD20, it was postulated that targeting the conserved surface antigen CD19 with tafasitamab may overcome rituximab-related resistance and improve outcomes in the R/R setting.[27,28] The combination of tafasitamab and lenalidomide was evaluated in 80 patients with R/R DLBCL in the single-arm phase II L-MIND study.[29] Patients received treatment for up to 12 cycles of 28 days each. In cycles 1 through 3, patients received tafasitamab intravenously on days 1, 8, 15, and 22, with an additional loading dose administered on day 4 of cycle 1. From cycle 4 onward, patients received tafasitamab on days 1 and 15. Patients self-administered lenalidomide 25mg orally once daily on days 1 through 21 of each cycle, with stepwise dose reduction if not tolerated. At median follow-up of 13.2 months, 48 patients (60%) achieved response (43% CR, 18% PR). The most common treatment-related AEs were hematologic, including neutropenia and thrombocytopenia. Given the promising efficacy and tolerability of this novel combination, tafasitamab and lenalidomide received accelerated FDA approval for use in transplant-ineligible patients with R/R DLBCL in August 2020.

Given the strong biologic and clinical rationale for therapeutic synergy of tafasitamab and lenalidomide in B-cell NHL, we hypothesize that this combination will improve upon outcomes associated with lenalidomide-based therapy for MCL in the post-BTKi R/R setting. Patients with R/R MCL typically receive rituximab and may develop resistance to it. Targeting CD19 is a clearly efficacious strategy in MCL given the high response rates associated with CD19-directed CAR-T therapy. However, this approach can be associated with significant toxicity and challenging to access, particularly in elderly patients who often present with comorbidities. Combination therapy with tafasitamab and lenalidomide may offer improved outcomes with minimal toxicity, potentially fulfilling an unmet need in a population with few acceptable treatment options.

## 3.1 Correlative Studies

In the course of this research it is possible that some patients whose tumors are analyzed through investigational "next-generation" profiling in a research (non-CUA) environment will be found to have somatic or germline mutations in genes that are known to be associated with an increased risk of cancer or other diseases. It will be stated in the consent that the participants will not receive any specific results from research tests. The consent will tell participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSK Clinical Genetics Service.

If in the course of this research a research finding is obtained that, in the opinion of the investigator, may be critical to the preventive care of the participant or their family, the investigator can communicate that finding to the IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. For MSK, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the reearch finding.

The following information must be provided to GAP for review:

- Participant Name/MRN #
- Type of Biospecimen (tissue, blood, saliva)
- Incidental Finding
- Collection Protocol #
- Contact: rtmgapirb@mskcc.org

**1. Effects of lenalidomide and tafasitamab on the peripheral immune system**

Lenalidomide has been shown to enhance the anti-tumor immune function of both T-cells and NK cells. The reinvigoration of dysfunctional immune cells can be monitored in the blood using multiparametric flow cytometry, including assessment of activation state, proliferative capacity, and expression of exhaustion markers. We hypothesize that patients responding to tafasitamab and lenalidomide will exhibit an increase in both the activation state and proliferative capacity of CDS+ T-cells and NK cells, while non-responding or progressing patients will exhibit an increase in exhaustion markers. To test these hypotheses, multiparametic flow cytometry will be performed in the laboratory of Dr. Vardhana. The Vardhana laboratory has already published several papers in using deep immune profiling and high-dimensional flow cytometry analysis of peripheral blood mononuclear cells in hematologic malignancy patients with COVID-19 infection (Bange, Han et al, *Nat Med* 2021, Lyudovyk, Han, Qualls et al *Cancer Cell,* in press).

These analyses will include:

- Assessment of CD4+ and CD8+ T-cell differentiation state (CD45RA, CD27, CCR?, TCF-1, T-bet, Eames, FoxP3)
- Activation state of T-cells and NK cells (CD38hi/HLA-DRhi)
- Proliferative capacity of T-cells and NK cells (Ki-67hi)
- Exhaustion state of T-cells and NK cells (expression of PD-1, LAG-3, Tim-3, and CTLA-4)

We have hypothesized that the combination of tafasitamab and lenalidomide will facilitate antigen spreading leading to a polyclonal, polyfunctional **T** and NK cell anti-tumor immune response. To determine whether tafasitamab and lenalidomide promote a diversified immune response, we will perform unbiased profiling of both PBMCs and, when possible, single-cell suspensions from primary tumor samples using CITE-Seq technology, in which surface protein and RNA expression are interrogated in single-cells. This will allow for clone-specific tracking of T and NK cell evolution in response to therapy. We plan to collect peripheral blood mononuclear cells (PBMCs) at day 1 of cycles 1, 2, and 3, and at progression. In addition, when possible, we will perform parallel studies on CD45+ cells from primary tumor biopsies (either lymph node, tumor, or bone marrow, if known involvement), which will be performed pre-treatment and at disease progression. There will also be an optional tumor biopsy performed between C1D22 and C1D28 of treatment. These studies will be performed in collaboration with MSKCC's Single Cell Research Institute (SCRI).

**2. Effect of lenalidomide and tafasitamab on the tumor microenvironment.**

The tumor microenvironment is known to suppress the effector function of tumor-infiltrating T- and NK-cells across multiple cancer subtypes. We therefore hypothesize that the composition of the local MCL microenvironment will be a key determinant of response to tafasitamab and lenalidomide. We will use two parallel strategies to test this hypothesis. First, single-cell suspensions will be generated from core biopsies and analyzed for intratumoral immune cell composition (including but not limited to T, B, NK cell, macrophages, and dendritic cells) via multi-parametric flow cytometry performed on fresh biopsy samples by MSKCC's Hematopathology service. Should additional tumor biopsy samples be available, we will analyze the composition of the tumor microenvironment both at baseline and in response to therapy using CITE-Seq technology identical to that described above. If we see evidence of increased immune cell recruitment, will pursue additional downstream assays such as multiplexed ion beam imaging (MIBI) in collaboration with the Immune Monitoring Facility. We will collect biopsy (either fine needle aspiration or core needle biopsy of lymph node or bone marrow) at baseline and at time of progression. There will also be an optional biopsy (either fine needle aspiration or core needle biopsy of lymph node or bone marrow) performed between C1D22 and C1D28 of treatment.

**3. Mechanism of synergy between lenalidomide and tafasitamab and mechanisms of resistance to combination therapy**

The mechanism by which lenalidomide alters immune function was recently described; lenalidomide binds and redirects cereblon, resulting in E3-dependent ubiquitylation and degradation of several proteins including the Ikaros family of transcription factors (including Ikaros and Aiolos). These transcription factors are expressed in most lymphocyte subsets, and therefore the mechanism by which lenalidomide alters both lymphoma cell and infiltrating immune cell function remains poorly characterized, particularly in mantle cell lymphoma. To interrogate the epigenetic effects of lenalidomide, we will perform single-cell ATAC-sequencing and paired CITE-sequencing of bone marrow samples isolated from patients both prior to initiation of therapy and at disease progression. The goal of this analysis will be

to determine whether progression of disease in patients occurs because a) activity of Ikaros family transcription factors is restored, orb) immune suppression persists in the absence of recurrent Ikaros-dependent transcriptional activation.

**4. Minimal residual disease (MRD)**
MRD assessment can further refine response assessment in MCL and provides prognostic information in MCL [33558202]. In this study, we will perform MRD assessment using a next generation immunosequencing (IS) MRD assay (Adaptive Biotechnologies, Seattle, WA). This IS MRD assay leverages multiplex PCR followed by NGS to identify and track rearrangements of IgH, V-J, D-J and IgK/L loci and translocations in Bcl1/2-IgH. Peripheral blood will be collected at screening, day 1 of cycles 3, 7, and 13, and at end of treatment for MRD analysis, and evaluated for association with progression-free survival.

**5. Clonal evolution in MCL.**
Dynamic molecular monitoring in MCL patients treated with biologically targeted agents, such as ibrutinib and venetoclax, have revealed mutations that mediate therapeutic resistance [30455436]. In this study, we aim to characterize the clonal evolution of MCL in serial patient samples on treatment with tafasitamab and lenalidomide. Patients will have ctDNA in peripheral blood collected and banked for genomic testing by high-depth targeted sequencing pretreatment and serially during therapy, in order to study the effect of protocol therapy on clonal composition of MCL and assess whether genetic alterations arise that are associated with resistance. An MSK platform for assessment of circulating tumor DNA in peripheral blood specimens will be utilized.

**6. Tumor molecular profiling and prognosis**
Molecular analysis of diagnostic tumor samples obtained during screening with paired normal tissue (saliva or nails) will be analyzed using the MSK IMPACT platform under IRB protocol 12-245. Genomic alterations in MCL will be analyzed for associations with key clinical outcomes including PFS, ORR, and OS.

# 4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

## 4.1 Design

A single-center, single-arm, open-label phase II study evaluating the combination of tafasitamab and lenalidomide for treatment of adults with R/R MCL who have previously failed or could not tolerate BTKi therapy. Patients will be eligible if they have received one or more prior lines of therapy, one of which must have been a BTKi. Patients will be enrolled according to a Simon two-stage design, described in 14.0, with early stop criteria for lack of efficacy.

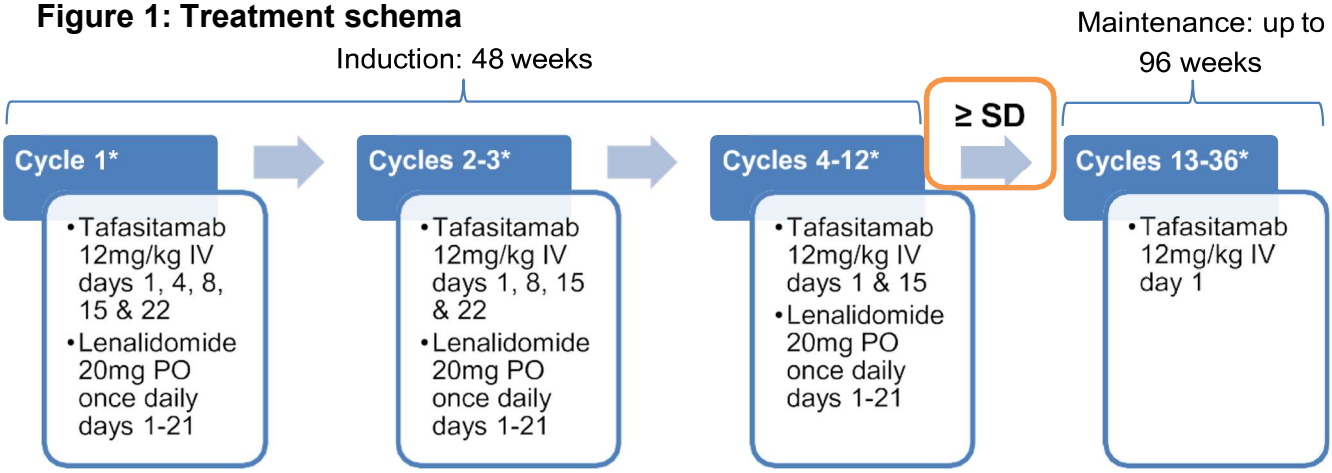
Tafasitamab will be administered intravenously and lenalidomide will be self-administered orally according to the treatment schema in 4.2. The primary endpoint is ORR (CR plus PR)

evaluated by PET/CT according to Lugano criteria at the end of cycle 12 or treatment discontinuation, whichever is earlier.[1,2]

### 4.2 Intervention

Patients will receive treatment with intravenous tafasitamab and oral lenalidomide for up to 12 cycles. Each cycle is 28 days in length. Lenalidomide will be self-administered at a dose of 20mg daily days 1-21 of cycles 1 through 12. During the first cycle, tafasitamab will be administered on days 1, 4, 8, 15, and 22. During cycles 2 and 3, tafasitamab will be administered weekly on days 1, 8, 15, and 22. During cycles 4 through 12, tafasitamab will be administered every other week on days 1 and 15. Upon earliest of completion of cycle 12 or EOT, patients will undergo radiologic evaluation of response. Patients who achieve SD, PR, or CR at completion of cycle 12 will continue tafasitamab maintenance therapy on day 1 of each cycle until the earliest of POD or 36 cycles (inclusive of the first 12 cycles).

**Figure 1: Treatment schema**




*One cycle = 28 days

## 5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

### 5.1 Tafasitamab

Tafasitamab, also known as MOR00208, is an intravenously-administered CD19 monoclonal antibody manufactured by Morphosys. The Morphosys tafasitamab investigational new drug (IND) application will be cross-referenced by MSKCC.

Dose Formulation: Tafasitamab-cxix will be supplied as 200mg lyophilized powder in single-use vials by Morphosys

- Preparation:

- Lyophilized powder should be reconstituted with 5ml sterile water for injection to a concentration of 40mg/ml
- Sterile water for injection should be directed toward the vial wall, then gently swirled until powder is completely dissolved (-5 minutes)
- The total volume of 40mg/ml reconstituted solution required should be calculated; equivalent volume should be removed from a 250ml bag of 0.9% sodium chloride
- The total volume of 40mg/ml reconstituted solution should be withdrawn and slowly injected into the bag of 0.9% sodium chloride, producing a diluted tafasitamab concentration of 2mg/ml to 8mg/ml in a total volume of 250ml
- Gently invert the bag (to not shake) to mix
- Unused reconstituted solution should be discarded

- Handling and storage
  - Unreconstituted vials should be protected from light, stored in refrigeration (2°C to 8°C; 36°F to 46°F), and must not be frozen
  - Reconstituted solution should be protected from light and used immediately; if not used immediately:
    - Do not freeze
    - Store in refrigeration (2°C to 8°C; 36°F to 46°F) for up to 18 hours, or
    - Store at room temperature (20°C to 25°C; 68°F to 77°F) for up to 12 hours, inclusive of time for infusion
- Source of Supply: investigational supply of tafasitamab will be supplied by Morphosys

### 5.2 Lenalidomide

Lenalidomide is an orally-administered IMiD manufactured by Celgene. Generic formulations of lenalidomide were approved by FDA in May 2021 and are anticipated to become available in March 2022. Information below is for lenalidomide manufactured under brand name by Celgene; details of generic manufacturers' formulations are not yet available. Lenalidomide will be obtained commercially based on an approved FDA indication in MCL.

- Dose formulation: Lenalidomide is available as capsules ranging in strength from 2.5mg to 25mg
  - 2.5mg (bottles of 28 or 100): white and blue-green opaque hard capsules, imprinted "REV" on one half and "2.5 mg" on the other half in black ink
  - 5mg (bottles of 28 or 100): white opaque capsules imprinted "REV" on one half and "5 mg" on the other half in black ink
  - 10mg (bottles of 28 or 100): blue/green and pale yellow opaque capsules imprinted "REV" on one half and "10 mg" on the other half in black ink
  - 15mg (bottles of 21 or 100): powder blue and white opaque capsules imprinted "REV" on one half and "15 mg" on the other half in black ink
  - 20mg (bottles of 21 or 100): powder blue and blue-green opaque hard capsules imprinted "REV" on one half and "20 mg" on the other half in black ink

  - 25mg (bottles of 21 or 100): white opaque capsules imprinted "REV" on one half and "25 mg" on the other half in black ink
- Packaging and labeling of lenalidomide will be determined by the external commercial specialty pharmacy filling the prescription, in accordance with governing regulatory agencies
- Handling and storage:
  - Lenalidomide should be stored at room temperature (20°C to 25°C; 68°F to 77°F) in the original packaging dispensed to the patient; excursions to 15°C to 30°C (59°F to 86°F) are permissible
  - Care should be taken in handling lenalidomide; capsules sould never be opened or broken
  - If a patient's skin comes into contact with powder from a lenalidomide capsule, the skin should be immediately and thoroughly washed with soap and water; if a patient's mucous membranes come into contact with powder from a lenalidomide capsule, immediately and thoroughly flush with water
- Source of supply:
  - Commercial supply of lenalidomide (branded or generic product as available and accessible for the patient) will be prescribed by the investigator to a commercial specialty pharmacy according to patient's and/or patient's prescription drug insurance's preference
  - For patients without prescription drug insurance, whose prescription drug insurance does not cover lenalidomide, or whose copay for lenalidomide is financially burdensome, enrollment in the BMS Access Support program will be sought prior to study initiation (see Section 9.0 Pre-Treatment)

## 6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

Patients will be relapsed or refractory MCL patients who have previously failed or did not tolerate BTKi therapy.

### 6.1 Participant Inclusion Criteria

Patients must meet fill of the following criteria to be eligible for inclusion in this study:

- Age ;:: 18 years at the time of signing Informed Consent
- Karnofsky performance status (KPS) ;:: 70% (see Appendix A)
- Pathologically confirmed diagnosis of R/R MCL
- Previously treated with at least one prior line of systemic therapy for MCL, at least one of which must have been a BTKi
- If patient previously received CD19-directed therapy (such as CAR-T therapy), then there must be evidence of CD19 expression confirmed by immunohistochemistry or flow cytometry per institutional guidelines. This must be confirmed on a biopsy performed after receipt of CD19-directed therapy.

- Previous systemic chemotherapy must have been discontinued at least 2 weeks prior to C1D1 and previous anti-cancer radiation therapy or targeted therapy must be discontinued prior to initiation of treatment on study
    - All adverse effects should resolve to grade 1 or baseline (excluding alopecia)
- Presence of evaluable disease
- Adequate bone marrow and organ function:
    - Absolute neutrophil count (ANC) 2: 1,500 cells/mcL, unless felt to be secondary to underlying MCL
    - Platelet count 2: 90,000 cells/mcL, unless felt to be secondary to underlying MCL
    - Renal function assessed by calculated Cockcroft-Gault creatinine clearance (CrCI; see Appendix B) 2: 30ml/min. See 10.0 Treatment Plan, Table 10-1, for lenalidomide dose adjustment for CrCI 2: 30ml/min and < 60ml/min.
    - Hepatic function:
        - Total bilirubin < 2.5x upper limit of normal (ULN), unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma. Patients with Gilbert's syndrome or documented liver involvement by lymphoma may be included if total bilirubin is s; 5x ULN.
        - Aspartate transaminase (AST) and alanine transaminase (ALT) s; 3x ULN, unless secondary to documented liver involvement by lymphoma. Patients with documented liver involvement by lymphoma may be included if AST and ALT ares; 5x ULN.
- Willingness to receive adequate prophylaxis and/or therapy for thromboembolic events, unless contraindicated in the opinion of the investigator
- Willingness to undergo confirmatory procedures for assessment of disease status and experimental studies as required by protocol, including bone marrow (BM) aspiration/biopsy, gastrointestinal endoscopy/colonoscopy with biopsy, and/or biopsy of other tissue when appropriate and medically feasible
- Each patient must sign Informed Consent form indicating that he or she understands the purpose of and procedures required for the study and are willing to participate
- Short course systemic corticosteroids (total daily dose equivalent of prednisone 100mg or less) are permissible for disease control, improvement of performance status, or non-cancer indication if administered for s; 10 days and discontinued prior to initiation of study treatment
- Willingness of patients who are able to become pregnant according to Revlimid/lenalidomide Risk Evaluation and Mitigation Strategy (REMS) criteria to undergo pregnancy testing in accordance with REMS requirements
- Willingness of all patients to adhere to contraception requirements mandated by the Revlimid/lenalidomide REMS

## 6.2 Participant Exclusion Criteria

Patients must not meet any if the following criteria to be eligible for inclusion in this study:

- Any life-threatening illness, medical condition, or organ system dysfunction that, in the opinion of the investigator, could compromise the patient's safety or put the study outcomes at undue risk
- History of human immunodeficiency virus (HIV) unless fill of the following criteria are met:31
    - CD4+ T-cell count 250 cells/mcl
    - No acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections within 1 year prior to signing Informed Consent form
    - Stable (no change in regimen for 4 weeks) and effective antiretroviral regimen, and HIV viral load < 400 copies/ml within 4 weeks prior to signing Informed Consent form
- Hepatitis B or C with detectable viral load requiring antiviral therapy
- Pregnant or lactating
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 2 weeks prior to cycle 1 day 1
- Clinical significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis
- Active central nervous system lymphoma
- Patients who, in the opinion of the investigator, have not recovered sufficiently from adverse effects of prior therapies
- Documented refractoriness to lenalidomide, defined as no response (PR or CR) within 6 months of therapy
- Lenalidomide exposure within 12 months prior to Day 1 of Cycle 1
- History of hypersensitivity to compounds of similar biological or chemical composition to tafasitamab, lenalidomide, and/or excipients contained in the study drug formulations
- Autologous stem cell transplantation (ASCT) within 3 months prior to signing the Informed Consent form. Patients with more distant history of ASCT must exhibit full hematologic recovery before enrollment into this study.
- Allogeneic stem cell transplantation within 3 months prior to signing the Informed Consent form, with evidence of graft-versus-host disease (GVHD), or receiving immunosuppressive therapy for GVHD.
- Concurrent use of other anticancer or experimental treatments
- No concurrent malignancy requiring active therapy within the last 3 years with the exception of basal cell carcinoma limited to the skin, squamous cell carcinoma limited to the skin, carcinoma in situ of the cervix or breast, adequately treated lentigo maligna melanoma, or localized prostate cancer. Adjuvant or maintenance therapy to reduce the risk of recurrence of other malignancy previously treated for curative intent is permitted.
- Administration of a live vaccine within 28 days prior to the start of study treatment (Cycle 1 Day 1).

# 7.0 RECRUITMENT PLAN

The study will be conducted at MSKCC. Patients will be treated by members of the lymphoma service at MSKCC. Every effort will be made to include women and minorities in this study. Patients will be recruited by the treating team of physicians and medical professionals. The consenting attending physician will inform patients of their diagnosis, current treatment options including standard treatment, and the risks, benefits, and experimental nature of this treatment program. All patients will be required to sign an Informed Consent form that conforms to FDA and MSKCC IRB guidelines.

## 7.1 Research Participant Registration

Eligibility will be confirmed as defined in section 6.0 Criteria for Participant Eligibility. Informed consent will be obtained by following procedures defined in section 8.0 Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

# 8.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants or their legally authorized representatives (LARs) will also be informed that they are free to withdraw from the study at any time. All participants/LARs must sign an IRS/PB-approved consent form indicating their consent to participate.

The consent form/research authorization meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature, objectives, potential risks, and benefits of the intended study.
2. The length of study, what it entails, and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

6. How the participants' data will be protected, who will have access to their PHI, and what data will be disclosed for research purposes

Prior to inclusion in the study and before protocol-specified procedures are carried out, the consenting professionals will explain the details of the protocol as outlined in the consent and research authorization to the participants/LARs. The participant/LAR will also be informed that they are free to withdraw from the study at any time. The consent discussion may occur in person or remotely via teleconference, telephone, or videoconference.

All participants/LARs must sign an IRB/PB-approved consent form/research authorization indicating their consent to participate. Each participant/LAR and consenting professional will sign and date the consent form. The participant/LAR must receive a copy of the signed informed consent form.

## 9.0 PRE-TREATMENT/INTERVENTION

### 9.1 Pre-treatment/intervention evaluations

All study-related evaluations and interventions are summarized in Section 11.0, Table 11-1.

Within 6 weeks prior to initiating study treatment:

- Pathologic confirmation of R/R MCL, with repeat biopsy prior to initiation of study treatment preferred
- Tumor genomic profiling on MSKCC protocol 12-245 (Integrated Mutation Profiling of Actionable Cancer Targets (IMPACT)) within 6 months prior to signing Informed Consent form, and preferably repeated for patients who did not have IMPACT performed after discontinuing their last line of treatment

Within 4 weeks prior to initiating study treatment (SOC, unless indicated otherwise):

- Physical exam, vital sign measurements, height and weight measurements, and assessment of KPS
- CT scans of chest, abdomen, and pelvis and FOG-PET scan for pretreatment staging (can include CT neck if appropriate per physician discretion)
- **BM** aspiration/biopsy
- Documentation of concomitant medications, including prescription drugs, over-the-counter drugs, herbal products, and supplements/medical foods
- Allergies
- Laboratory testing:
    - Hepatitis B virus (HBV) surface antigen (HbsAg) and core antibody (HbcAb); if either is positive, HBV viral load
    - Hepatitis C virus antibody
    - HIV 1/2 antibodies
- Enrollment in the Revlimid/lenalidomide REMS program

- Pregnancy testing according to Revlimid/lenalidomide REMS requirements if applicable
- OPTIONAL: fine needle aspirate or other biopsy of involved peripheral nodal tissue (paired with cycle 1 day 22 follow-up biopsy- see Table 11-1)

Within 1 week prior to initiating study treatment (SOC, unless indicated otherwise):

- Laboratory testing:
    - Complete blood count (CBC) with differential
    - Comprehensive metabolic panel (CMP)
    - Phosphorus
    - Uric acid
    - Lactate dehydrogenase (LOH)

## 9.2 Concomitant therapy

### 9.2.1 Permitted concomitant therapies

- Standard therapies for concurrent medical conditions
- Inactivated vaccines (eg, injectable influenza vaccine)
- Herbal product and supplement use is discouraged (with the exception of medicinal cannabis administered under the direction and monitoring of an appropriately credentialed health care provider) but not prohibited, provided the given product(s) do not, in the opinion of the investigator, place the patient's safety and/or study outcomes at undue risk
- Antimicrobial prophylaxis
- Palliative and supportive therapies, including but not limited to:
    - Prophylactic and as-needed use of antiemetics
    - Use of granulocyte colony stimulating factor (G-CSF) for prophylaxis or treatment of neutropenia
    - Short-term systemic corticosteroid use, including as antiemetic prophylaxis or management of acute conditions

### 9.2.2 Prohibited concomitant therapies

- Other investigational and antineoplastic therapies
- Live vaccines
- Immunosuppressive therapies other than corticosteroids as described in 9.2.1

### 9.2.3 Drug-drug interactions

While lenalidomide is a minor substrate of P-glycoprotein (P-gp), it is not anticipated to have clinically significant interactions with inhbitors or inducers of P-gp.[32] Lenalidomide does not undergo phase I or II metabolism, nor is it a known substrate of membrane drug transporters, thus there are no anticipated interactions anticipated when co-administered with cytochrome P450 isozyme or drug transporter inhibitors, inducers, or substrates.

Tafasitamab has not undergone dedicated food-drug or drug-drug interactions. Because its mechanism does not include direct inflammation and it is not extensively hepatically metabolized, it is not anticipated to affect nor be affected by drugs metabolized by, inhibiting, or inducing cytochrome P450 isozymes.

## 10.0 TREATMENT/INTERVENTION PLAN

### 10.1 Tafasitamab

Tafasitamab will be administered intravenously according to the MSK tafasitamab infusion guideline on the following schedule:

- Induction:
  - Cycle 1 (28 days): days 1, 4, 8 , 15, and 22
  - Cycles 2 and 3 (28 days each): days 1, 8, 15, and 22
  - Cycles 4 through 12 (28 days each): days 1 and 15
- If SD, PR, or CR after cycle 12, maintenance:
  - Cycles 13-36 (28 days each): day 1

The dose of each tafasitamab infusion is 12mg/kg according to total (actual) body weight. Dose rounding will be performed according to institutional standard. No dose reductions of tafasitamab will be permitted.

### 10.2 Lenalidomide

Lenalidomide will be self-administered by patients orally on days 1-21 of each 28-day cycle of induction (cycles 1 through 12). Patients will be instructed to take each dose of lenalidomide at about the same time each day with approximately 8 ounces (240ml) of water, without regard to food. Lenalidomide must be swallowed whole; patients should not open or break the capsules. If a dose is missed, the dose may be taken if within 12 hours of usual dosing time. If more than 12 hours have elapsed since usual dosing time, the patient should skip the missed dose and take the next dose at the usual dosing time. If a patient vomits after taking a dose, the dose should not be made up.

Research personnel will review the dosing instructions with patients. Patients will be provided with a medication diary and asked to record the drug administration. Patients will be asked to bring any unused drug and empty drug containers to the research personnel at the beginning of each cycle. Site staff will count and record the number of used and unused drug at the beginning of each cycle and reconcile their findings with the patient diary.

The daily dose of lenalidomide in patients with normal renal function (CrCl 2: 60ml/min) is 20mg. Renal adjustments are outlined in Table 10-1. In patients with impaired renal function at baseline who qualify for study inclusion (CrCl < 60ml/min but 2: 30ml/min), the daily dose of lenalidomide is 10mg daily, with escalation to 15mg daily permitted after 2 cycles if tolerating treatment in the opinion of the investigator. Patients who subsequently develop severe renal dysfunction (CrCl 30ml/min) after initiation of study treatment may continue treatment with lenalidomide at a reduced dose as noted in Table 10-1. Note that renal

dysfunction resulting from toxicity suspected to be related to tafasitamab and/or lenalidomide (eg, due to tumor lysis syndrome) may warrant interruption and/or discontinuation of either or both drugs, as outlined in Table 10-4.

| **Table 10-1: Lenalidomide dose adjustment for renal dysfunction prior to or after study initiation** | | |
|---|---|---|
| Cockcroft-Gault CrCl (see Appendix B) | Daily lenalidomide dose (days 1-21 of cycles 1-12) | Note |
| 30ml/min and < 60ml/min | 10mg | May increase to 15mg once daily after 2 cycles if tolerating treatment in the opinion of the investigator |
| **Severe renal dysfunction after study treatment initiation*** | | |
| < 30ml/min not requiring dialysis | 5mg once daily | |
| < 30ml/min requiring dialysis | 5mg once daily; for doses on dialysis days, administer after dialysis | |

*CrCl must be 30ml/min to be eligible for participation in the study; dose adjustments for CrCl < 30ml/min apply only to patients who met inclusion criteria, initiated treatment with the appropriate initial lenalidomide dose, and subsequently developed severe renal dysfunction

### 10.3 Required prophylaxis

The following prophylactic measures are required:

- Tafasitamab infusion-related reaction **(IRR)** prophylaxis (per the MSK tafasitamab infusion guideline)
- Lenalidomide-associated venous thromboembolism (VTE) prophylaxis: Patients must receive VTE prophylaxis throughout the induction phase
- HBV reactivation prophylaxis: in patients positive for HBcAb and/or HBsAg without detectable viral load, prophylaxis against reactivation (eg, entecavir 0.5mg PO daily; consult pharmacist for dosing in patients with renal dysfunction) should be administered throughout study treatment and 6 months after EOT
- Tumor lysis syndrome (TLS) prophylaxis:
    - Patients must be screened for risk of TLS prior to study treatment initiation according to the MSK guideline for prevention and management of TLS in adults
    - Patients at risk of TLS should undergo risk-adapted prophylaxis and monitoring according to the institutional guideline and investigator's discretion

### 10.4 Study duration

The maximum duration of treatment for this study is planned to be a total of 36 cycles (12 cycles of tafasitamab plus lenalidomide induction, 24 cycles of tafasitamab maintenance), not to exceed 36 months.

After discontinuation of both study drugs, patients will complete an EOT visit within 7 days from the date of official treatment discontinuation. If treatment must be discontinued due to prolonged interruption for toxicity (see 10.5.7), the EOT visit will occur within 7 days of the decision to permanently discontinue treatment.

All patients will be followed for adverse events for at least 30 days following the last dose of study treatment or until initiation of new therapy, whichever comes first. Patients who proceed to tafasitamab maintenance will be followed for disease status updates for up to three years. After completing study treatment, survival, relapse, and new anti-lymphoma therapy information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months until death, loss to follow up or consent withdrawal, whichever comes first.

### 10.5 Dose continuation, modification, and interruption

Patients will be evaluated for AEs at each visit and will undergo laboratory evaluations according to the schedule in Section 11.0 and Table 11-1. CTCAE version 5.0 will be utilized for toxicity grading.

The course of action for treatment interruption, modification, and/or reinstatement for specific toxicities is outlined below. Any other treatment interruption considered medically necessary by the investigator is permitted, and the decision and rationale should be documented.

#### 10.5.1 Parameters for treatment continuation

Patients may initiate treatment on day 1 of each cycle provided that:

- ANC 1,000 cells/mcl (unless felt to be secondary to underlying MCL)
- Platelets 50,000 cells/mcl (unless felt to be secondary to underlying MCL)
- No serious organ or other toxicity present

#### 10.5.2 Tafasitamab infusion-related reactions

##### 10.5.2.1 Monitoring, grading, and acute management of tafasitamab IRR

Vital signs will be monitored during tafasitamab infusion as outlined in Section 11.0, Table 11-1. Body temperature, systolic and diastolic blood pressure (mmHg), heart rate (beats per minute), and respiratory rate (respirations per minute) will be measured immediately prior to infusion, at 15 ± 5 and 30 ± 10 minutes after initiating infusion, every 60 ± 15 minutes

thereafter, and at the end (± 20 minutes) of infusion. If the infusion is interrupted and/or subsequently restarted, vital signs should be assessed every 60 ± 15 minutes after the first hour. Vital signs may be monitored more frequently if clinically indicated.

All patients will receive IRR prophylaxis for at least the first 3 doses of tafasitamab as described in Section 10.3. IRRs will be assessed according to CTCAE version 5.0 grading:

**Table 10-2: Tafasitamab infusion-related reaction grading**

| Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|
| Mild, transient reaction; infusion interruption not indicated; intervention not indicated | Therapy or infusion interruption indicated but respond promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for :5 24 hours | Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae | Life-threatening consequences; urgent intervention indicated |

Precautions for anaphylaxis will be observed during tafasitamab infusion. Emergency resuscitation equipment and medications will be readily available, including medications in the Hypersensitivity Order Set (Chemo_Adult_Hypersensitivity_Order_Set (Outpatient)). Acute management of signs and symptoms of IRR will be according to the MSK institutional standard (Appendix C).

#### 10.5.2.2 Rechallenge after tafasitamab IRR

For grade 2 and 3 IRRs, once symptoms have resolved to grade :5 1 according to investigator assessment, the infusion may be resumed according to the MSK tafasitamab infusion guideline.

For grade 4 IRRs, the patient must not receive further treatment with tafasitamab. Treatment with lenalidomide alone may continue.

### 10.5.3 Lenalidomide-associated diarrhea

Diarrhea suspected to be secondary to lenalidomide will be graded according to CTCAE version 5.0. Interruptions of lenalidomide and dose reductions will be based on grade:

| Table 10-3: Lenalidomide-associated diarrhea grading and dose interruption/reduction | | |
|---|---|---|
| Grade 1-2 | Increase of:::; 4-6 stools per day over baseline; mild-moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily living (AOL) | No interruption or dose reduction required<br>Implement supportive care measures; see suggested symptom management measures (Appendix D) |
| Grade 3-4 | Increase of 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care AOL; life-threatening consequences; urgent intervention indicated | Interrupt lenalidomide dosing<br>Implement supportive care measures; see suggested symptom management measures (Appendix D) |
| | Resolution to grade :::; 2 | Resume lenalidomide dosing at the next lower dose level (Table 10-6) |

### 10.5.4 Hematologic and other toxicities

Toxicities suspected to be related to study medications will be graded according to CTCAE version 5.0 and managed according to Tables 10-4 and 10-5 below.

| Table 10-4: Hematologic and other toxicities suspected to be related to either study medication | | |
|---|---|---|
| Thrombocytopenia grade 3-4 | Platelets < 50,000 cells/mcL | Cycles 1 through 3: interrupt both tafasitamab and lenalidomide<br>Cycle 4: interrupt lenalidomide only<br>Obtain CBC every 7 days |
| | Platelets recover to 50,000 cells/mcL | Provided other criteria for dosing are met (see 10.5.1), resume study treatment.<br>If lenalidomide is being continued, it should be resumed at the next lower dose level. Dose re-escalation is permitted in certain circumstances (Table 10-6). |

| | | |
|---|---|---|
| Neutropenia grade 3-4 | ANC < 1,000 (but 500) cells/mcl for 7 days<br>Or<br>ANC < 1,000 cells/mcl with fever 38.5°C (101°F)<br>Or<br>ANC < 500 cells/mcl | Cycles 1 through 3: interrupt both tafasitamab and lenalidomide<br>Cycle 4: interrupt lenalidomide only<br>Obtain CBC every 7 days<br>GCSF use is strongly encouraged |
| | ANC recovers to 1,000 cells/mcl | Provided other criteria for dosing are met (see 10.5.1), resume lenalidomide.<br>If lenalidomide is being continued, it should be resumed at the next lower dose level. Dose re-escalation is permitted in certain circumstances (Table 10-6). |
| Other clinically significant toxicities (except those attributable to lenalidomide below) | Grade 3-4 | Interrupt the study drug(s) to which the toxicity is suspected to be attributable. |
| | Resolution to grade :s; 2 | Provided other criteria for dosing are met (see 10.5.1), resume previous treatment.<br>If lenalidomide was interrupted and is being continued, it should be resumed at the next lower dose level (Table 10-6) |

**Table 10-5: Other toxicited suspected to be related to lenalidomide**

| | | |
|---|---|---|
| Thromboembolic events | Grade 3-4 | Interrupt lenalidomide dosing<br>Start anticoagulation as per MSK anticoagulation guideline and investigator's discretion |
| | Resolution to grade :s; 2 | Resume lenalidomide at investigator's discretion (maintain dose level) |

| | | |
|---|---|---|
| Allergic reaction or hypersensitivity grade 3-4 (including but not limited to Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative or bullous rash, angioedema) | | Discontinue lenalidomide permanently |
| Desquamating {blistering) rash grade 3-4 | | Discontinue lenalidomide permanently |
| Nondesquamating rash | Grade 1 (< 10% of body surface area (BSA)) | Treat with topical corticosteroids and oral antihistamines until resolution of rash/symptoms; short course of low-dose oral corticosteroid is permitted |
| | Grade 2 (10-30% of BSA) | Consider interrupting lenalidomide dosing until grade :5 1<br>Treat with topical corticosteroids and oral antihistamines until resolution of rash/symptoms to grade s; 1; short course of low-dose oral corticosteroid is permitted |
| | Grade 3 (> 30% of BSA) | Interrupt lenalidomide dosing until grade s;<br>Treat with topical corticosteroids and oral antihistamines until resolution of rash/symptoms to grade :5 1; short course of low-dose oral corticosteroid is permitted |
| | Grade 4 (life-threatening) | Discontinue lenalidomide permanently |
| Tumor flare reaction grade 1-2 | Continue lenalidomide at current dose level or interrupt lenalidomide at investigator's discretion | |

| | | |
|---|---|---|
| Tumor flare reaction grade 3-4 | Grade 3-4 (see 10.5.5) | Interrupt lenalidomide dosing |
| | Resolution to grade 1 | Resume lenalidomide (maintain dose level) |

**10.5.5 Lenalidomide-associated tumor flare**

Patients should be monitored at each visit for tumor flare reactions (TFRs). TFR is defined as a sudden and tender increase in the size of the disease bearing sites (such as lymph nodes, spleen, and/or liver), often accompanied by low-grade fever, non-pruritic diffuse rash, and in some cases, an increase in peripheral blood lymphocyte count. Such reactions are expected with lenalidomide, especially in patients with a high burden of disease and may mimic disease progression. Therefore, careful monitoring and evaluation is important prior to discontinuing a study patient for progressive disease in the initial cycles of lenalidomide therapy. There are currently no laboratory oor radiological tests to help distinguish TFR from POD. The distinction should be made on clinical grounds, incorporating observations such as associated physical findings, laboratory findings, and pace of disease before and after study treatment initiation. TFR should be recorded as an AE of special interest, graded using CTCAE version 5.0, and not as POD.

Treatment of TFR is at the discretion of the investigator.

**10.5.6 Lenalidomide dose reductions for toxicity**

If lenalidomide dosing was interrupted during the previous cycle, restarted at the next lower dose level during the same cycle in which it was interrupted, and did not require interruption for the remainder of the cycle, then that reduced dose level will be initiated on day 1 of the next cycle. There will be no more than one dose reduction from one cycle to the next.

A dose reduction of lenalidomide constitutes a 5mg decrease in the daily dose from the previous dose, including in patients who initiate treatment at a decreased dose due to renal dysfunction. Patients who are unable to tolerate the lowest dose of 5mg once daily should discontinue lenalidomide but continue treatment with tafasitamab alone.

| **Table 10-6: Lenalidomide dose reductions for toxicity** | | **Note** |
|---|---|---|
| **Starting dose** | 20mg once daily days 1-21 of each 28-day cycle | In patients who required lenalidomide dose reduction for hematologic toxicity early in the treatment course due, in the opinion of the investigator, to bone marrow and/or splenic disease |
| **Dose level -1** | 15mg once daily days 1-21 of each 28-day cycle | |
| **Dose level -2** | 10mg once daily days 1-21 of each 28-day cycle | |

| | | |
|---|---|---|
| **Dose level -3** | 5mg once daily days 1-21 of each 28-day cycle | involvement, re-escalation to the previous dose level is permitted |
| **Further reduction indicated** | Discontinue | |

### 10.5.7 Maximum duration of treatment interruption

If treatment is interrupted for 28 consecutive days, treatment should continue at the next protocol scheduled visit. No missed visits or doses of either drug should be made up.

If treatment with one study drug is interrupted for more than 28 consecutive days, that drug is to be permanently discontinued and the patient will continue treatment with the other study drug per protocol. If treatment with both study drugs is interrupted for more than 28 consecutive days, the EOT visit will be performed as noted in 10.4.

# 11.0 EVALUATION DURING TREATMENT/INTERVENTION

## 11.1 General overview of evaluations

Evaluations during screening and study treatment are as indicated in Table 11-1.

**Table 11-1. Schedule of evaluations (screening through cycle 3).**

| | Screening | | Cycle 1 (28 days) | | | | | Cycle 2 (28 days) | | | | Cycle 3 (28 days) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Day** | **S 28 days** | **S 7 days** | **1** | **4** | **8** | **15** | **22** | **1** | **8** | **15** | **22** | **1** | **8** | **15** | **22** |
| **Window** | **before C1D1** | **before C1D1** | | | **±1** | **±1** | **±1** | **±1** | **±1** | **±1** | **±1** | **±1** | **±1** | **±1** | **±1** |
| Informed consent | X | | | | | | | | | | | | | | |
| Inclusion/exclusion checklist | X | | X6 | | | | | | | | | | | | |
| Biopsy and pathologic confirmation of MCL | X | | | | | | | | | | | | | | |
| PET | X | | | | | | | | | | | X | | | |
| CT CAP (+neck if indicated) | X | | | | | | | | | | | X | | | |
| KPS | X | | X | | | | | X | | | | X | | | |
| Vital signs[1] | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | | | X | | | | | | | | | | | | |
| Weight | | | X | | | | | X | | | | X | | | |
| CBC with differential | | X | X | | X | X | X | X | X | X | X | X | X | X | X |
| Chemistry[2] | | X | X | | | | | X | | | | X | | | |
| Hepatitis B serology | X | | | | | | | | | | | | | | |
| Hepatitis C serology | X | | | | | | | | | | | | | | |
| HIV serology | X | | | | | | | | | | | | | | |
| Pregnancy test (if applicable)[3] | X | | X | | | | | X | | | | X | | | |
| Consent to 12-245 IMPACT and sample collection[4] | X | | | | | | | | | | | | | | |
| BM aspirate and biopsy | X | | | | | | | | | | | | | | |
| Research blood tests | | | X | | | | X | X | | | | | | | |
| Optional research biopsy[5] | X | | | | | | X | | | | | | | | |
| (S)AE assessment | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tafasitamab administration | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Lenalidomide administration | | | Patients will self-administer Days 1-21 of each Cycle | | | | | | | | | | | | |

| Table 11-1 (continued). Schedule of evaluations (cycles 4 through EOT). | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cycle 4 (28 days) | | Cycle 5 (28 days) | | Cycle 6 (28 days) | | Cycle 7 (28 days) | | Cycle 8 (28 days) | | Cycle 9 (28 days) | | Cycle 10 (28 days) | | Cycle 11 (28 days) | | Cycle 12 (28 days) | | Cycle 13 (28 days) | Cycles 14-36 (28 days each) | EOT visit |
| Day | 1 | 15 | 1 | 15 | 1 | 15 | 1 | 15 | 1 | 15 | 1 | 15 | 1 | 15 | 1 | 15 | 1 | 15 | 1 | 1 | +7 days post discontinuation |
| | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | |
| PET Scan | | | | | X | | | | | | | | | | | | | | X | X[8] | X[9] |
| CT CAP | | | | | X | | | | | | X[7] | | | | | | | | X | X[8] | X[9] |
| Biopsy | | | | | | | | | | | | | | | | | | | | | X[10] |
| KPS | X | | X | | X | | X | | X | | X | | X | | X | | X | | | | |
| Vital signs[1] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Weight | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | X | X |
| CBC with differential | X | | X | | X | | X | | X | | X | | X | | X | | X | | | | |
| Chemistry[2] | X | | X | | X | | X | | X | | X | | X | | X | | X | | | | |
| Pregnancy test (if applicable)[3] | X | | X | | X | | X | | X | | X | | X | | X | | X | | | | |
| BM aspirate and biopsy | | | | | | | | | | | | | | | | | | | | | X[10] |
| Research blood tests | X | | | | | | X | | | | | | | | | | | | X | | X[10] |
| Optional research biopsy[5] | | | | | | | | | | | | | | | | | | | | | X |
| (S)AE assessment | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tafasitamab administration | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| Lenalidomide administration | Patients will self-administer Days 1-21 of each Cycle | | | | | | | | | | | | | | | | | | | | |

[1]Vitals: Blood Pressure, Pulse, Respiratory Rate, and Temperature

[2]Chemistry: CMP, Phosphorus, Uric Acid, and LDH

[3]Patients able to become pregnant must have pregnancy testing performed according to Revlimid/lenalidomide REMS requirements: one test (sensitive to at least 50mIU/mL) 10-14 days before writing the initial lenalidomide prescription, and a second test within 24 hours prior to writing the initial lenalidomide prescription. Subsequent pregnancy testing should occur every 4 weeks.

[4]Unless previously performed within 6 months of study initiation

[5]Optional biopsy can be a fine needle aspirate or other biopsy of involved peripheral lymph node tissue, and/or bone marrow aspirate (if MCL involvement of marrow was demonstrated pre-treatment). Optional biopsy/aspirate occurs at baseline, cycle 1 between day 22-28, and at end of treatment/disease progression. Note that the biopsy performed for required confirmation of R/R MCL diagnosis is acceptable for the first research biopsy, provided that tissue is available, the biopsy was performed within the screening period, and the site can be re-biopsied at cycle 1 day 22.

[6]Prior to study drug administration

[7]Evaluation by CT CAP with IV contrast (include neck if disease involvement).

[8]Evaluation by PET/CT approximately every 6 months from previous scan

[9]Only required if not performed in the cycle before the EOT visit

[10]Only required for discontinuation for POD

### 11.2 Correlative studies

Patients will have tumor samples analyzed for genomic alterations via 12-245 IMPACT targeted sequencing platform.

Additionally, ctDNA will be collected serially according to Table 11-1 to evaluate tumor clonal evolution. See lab manual for collection instructions.

MRD assessment via IS MRD assay will be performed using serial peripheral blood draws according to the schedule in Table 11-1. See lab manual for collection and shipping instructions.

Serial peripheral blood samples for PBMCs according to schedule in Table 11-1 will be obtained for 1) T-cell and NK-cell profiling and 2) CITE-Seq. See lab manual for collection instructions.

An optional pair of biopsies of involved peripheral nodal tissue at baseline and during cycle 1 between days 22-28 will be obtained to assess effect of therapy on the tumor microenvironment. See lab manual for collection instructions.

## 12.0 CRITERIA FOR REMOVAL FROM STUDY

Patients may voluntarily withdraw from the study or be removed from the study at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur:

- Disease progression
- Ineligibility (at the cycle 1 day 1 evaluation or earlier) as defined in the inclusion/exclusion criteria
- Treatment will be discontinued at the request of the patient, refusal of therapy, non-compliance, or upon development of an intercurrent significant medical illness
- Significant protocol violation
- Unacceptable toxicity necessitating drug discontinuation as outlined in 10.5
- Decision by the investigator that termination is in the patient's best medical interest
- Loss to follow-up
- Development of active HBV, HCV, or HIV infection
- Pregnancy or positive pregnancy test
- Death of the patient
- Start of any other antineoplastic therapy

## 13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

### 13.1 Criteria for Therapeutic Response/Outcome Assessment

Response and progression of disease will be evaluated using the Lugano criteria (Figure 3).[1,2] Clinical evaluation and tumor assessments will be performed periodically as indicated in Table 11-1. Clinical suspicion of disease progression at any time will require physical

examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment. In case of an unscheduled or delayed tumor assessment for any reason, subsequent tumor assessments must be performed according to the originally planned schedule.

### 13.2 Criteria for Study Endpoint Evaluability

All patients who received at least one dose of tafasitamab and one dose of lenalidomide will be considered evaluable for the primary endpoint of ORR and all secondary endpoints. This will be the primary analysis. Safety endpoints will be evaluated in all patients who received at least one dose of tafasitamab or one dose of lenalidomide. Any patient that is removed from the study for reasons other than progression will be counted as a failure for ORR analysis and as an event for PFS analysis (as long as they have received at least 1 dose of tafasitamab and 1 dose of lenalidomide). For OS analysis, patients who are removed from the study for any reason other than death will be censored at the time of study removal. The study will continue enrollment until the required number of evaluable patients (those that receive at least one dose of both study drugs) is reached in each stage of the study.

The primary and secondary endpoints will also be evaluated in the per-protocol cohort (patients who did not have any major protocol violations) as a supportive, secondary analysis.

## 14.0 BIOSTATISTICS

Objectives:

The primary objective is to estimate the ORR, defined as the percent of patients (relative to the total number considered evaluable as in 13.2) who achieve CR or PR. The primary endpoint will be analysed when all patients have completed 12 cycles of treatment or at treatment discontinuation, whichever comes first.

Secondary objectives are estimates of OCR, DOR, PFS, OS, and TTP, and descriptions of incidence and severity of AEs. Exploratory objectives include rate of conversion to undetectable MRD, ctDNA/clonal evolution, antitumor immune response, and effects on tumor microenvironment immunosuppression.

Exploratory objectives are described in Section 3.1 Correlative studies.

Study design:

The primary endpoint is ORR and the study is designed to determine preliminary clinical effectiveness of tafasitamab and lenalidomide. Based upon limited data available for lenalidomide and associated combinations in the post-BTKi setting, the combination of tafasitamab and lenalidomide will be considered worthy of further evaluation if the ORR is greater than 30%. This combination will be considered promising in the R/R setting if the ORR is greater than 50% given multiple evolving treatment options for patients post-BTKi failure or intolerance. To this end, , a single-arm Simon's two-stage minimax design will

utilize a null (non-promising) ORR of 30% and an alternative (promising) ORR of 50%. In the first stage, a total of 19 patients will accrue. If 6 or fewer have objective response, the trial will close due to a lack of efficacy; otherwise, an additional 20 patients will accrue. If at the end of the study, 17 or more out of 39 have an objective response, the trial will be considered promising for future development. This design will give 80% power with a type I error rate of 5%. Patients will continue to enroll without holding enrollment while the interim analysis is evaluated in the first 19 patients.

The anticipated accrual rate for this study is 1 to 2 patients per month. We anticipate total accrual will be completed in 2-3 years. The study will continue enrollment until the required number of evaluable patients (those that receive at least one dose of both study drugs) is reached in each stage of the study.

Methods:

Primary objectives: ORR will be calculated as a proportion and summarized along with 95% confidence intervals. Patients who withdraw prior to response evaluation will be classified as nonresponders for the primary objective.

Secondary objectives: OCR will be defined as the percent of patients who achieve CR, PR or stable disease (SD) at the time of ORR assessment. Patients who withdraw prior to response evaluation will be classified as failures. The OCR will be estimated by proportion along with 95% confidence intervals. DOR will be defined as the time from achievement of PR or CR to progression of disease (POD) according to Lugano criteria or death. PFS will be defined as the time from initiation of study treatment to the earlier of POD or death from any cause. OS will be defined as the time from initiation of treatment to death from any cause. Kaplan-Meier estimates of DOR, PFS, and OS will be calculated and presented with 95% confidence intervals. TTP will be defined as the time from start of treatment to POD or death specially from MCL, and will be estimated with 95% confidence intervals by cumulative incidence function. Death from other causes will be treated as a competing risk. Frequency and severity of adverse events will be summarized descriptively.

Exploratory objectives will be performed in conjunction with collaborating laboratories at MSK. Study designs and analytic approaches are detailed in Section 3.1. Most objectives will be summarized descriptively. For assessing association between minimal MRD and PFS, the log rank test will be used and Kaplan-Meier curves will be presented. For assessing association between genomic alterations discovered through MSK-IMPACT sequencing and time-to-event outcomes PFS and OS, Cox regression will be used and hazard ratios with 95% confidence intervals will be presented. For assessing association between genomic alterations and ORR, Fisher's exact test will be used, and p-values will be adjusted for multiple testing with the false discovery rate (FDR).

14.1 Populations for analysis include the following:

- Primary analysis (primary endpoint and all secondary endpoints): All patients who received at least one dose of tafasitamab and one dose of lenalidomide
- Safety analysis: All patients who received at least one dose of tafasitamab or one dose of lenalidomide
- Secondary per-protocol analysis (primary endpoint and all secondary endpoints): All patients who did not have any major protocol violations, identified for each patient with a protocol violation before database closure

## 15.0 TOXICITIES/RISKS/SIDE EFFECTS

An AE is defined as the appearance of (or worsening of any pre-exisintg) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed Informed Consent form has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require treatment (eg, hematologic abnormality that requires transfusion or hematologic stem cell support), or require changes in study medication(s).

AEs that begin or worsen after informed consent should be recorded in Medidata. Conditions that were already present at the time of informed consent should be recorded in the Medical History in Medidata. AE monitoring should be continued for at least 30 days following the last dose of study treatment or until initiation of new therapy, whichever comes first. AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

CTCAE Version 5 will be utilized for toxicity evaluation. If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, and life-threatening, corresponding to grades 1-4, will be used. CTCAE grade 5 (death) will not be used - rather, information about deaths will be collected through a Death form.

The occurring of AEs should be sought by non-directive questioning of the patient during the screening process after signing Informed Consent form and at each visit during the study. AEs also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, orother assessments. As far as possible, each AE should be evaluated to determine:

- The severity grade (CTCAE grade 1-4)
- Its duration (start and end dates)
- Its relationship to the study treatment (reasonable possibility that AE is related: yes or no)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, or not applicable)
- Whether medication or therapy taken (no concomitant medication/non-drug therapy or concomitant medication/non-drug therapy)

- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, or unknown)
- Whether it is serious, as defined below
- All AEs should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded in Medidata.
- Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome
- Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (Lugano criteria), should not be reported as an SAE
- AEs separate from POD (eg, deep vein thrombosis at time of progression or hemoptysis concurrent with finding of POD) will be reported as per usual guideline for such events with proper attribution regarding relatedness to the drug

Adverse events of special interest (AESIs) are a subset of events of scientific and medical concern specific to this study. Such an event may require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (eg, regulatory authorities) may also be warranted. AESIs include IRRs, overdoses (defined as exceeding the planned dose by more than 20%), second primary malignancies, TFR, thromboembolic events, and TLS.

The 5 most common adverse events associated with tafasitamab/lenalidomide in the L-MIND study were neutropenia (51%), fatigue (38%), anemia (36%), diarrhea (36%), and thrombocytopenia (31%). Details on adverse events are described in Table 15-1.

**Table 15-1: Adverse reactions in patients with relapsed or refractory diffuse large B-cell lymphoma who received tafasitamab in L-MIND (n = 81)**

| Adverse reactions occurring in 10% | All-grade% | Grade 3-4 % |
|---|---|---|
| **Dermatologic** | | |
| Pruritus | 10 | 1.2 |
| Rash | 15 | 2.5 |
| **Gastrointestinal** | | |
| Abdominal pain | 15 | 1.2 |
| Constipation | 17 | 0 |
| Decreased appetite | 22 | 0 |
| Diarrhea | 36 | 1.2 |
| Nausea | 15 | 0 |
| Vomiting | 15 | 0 |
| **Hematologic** | | |
| Anemia | 36 | 7 |
| Febrile neutropenia | 12 | 12 |

| | | |
|---|---|---|
| Neutropenia | 51 | 49 |
| Thrombocytopenia | 31 | 17 |
| **Musculoskeletal** | | |
| Back pain | 19 | 2.5 |
| Muscle spasms | 15 | 0 |
| **Other** | | |
| Fatigue | 38 | 3.7 |
| Hypokalemia | 19 | 6 |
| Peripheral edema | 24 | 0 |
| Pyrexia | 24 | 1.2 |
| **Respiratory** | | |
| Bronchitis | 16 | 1.2 |
| Cough | 26 | 1.2 |
| Dyspnea | 12 | 1.2 |
| Respiratory tract infection | 24 | 4.9 |
| **Urologic** | | |
| Urinary tract infection | 17 | 4.9 |

### 15.1 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30 days after the participant's last investigational treatmenUintervention. Any event that occurs after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (e.g., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP Office per IRB SOP RR-408 'Reporting of Serious Adverse Events,' the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
    - If the SAE is an Unanticipated Problem

**15.2 External SAE Reporting**

SAE Reporting to Incyte
The Principal Investigator (PI) must report all SAEs to Incyte within 24 hours of learning of an event, regardless of the PI's causality assessment. This notification should be provided on a completed SAE form. SAE reporting for each subject begins the day the informed consent is signed by the patient and within 30 days after subject has completed or discontinued from the study or has taken last dose of the study drug, or as described in the protocol.

SAEs, occurring using Incyte study drug, are reported in accordance with the effective protocol. SAEs occurring with any other commercial drug are reported to the manufacturer of that drug in accordance with regulations and protocol.

Initial SAEs and/or subsequent follow-up reports should be reported via email to SafetyReporting@Incyte.com or fax(+) 1-866-981-2057. SAE reports should be for a single subject. SAE forms should be sent with a cover sheet and any additional attachments.

All SAEs incurred while a patient is on study will be reported to the IRB at MSKCC and Incyte. All SAEs and relevant laboratory findings will be reported to the principal investigator immediately. All information regarding SAEs must be recorded on the form provided. Patient ssuffering SAEs must be carefully followed and all follow-up information also recorded.

All life-threatening and lethal known, unknown, or suspected reactions must be reported to the principal investigator. It is the treating physician's responsibility to investigate and report the date and cause of death of any patient entered on this trial.

Reporting of Pregnancy to Incyte
An "Initial Pregnancy Report" or equivalent must be completed in full and emailed to SafetyReporting@Incyte.com or faxed to(+) 1-866-981-2057 within 24 hours of discovery of a pregnancy of a subject who has taken the Incyte product. The "Follow-up Pregnancy Report Form" or equivalent must be completed and emailed to SafetyReporting@Incyte.com or faxed to(+) 1-866-981-2057 within 30 days after delivery, so that Incyte is provided with information regarding the outcome of the pregnancy. If the pregnancy results in any events which meet the serious criteria (i.e., miscarriage or termination), the SAE reporting process needs to be followed and the timelines associated with a SAE should be followed.

The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office.

### 15.3 Pregnancy

Lenalidomide is related to thalidomide. Thalidomide is known to cause severe, life-threatening human birth defects. Lenalidomide is known to cause birth defects in animals. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females must not become pregnant or breastfeed while taking lenalidomide. Because lenalidomide carries a risk of causing thromboembolism, it is recommended that patients avoid taking oral contraceptives or hormone replacement therapy before discussing with the investigator and considering risks and benefits of these choices. In men taking lenalidomide, the drug is present in the semen at very low levels for three days after discontinuing, and may be present longer in those with impaired drug elimination (eg, renal dysfunction). All patients must adhere to the contraception requirements of the Revlimid REMS program. Patients should not donate blood during treatment or for 28 days following discontinuation of lenalidomide.

If a patient inadvertently becomes or is suspected to have become pregnant while receiving study treatment, the patient will immediately be removed from the study. The investigator will follow the reporting and monitoring requirements of the Revlimid REMS program.

## 16.0 PROTECTION OF HUMAN PARTICIPANTS

Potential risks to human subjects include drug-related toxicity; pain and discomfort associated with therapy; treatment side effects; phlebotomy; and possible psychologic discomfort from the stresses associated with obtaining imaging studies.

The side effects and potential toxicities of all agents are listed in section 15.0. All efforts will be made to avoid any complication by completely reviewing patients' symptoms, providing appropriate management, and monitoring blood tests.

If an AE occurs, the patient will first contact the primary oncologist or the principal investigator. At nights and weekends, there is an oncology physician on call at all times. Patients may either call or come directly to the Urgent Care Center at Memorial Hospital (or to their local emergency room) to be seen.

Costs to the patient (third party insurer) will include the cost of blood tests and diagnostic studies, office visits, those admissions which may be required as a consequence of treatment-related complications, and the costs of obtaining lenalidomide.

### 16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized, de-identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information, which will not include protected health information such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

### 16.2 Data Management

A Clinical Research Associate (CRA) will be assigned to the study. The responsibilities of the CRA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database (Medidata) at MSKCC. Source documentation will be available to support the computerized patient record. Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

### 16.3 Quality Assurance

Registration reports will be generated on an ongoing basis to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team at a minimum of two times per year and more frequently if indicated.

### 16.4 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data safety and quality. At a departmental/PI level, there exist procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA, and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief of Clinical Research.

The degree of monitoring required will be determined based on level of risk and documented.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator-Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant, or by the end of the year one if no accruals, and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

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## 18.0 APPENDICES

**Appendix A: Karnofsky performance status[33,34]**

| % | Performance status description |
|---|---|
| 100 | Normal. No complaints. No evidence of disease. |
| 90 | Able to carry on normal activity. Minor signs or symptoms of disease. |
| 80 | Normal activity with effort. Some signs or symptoms of disease. |
| 70 | Cares for self. Unable to carry on normal activity or to do active work. |
| 60 | Requires occasional assistance, but is able to care for most of their personal needs. |
| 50 | Requires considerable assistance and frequent medical care. |
| 40 | Disabled. Requires special care and assistance. |
| 30 | Severely disabled. Hospitalization is indicated although death is not imminent. |
| 20 | Hospitalization necessary, very sick, active supportive treatment necessary. |
| 10 | Moribund. Fatal processes progressing rapidly. |
| 0 | Dead. |

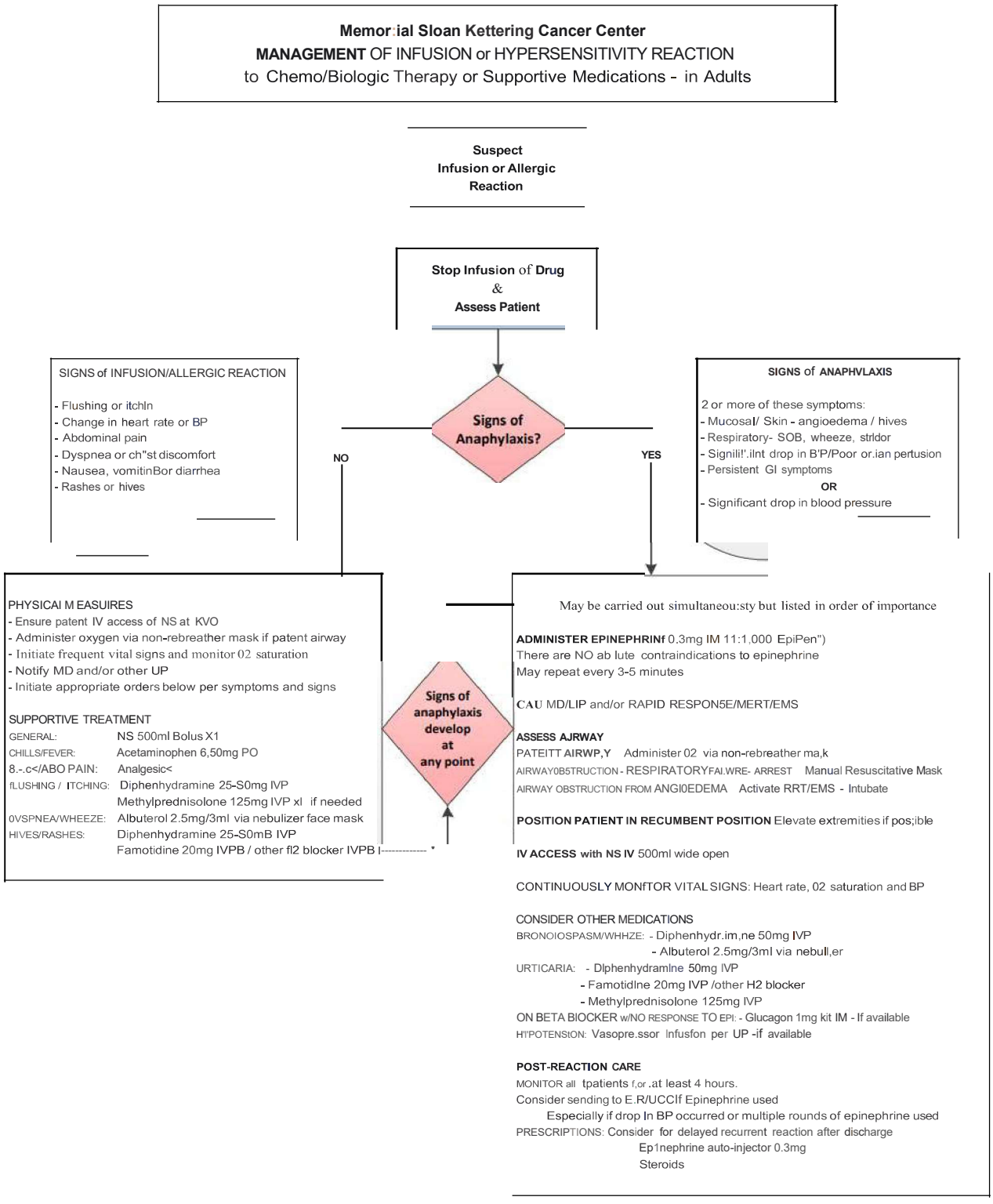
**Appendix B: Cockcroft-Gault CrCl3[5,36]**

1. Determine weight to be used:
    a. Calculate ideal body weight (IBW) in kilograms:
        i. Female: 45.5 + (2.3 x *([height, **inches**]* - 60))
        ii. Male: 50 + (2.3 x *([height, **inches**]* - 60))
    b. If IBW > total (actual) body weight (TBW), use TBW in kilograms
    c. If IBW :s; TBW:
        i. If $\frac{TBW}{IBW}$ < 1.3, use IBW in kilograms
        ii. If $\frac{TBW}{IBW}$ 1.3, use adjusted body weight (AdjBW) in kilograms:

        *[IBW, **kilograms**]*+ (0.4 x *([TEW, **kilograms**]* - *[IBW, **kilograms**])*
2. Calculate CrCl using weight determined in step 1:

$$CrCl\ (\text{-}.\ \text{mm}\ \textit{ml}) = \frac{(140 - \textit{[age, years]}) \times \textit{[weight, kilograms]}}{72 \times \textit{serum creatinine, dL}} \times (0.85\ \textit{only if female})$$

## Appendix C: Acute management of infusion-related reactions



**Appendix D: Suggested symptom management of lenalidomide-associated diarrhea**

Lenalidomide-associated diarrhea is caused by bile acid malabsorption, and can be managed using bile acid sequestrants.[37] Tafasitamab is not expected to contribute to diarrhea incidence.[25] Gastrointestinal opioid agonists (eg, loperamide, diphenoxylate) are frequently ineffective against lenalidomide-induced diarrhea and may produce constipation and other untoward effects. Use of bile acid sequestrants as first-line management of non-infectious diarrhea according to the decision tree below is suggested, but is left to the investigator's discretion.

**Suggested symptom management for lenalidomide-associated diarrhea**