Winship Protocol #: *4457-18; Version* 6.0 04 05 2021

TITLE: A Randomized Phase 2 Study of Rituxan Hycela in patients with advanced melanoma undergoing combination immune checkpoint blockade with nivolumab and ipilimumab.

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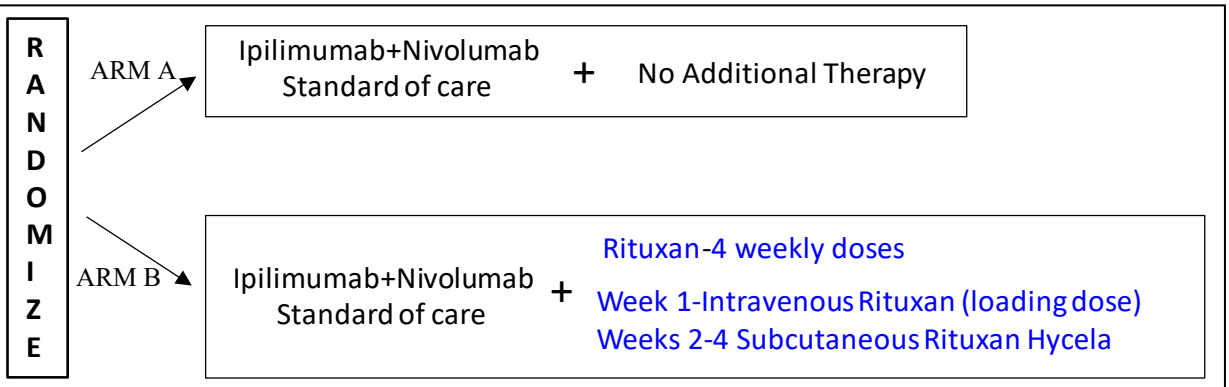
Supplied Agent: Rituximab *(supplied by Genentech, South San Francisco, CA)*

IND: Exempt

SCHEMA



Trial Design. All patients have chosen ipi/nivo as standard of care (SOC) treatment. They will be randomized prior to the first dose of ipi/nivo to receive either ARM A: SOC Ipilimumab + Nivolumab only with no additional therapy or ARM B: Standard of care Ipilimumab and Nivolumab, + 4 weekly doses of Rituxan (first dose of IV Rituxan followed by 3 weekly doses of subcutaneous Rituximab hycela) beginning 1-2 days following the first dose of Ipilimumab and Nivolumab.
SOC Ipi/Nivo is ipilimumab 3mg/kg every 3 weeks for 4 doses and nivolumab 1mg/kg every 3 weeks for 4 doses followed by nivolumab 480 mg IV every 4 weeks x 12 doses or until disease progression or intolerant adverse event.

This is a prospective randomized trial to test the efficacy of preemptive Rituxan in melanoma patients in reducing Immune-related adverse events (IRAEs) following combination checkpoint blockade (CCB). All eligible patients will undergo baseline evaluation to assess the status of disease as well as a baseline tumor biopsy. Combination checkpoint blockade will be administered as per current FDA approved standard of care, consisting of nivolumab at a dose of 1 mg/kg and ipilimumab at a dose of 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab maintenance at a dose of 480 mg every 4 weeks x 1 year. Patients will be randomly assigned to no additional therapy (ARM A control) or 4 weekly doses of Rituxan for B cell depletion (ARM B). Rituxan will be administered as 375 mg/m2 IV for the first dose followed by weekly subcutaneous dosing at 1400 mg dose of Rituxan Hycela for weeks 2-4, as per recommended dosing for the FDA approval in the setting of lymphoma. All patients will be clinically monitored for the development of IRAEs utilizing NCI Common Toxicity Criteria v5.0. Any patient who received at least one dose of study drug will be included in safety analysis, and safety assessment will continue through treatment phase and up to 100 days after the last dose of study drug. Tumor response will be assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and irRECIST at 12 weeks and every 12 weeks thereafter. All patients will also undergo pre treatment and post treatment biopsies if possible.

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1. OBJECTIVES

1.1 Primary Objectives

- To compare rates for Grade 3-4 IRAEs in the first 6 months in patients treated with combination checkpoint blockade (CCB) therapy (anti-CTLA4 and anti-PD1) as a part of standard of care for advanced melanoma who are treated with a single course of 4 weekly doses of Rituxan therapy versus those who are not treated with Rituxan.

1.2 Secondary Objectives

- To evaluate the safety and tolerability (in terms of Rituxan-related adverse events) in patients with melanoma receiving CCB.
- To compare objective response rate in patients receiving CCB therapy + Rituxan versus CCB therapy alone.
- To compare 1 year overall and progression-free survival in patients receiving CCB therapy + Rituxan versus CCB therapy alone.
- To compare changes in $CD21^{lo}$ B cells in patients receiving CCB therapy + Rituxan versus CCB therapy alone.
- To compare changes in T cells in patients receiving CCB therapy + Rituxan versus CCB therapy alone.

Exploratory Objectives

- To compare treatment induced changes in tumor tissue in patients receiving CCB therapy + Rituxan versus CCB therapy alone.

2. BACKGROUND

2.1 *Study Disease(s)*

Stage IIII or IV unresectable melanoma

2.2 IND Agent(s)

Rituxan Hycela
Rituxan Hycela is a combination of rituximab, a CD20-directed cytolytic antibody, and hyaluronidase human, an endoglycosidase, indicated for the treatment of adult patients with Follicular Lymphoma (FL), Diffuse Large B-cell Lymphoma (DLBCL), and Chronic Lymphocytic Leukemia (CLL). Rituxan has also been extensively utilized for therapy of autoimmune disorders such as immune thrombocytopenic purpura. The proposed use of Rituxan in this study is based on new data from the PI regarding the role of $CD21^{lo}CD20^{+}$ B cells in the pathogenesis of immune related adverse events following combination checkpoint blockade.

Please note Rituxan Hycela is always given as Rituximab IV as the first dose, if no reaction can proceed to Rituxan Hycela.

2.3 Rationale

Immune related adverse events (IRAEs) as a limiting toxicity of combination checkpoint blockade:
Blockade of T cell immune checkpoints PD-1/PD-L1 and CTLA-4 has emerged as an effective therapy for melanoma(1-4). Immune checkpoint blockade with monotherapy (anti-CTLA4 or anti-PD-1 alone) leads to tumor regression in only a subset of patients and combination therapy has therefore, been explored as a strategy to enhance clinical efficacy. The best studied combination therapy (concurrent administration of PD-1 and CTLA-4 blockade) leads to high response rates in advanced melanoma(5-10). However, increase in tumor regressions following combination therapy is associated with a marked increase in Grade 3 and 4 IRAEs resulting in significant morbidity and discontinuation of therapy in up to one third of patients(11, 12). Reduction in antibody dosages may be one way to partly reduce the risk for IRAEs with combination therapy, however the impact of such strategy on clinical efficacy remains to be resolved(13). There remains an urgent need to better understand the pathogenesis of IRAEs following CCB therapy and how/whether they can be prevented. Ability to prevent these IRAEs will have a major impact on the applicability of combination immune checkpoint blockade as therapy in melanoma as well as other cancers. This is not just because of short-and long-term morbidity and costs associated with IRAEs, but also because IRAEs often prevent delivery of planned therapy in several patients.

Importance of human studies to test biomarkers and prevention of IRAEs following checkpoint blockade:
As discussed above, clinical studies have shown that immune checkpoint blockade therapies can lead to distinct patterns of autoimmunity in the clinic. Importantly, the pattern or spectrum of autoimmune manifestations observed in the clinic were not entirely predictable from preclinical studies of immune checkpoint blockade(14-16). Whether these differences related to species-specific (human versus mouse) differences in the biology of the target organ(s), or the immune system remain to be clarified. A relevant example are the findings about changes in B cells in humans with CTLA4 deficiency, which were not anticipated from prior studies in CTLA4-deficient mice. In addition, the biology of the specific immune cell types may also potentially differ between mouse and man. However, these considerations do raise the importance of directly studying patients to gain fundamental insights into effects of immune checkpoint blockade. Mechanistic studies in humans are limited, but controlled studies that link targeted manipulation of specific cell types or pathways provide an opportunity to gain fundamental mechanistic insights with immediate translational potential.

Changes in B cells and risk of IRAEs following combination checkpoint blockade:
Our studies are among the first to identify that early changes in circulating B cells correlate with the development of IRAEs following checkpoint blockade(17). Much of the attention in terms of understanding biomarkers of response or efficacy in this setting has to date been focused on T cell responses. Changes in B cells have received less attention(18). In our preliminary studies, changes in B cells not only correlated with the development and severity of IRAEs, these

changes preceded the clinical manifestations of IRAEs by several weeks. Our studies will therefore provide a novel biomarker to help identify patients at risk for the development of IRAEs following checkpoint blockade. Importantly, these studies involve flow-based assays on circulating immune cells, and therefore can be easily incorporated into routine clinical practice.

B cell depletion as a preemptive strategy to lower IRAEs:
The discovery that patients who experience early changes in B cells following CCB therapy are at higher risk for subsequent development of IRAEs provides the opportunity to prevent IRAEs in this cohort. These studies will test a novel strategy of B cell depletion to reduce the risk of autoimmunity following combination checkpoint blockade. This is feasible because CCB-emergent changes in B cells not only precede autoimmune complications but are also directly amenable to targeting via anti-CD20 antibodies. It is important to note that even if this approach does not work clinically, it will provide biologically and clinically important information. For example, it would then suggest a role of other immune cells in mediating IRAEs. Recent studies have suggested that B cell depletion may also enhance anti-tumor effects in melanoma and therefore this combination may not only reduce toxicity but also improve efficacy(19).

2.4 Correlative Studies Background

$CD21^{lo}$ B cells as targets in IRAEs following combination checkpoint blockade:
Our studies are also among the first to identify a role for $CD21^{lo}$ subset of B cells in CCB-induced IRAEs. Our preliminary data indeed identified this as a specific subset of human B cells that express PD1. Improved understanding of the biology of this specific B cell subset in melanoma patients and changes in these cells following CCB will therefore provide novel mechanistic insights into CCB-induced IRAEs. These studies may also suggest novel approaches to specifically target this specific subset, as opposed to the current strategy targeting all B cells to lower the risk of IRAEs.

Contributions of B cells to protective immunity mediated by combination checkpoint blockade:
While the role of T cells in protective immunity is well established, the relative contribution of B cells to the anti-tumor effects of checkpoint blockade remain to be clarified, particularly in human studies. In preclinical models, depletion of B cells did not lead to reduction in anti-tumor effects of checkpoint blockade(19). The application of B cell depleting antibody with Rituxan in patients undergoing CCB will provide direct and novel insights into the role of B cells in both IRAEs and tumor immunity. The latter is particularly relevant because approaches targeting IRAEs will only be clinically viable if they do not adversely impact protective tumor immunity or alter the frequency or durability of clinical tumor regressions following CCB therapy.

3. PATIENT SELECTION

3.1 Eligibility Criteria

Inclusion Criteria
Subjects must meet all of the inclusion criteria before enrollment can occur.

- Clinically eligible to receive FDA approved standard of care combination immune

checkpoint therapy with Ipilimumab and Nivolumab for unresectable Stage III or stage IV melanoma.

- Age ≥18 years.
- Patients with progression on anti-PD-1 as a single agent are allowed to enroll on the study
- No therapy with immune checkpoint inhibitors other than anti-PD-1 within 1 year prior to starting combination checkpoint therapy. Prior adjuvant ipilimumab as single agent is allowed if greater than 1 year since last treatment. Patient had no Grade 3 or 4 toxicities from the checkpoint inhibitors including prior single agent PD-1 or anti-CTLA4 therapy. History of adjuvant interferon is allowed.
- Patients must have the following required values for laboratory tests obtained within three weeks prior to randomization (ULN: institutional upper limit of normal):
    - -Adequate blood counts: White Blood Count ≥ 3,000/uL ANC ≥1,500/uL, Platelet Count ≥ 100,000/uL, Hemoglobin ≥ 9 g/dL,
    - -Adequate renal function: Serum creatinine ≤1.5 x ULN or serum creatinine clearance (CrCl) ≥ 40ml/min. (CrCl= Wt (kg) x (140- age)*/72 x Cr. level, *female x 0.85)
    - -Adequate liver function: AST and ALT ≤3 x ULN (≤5 x ULN for patients with documented liver metastases), Alkaline phosphatase ≤ 2X ULN (≤5XULN for those with bone metastasis), Total bilirubin ≤ 1.5 X ULN except those with direct bilirubin or gilberts syndrome, serum LDH ≤10 X ULN).

Exclusion Criteria

Subjects will be ineligible for enrollment if they meet any of the following criteria.

- Allergy to Rituximab, or any of the ingredients in Rituximab injection or Rituximab and hyaluronidase human injection.
- Patients with active CNS metastatic disease or leptomeningeal disease. Patients with CNS metastatic disease that has been treated with surgical resection or stereotactic radiosurgery are eligible if lesions are stable. If patient required steroid therapy for his CNS metastatic disease, the patient maybe enrolled 2 weeks after stopping steroids. Prior therapy with immune checkpoint blocking antibodies (monotherapy given at least 1 year prior to starting combination therapy and no Grade 3-4 toxicities while on monotherapy are allowed, prior vaccines or IL2 given at least one year prior is also allowed)
- Patients may have had prior systemic therapy in the adjuvant setting (e.g. interferon, BRAF, or MEK agents). Adjuvant ipilimumab as single agent is allowed if greater than 1 year since last treatment and patient had no Grade 3 or 4 toxicities from the checkpoint inhibitors. Prior anti-PD-1 therapy is allowed if patients progress and have had no grade 3 or 4 toxicities related to anti-PD-1 therapy.
- Women must not be pregnant or lactating. Must have negative urine or blood pregnancy test within 1 week of starting therapy.
- Patients with known HIV are ineligible
- Patients with active Hepatitis B Virus (HBV) or Hepatitis C virus (HCV) are ineligible. Patients with prior history of, or serology suggestive of prior infection with

Hepatitis B Virus (HBV) or Hepatitis C virus (HCV) are also ineligible.
- Patients with active, known or suspected autoimmune disorders including lupus and type I diabetes are ineligible. Patients with history of vitiligo, thyroiditis are eligible.
- Patients with active or history of inflammatory bowel disease are ineligible.
- Patients cannot be on corticosteroid therapy except as physiologic replacement therapy.
- Patients receiving ongoing corticosteroid therapy for autoimmune disorders are ineligible. Occasional steroid inhaler use or nasal spray are allowed. Patients receiving replacement doses of steroids for adrenal insufficiency are eligible.
- Patients must not have any serious underlying medical conditions or take medications that in the investigators opinion may interfere with compliance or interpretation of IRAEs.

3.2 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. Due to melanoma being at a much higher incidence in Caucasians as compared to other races, we expect the vast majority of subjects to be Caucasian.

4. REGISTRATION PROCEDURES

4.1 Central Registration Process

This occurs at the time a subject is consented.

4.1 a Local Winship Procedures

To register a patient, the following documents should be completed by the Study Coordinator and e-mailed to Clinical Research (OCR) ocr@emory.edu and Winship Central Subject Registration (WCSR) winshipcsr@emory.edu within 24 hours or 1 business day:
- Signed patient consent form
- HIPAA authorization form
- Emory Research Management System (ERMS) Enrollment Fax Cover
    - printed from ERMS (*https://erms.emory.edu)* after subject registered

Enrolling a subject requires careful screening and determination of eligibility.

Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator.

Agents may be ordered by a participating site only after the initial IRB approval.

4.2a Local Site

When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. Once the investigator has signed the eligibility checklist, randomization and or enrollment may proceed. Oncore and ERMS must be updated to

reflect eligibility and on treatment status.

5. TREATMENT PLAN

5.1 Agent Administration

Once the investigator has signed the eligibility checklist, randomization may proceed. Patients meeting study entry criteria will be randomized to treatment ARM A or Arm B by the study statistician, Dr. Goyal. Eligible subjects (eligibility confirmed and checklist signed) will be assigned to a treatment arm until 44 subjects (22 in each arm) have been enrolled. The study coordinator will update Oncore and ERMS reflect randomization information.

Following randomization, patients should begin protocol treatment within 5 business days. Issues that would cause treatment delays should be discussed with the Principal Investigator.

Treatment will be administered on an *outpatient* basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Patients will be randomly assigned 1:1 using block randomization with a block of 6 patients. Randomization schema will be kept in the research pharmacy.

Patients with unresectable stage III or stage IV melanoma being treated with FDA approved standard of care immune checkpoint combination therapy with Ipilimumab and Nivolumab are eligible for this trial.

Patients will be randomized 1:1 to either continue therapy with standard of care Ipilimumab and Nivolumab (ARM A) or standard of care Ipilimumab and Nivolumab plus **4 doses of weekly Rituxan** (ARM B).

Patients enrolling on this study following treatment failure on single agent anti-PD-1 will be distributed equally between arms A and B of the study.

Induction Phase:

<u>ARM A: Cycles 1-4</u>
Each cycle is 21 days and includes Ipilimumab (3 mg/kg) on day 1 plus Nivolumab (1 mg/kg) on Day 1.

<u>ARM B. Cycles 1-4</u>
Each cycle is 21 days and includes Ipilimumab (3 mg/kg) on day 1 plus Nivolumab (1 mg/kg) on

Day 1. In addition, patients will receive 4 weekly doses of Rituxan (first dose 375 mg/m2 IV and then 3 weekly doses of 1400 mg Rituxan Hycela subcutaneous, as per current label for Rituxan Hycela).
First dose of Rituxan will be administered 1 week after start of Ipi/Nivolumab therapy. 3rd dose of Rituxan will be administered on day 2 of cycle 2 after infusion of Ipi/Nivo on week4.

Continuation Phase:
All patients will receive Nivolumab 480 mg every 4weeks for up to 13 doses (52 weeks) until disease progression or intolerable adverse events.

All treatments will have a +/-3 business day window for administration.

5.1.1 *IND Agent(s)*

Rituximab (RITUXAN) (for IV use)

Dosage and administration:
Do not administer as an intravenous push or bolus. RITUXAN should only be administered by a healthcare professional with appropriate medical support to manage severe infusion-related reactions that can be fatal if they occur. Pre-medicate before each infusion.

Prior to First Infusion: Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with RITUXAN. Obtain complete blood counts including platelets (CBC) prior to the first dose.

During RITUXAN Therapy: In patients with lymphoid malignancies, during treatment with RITUXAN monotherapy, obtain complete blood counts (CBC) with differential and platelet counts prior to each RITUXAN course. During treatment with RITUXAN and chemotherapy, obtain CBC with differential and platelet counts at weekly to monthly intervals and more frequently in patients who develop cytopenias. In patients with RA, GPA or MPA, obtain CBC with differential and platelet counts at two to four month intervals during RITUXAN therapy. Continue to monitor for cytopenias after final dose and until resolution.
First Infusion: Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Storage and Handling:
RITUXAN vials [100 mg/10 mL single-use vials (NDC 50242-051-21) and 500 mg/50 mL single-use vials (NDC 50242-053-06)] are stable at 2°C–8°C (36°F–46°F). RITUXAN vials should be protected from direct sunlight. Do not freeze or shake.

Rituxan Hycela:

RITUXAN HYCELA is for subcutaneous use only. RITUXAN HYCELA should only be administered by a healthcare professional with appropriate medical support to manage severe reactions that can be fatal if they occur. All patients must first receive at least one full dose of a rituximab product by intravenous infusion without experiencing severe adverse reactions before

starting treatment with RITUXAN HYCELA. If patients are not able to receive one full dose by intravenous infusion, they should continue subsequent cycles with a rituximab product by intravenous infusion and not switch to RITUXAN HYCELA until a full intravenous dose is successfully administered. Refer to the prescribing information for a rituximab product for intravenous infusion for additional information (Rituxan prescribing information, Genentech).

Premedicate approximately 30 minutes before each dose of RITUXAN HYCELA. Dose reductions of RITUXAN HYCELA are not recommended. The recommended dose is RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously at a fixed dose irrespective of patient's body surface area. **The dosing for Rituxan Hycela utilized in this protocol is similar to that FDA approved for follicular lymphoma**.

Recommended Premedication and Prophylactic Medications:
Premedicate with acetaminophen and an antihistamine before each dose of RITUXAN HYCELA.

Administration and Storage
RITUXAN HYCELA is ready to use. To avoid needle clogging, attach the hypodermic injection needle to the syringe immediately prior to administration. RITUXAN HYCELA is compatible with polypropylene and polycarbonate syringe material and stainless steel transfer and injection needles. Use the product immediately. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. RITUXAN HYCELA should be a clear to opalescent and colorless to yellowish liquid. Do not use vial if particulates or discoloration is present.

Administration
- Inject RITUXAN HYCELA into the subcutaneous tissue of the abdomen over approximately 5–7 minutes and never inject into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars. No data are available on performing the injection at other sites of the body.
- Inject 11.7 mL of RITUXAN HYCELA 1,400 mg/23,400 Units vial (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously into the abdomen over approximately 5 minutes.

If administration of RITUXAN HYCELA is interrupted, continue administering at the same site, or at a different site, but restricted to the abdomen.

During treatment with RITUXAN HYCELA, do not administer other medications for subcutaneous use at the same sites as RITUXAN HYCELA.

Storage:
After the solution of RITUXAN HYCELA is withdrawn from the vial, it should be labeled with the peel-off sticker and used immediately. If not used immediately, prepare in controlled and validated aseptic conditions. Once transferred from the vial into the syringe, store the solution of RITUXAN HYCELA in the refrigerator at 2°C–8°C (36°F–46°F) up to 48 hours and

subsequently for 8 hours at room temperature up to 30°C (86°F) in diffuse light.

5.2 Duration of Therapy

The protocol-specific therapy in this study is restricted to only 4 weekly doses of rituximab in patients randomized to the Rituximab-arm.

In the absence of treatment delays due to adverse event(s), treatment may continue for *4 weekly doses of Rituxaimab (or observation)* or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.3 Duration of Follow Up

Patients will be followed for *4 weeks* after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.4 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.2 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

There is no dose modification for Rituxan in this study. Patients who experience Rituxan-related grade 3 or greater toxicity will not receive further Rituxan, and will be followed on the Rituxan-arm on an intent to treat basis.

Management of Ipilimumab and Nivolumab therapy in this protocol will be as per FDA approved standard of care guidelines and per the discretion of the treating investigator.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The

following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List

The Adverse Event and Potential Risks list provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system.

Rituxan Hycela:

The information below describes the potential warnings, precautions and adverse events with Rituxan Hycela. Please refer to the prescribing drug information for details. (Genentech, South San Francisco, CA).

WARNINGS AND PRECAUTIONS

Severe Mucocutaneous Reactions
Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab containing products, including RITUXAN HYCELA. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. Discontinue RITUXAN HYCELA in patients who experience a severe mucocutaneous reaction. The safety of re-administration of a rituximab-containing product, including RITUXAN HYCELA, to patients with severe mucocutaneous reactions has not been determined.

Hepatitis B Virus Reactivation
Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including rituximab-containing products. HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA levels or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur. Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with a rituximab-containing product. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during treatment with a rituximab containing product. Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following RITUXAN HYCELA. HBV reactivation has been reported up to 24 months following completion of therapy containing rituximab. In patients who develop reactivation of HBV while on RITUXAN HYCELA, immediately discontinue treatment and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming RITUXAN HYCELA treatment in patients who develop HBV reactivation.

Resumption of RITUXAN HYCELA treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

Progressive Multifocal Leukoencephalopathy (PML)
JC virus infection resulting in PML and death has been observed in patients receiving rituximab containing products, including RITUXAN HYCELA. Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue RITUXAN HYCELA and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

Hypersensitivity and other Administration Reactions
Systemic Reactions Patients must receive at least one full dose of a rituximab product by intravenous infusion before receiving RITUXAN HYCELA due to the higher risk of hypersensitivity and other acute reactions during the first infusion. Beginning therapy with a rituximab product by intravenous infusion allows management of hypersensitivity and other administration reactions by slowing or stopping the intravenous infusion. Rituximab-containing products, including RITUXAN HYCELA, are associated with hypersensitivity and other administration reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions. This set of reactions which includes syndrome of cytokine release, tumor lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route of administration of a rituximab-containing product. Severe infusion-related reactions with fatal outcome have been reported with the use of intravenous formulations of rituximab products, with an onset ranging within 30 minutes to 2 hours after starting the first intravenous infusion. They were characterized by pulmonary events in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms. Anaphylactic and other hypersensitivity reactions can also occur. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Severe cytokine release syndrome is characterized by severe dyspnea, often associated by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with acute respiratory failure and death. Cytokine release syndrome may occur within 1–2 hours of initiating the infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at a greater risk of poor outcome. Rituximab product administration should be interrupted immediately and aggressive symptomatic treatment initiated. During RITUXAN HYCELA administration, the injection should be interrupted immediately when observing signs of a severe reaction and aggressive symptomatic treatment should be initiated. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (≥ 25,000/mm3). Premedicate patients with an antihistamine and acetaminophen prior to each administration of RITUXAN HYCELA. Premedication with glucocorticoids should also be considered in the event of severe anaphylaxis or per treating physician. Observe patients for at least 15 minutes following RITUXAN HYCELA. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions.

Local Cutaneous Reactions
Local cutaneous reactions, including injection site reactions, have been reported in patients receiving RITUXAN HYCELA. Symptoms included pain, swelling, induration, hemorrhage, erythema, pruritus, and rash. Some local cutaneous reactions occurred more than 24 hours after RITUXAN HYCELA administration. The incidence of local cutaneous reactions following administration of RITUXAN HYCELA was 16%. Reactions were mild or moderate and resolved without any specific treatment. Local cutaneous reactions of any Grade were most common during the first RITUXAN HYCELA cycle (Cycle 2; 5%) with the incidence decreasing with subsequent injections.

Tumor Lysis Syndrome (TLS)
TLS can occur within 12–24 hours after administration of a rituximab-containing product, including RITUXAN HYCELA. A high number of circulating malignant cells (≥ 25,000/mm3) or high tumor burden confers a greater risk of TLS. Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Infections
Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of therapy with rituximab-containing products, including RITUXAN HYCELA. The incidence of infections with RITUXAN HYCELA vs rituximab was 56% and 49% respectively in patients with CLL, and 46% and 41% respectively in patients with FL/DLBCL in combination with chemotherapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia > 11 months after rituximab exposure). New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue RITUXAN HYCELA for serious infections and institute appropriate anti-infective therapy.

Cardiovascular Adverse Reactions
Cardiac adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock may occur with rituximab-containing products, including RITUXAN HYCELA. Discontinue RITUXAN HYCELA for serious or life threatening cardiac arrhythmias. Perform cardiac monitoring during and after all administrations of RITUXAN HYCELA for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.

Renal Toxicity
Severe, including fatal, renal toxicity can occur after administration of rituximab-containing products, including RITUXAN HYCELA. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and RITUXAN HYCELA is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue RITUXAN HYCELA in patients with a rising serum creatinine or oliguria.

Bowel Obstruction and Perforation
Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA, in combination with chemotherapy. In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1–77) days. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

Immunization The safety of immunization with live viral vaccines following rituximab-containing products, including RITUXAN HYCELA, therapy has not been studied and vaccination with live virus vaccines is not recommended before or during treatment.

Embryo-Fetal Toxicity
Based on human data, rituximab-containing products can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in-utero. Advise pregnant women of the risk to a fetus. Females of childbearing potential should use effective contraception while receiving RITUXAN HYCELA and for 12 months following the last dose of rituximab-containing products, including RITUXAN HYCELA.

Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to RITUXAN HYCELA and rituximab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. In the SABRINA study, where previously untreated patients with follicular lymphoma were treated with RITUXAN HYCELA or rituximab in combination with CVP or CHOP, the incidence of treatment-induced/enhanced anti-rituximab antibodies in the RITUXAN HYCELA group was similar to that observed in the rituximab group (2.0% RITUXAN HYCELA vs. 1.5% rituximab). The incidence of treatment-induced/enhanced anti-recombinant human hyaluronidase antibodies was 13% in the RITUXAN HYCELA group compared with 8% in the rituximab group, and the overall proportion of patients found to have anti-recombinant human hyaluronidase antibodies remained generally constant over the follow-up period in both cohorts. All patients who tested positive for anti-recombinant human hyaluronidase antibodies at any point during the study were negative for neutralizing antibodies. In the SAWYER study, where previously untreated patients with CLL were treated with RITUXAN HYCELA or rituximab in combination with FC, the incidence of treatment induced/enhanced anti-rituximab antibodies was 2.4% in the RITUXAN HYCELA group vs. 6.7% in rituximab group. The incidence of treatment-induced/enhanced anti-recombinant human hyaluronidase antibodies was 10.6% in the RITUXAN HYCELA treatment arm. None of the patients who tested positive for anti-recombinant human hyaluronidase antibodies tested positive for neutralizing antibodies. The clinical relevance of the development of anti-rituximab or anti-recombinant human hyaluronidase antibodies after treatment with RITUXAN HYCELA is not known.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of rituximab containing products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hematologic: prolonged pancytopenia, marrow hypoplasia, Grade 3–4 prolonged or late onset neutropenia, hyperviscosity syndrome in Waldenstrom's macroglobulinemia, prolonged hypogammaglobulinemia
- Cardiac: fatal cardiac failure
- Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- Infection: viral infections, including progressive multifocal leukoencephalopathy (PML), increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence of Grade 3 and 4 infections
- Neoplasia: disease progression of Kaposi's sarcoma.
- Skin: severe mucocutaneous reactions.
- Gastrointestinal: bowel obstruction and perforation.
- Pulmonary: fatal bronchiolitis obliterans and fatal interstitial lung disease.

7.2 Adverse Event Characteristics

SAFETY REPORTING OF ADVERSE EVENTS

ASSESSMENT OF SAFETY

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerges during the protocol-specified AE reporting period, including signs or symptoms associated with melanoma those were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the
- Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc.in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the Rituxan IV/Rituxan Hycela (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of Rituxan IV/Rituxan Hycela , and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to Rituxan IV/Rituxan Hycela; and/or the AE abates or resolves upon discontinuation of Rituxan IV/Rituxan Hycela, or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than Rituxan IV/Rituxan Hycela (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to Rituxan IV/Rituxan Hycela administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section I), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:
- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

e. Pregnancy

If a female subject becomes pregnant while receiving Rituxan IV/Rituxan Hycela or within 12 months after the last dose of Rituxan IV/Rituxan Hycela, or if the female partner of a male study subject becomes pregnant while the study subject is receiving Rituxan IV/Rituxan Hycela or within 160 days after the last dose of Rituxan IV/Rituxan Hycela, a report should be completed and expeditiously submitted to Genentech, Inc.

Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

f. AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to Genentech is required. Such an event might 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 (e.g., Regulatory Authorities) may also be warranted.

Though there are no specific adverse event of special interest for Rituxan IV/Rituxan Hycela.

Adverse events of special interest for this study include the following:
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:

  - Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
  - Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study drug, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

g. Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

h. Product complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

i. Post-Study Adverse Events

For studies involving collection of survival data the investigator after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject including pregnancy occurring in the partner of a male study subject who participated in the study that is believed to be related to prior exposure to study drug.

Case Transmission Verification will be performed by both parties during this period to ensure successful transmission of Single case reports.

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

- **For expedited reporting purposes only:**
  - AEs related to the agent should be reported to the FDA/IRB within 24 hours of awareness. Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must be reported to the FDA/IRB and Genentech within 24 hours of awareness of the event. These requirements are briefly outlined in the tables below (Section 7.3.2).

7.3.2 Expedited Reporting Guidelines

Use the protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

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

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

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the Sponsoring IRB/FDA and Genentech within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported to the IRB/FDA and Genentech within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

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

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. ALL **AEs are to be reported through ONCORE.**

EXCHANGE OF SINGLE CASE REPORTS TO GENENTECH

Dr. Kavita Dhodapkar will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product. The completed MedWatch form should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should call via:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Serious Adverse Drug Reactions (SADRs)	*15 calendar days of the awareness date*
Other SAEs	30 calendar days of the awareness date.
Special Situation Reports (Pregnancy) Special Situation Reports (Other)	30 calendar days of the awareness date. 30 calendar days of the awareness date.
Product Complaints	15 calendar days of the awareness date.
AESIs	15 calendar days of the awareness date.

- **Serious Adverse Drug Reactions (SADRs)**

Serious AE reports that are related to the Product or where the causality is assessed as unknown or not provided shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**

Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **Special Situation Reports**
  - **Pregnancy reports**

While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genetech within thirty (30) calendar days of the awareness date. Pregnancies will be followed-up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 160 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

  - **Other Special Situation Reports**, as defined above, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **Product Complaints**

All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

- **AESIs**

AESIs requiring expedited reporting (related or possibly related to Genentech product or where the causality is assessed as unknown or not provided) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date. Others (non-related to Genentech product) shall be sent within thirty (30) calendar days.

Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via Dr. Kavita Dhodapkar emailing Genentech a Quarterly line-listing documenting single case reports sent by Dr. Kavita Dhodapkar to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the

discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Dr. Kavita Dhodapkar to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

- Additional information may be added to a previously submitted report by any of the following methods:
- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at
https://www.fda.gov/media/69876/download

8. REPORTING TO REGULATORY AUTHORITIES, ETHICS COMMITTEES AND INVESTIGATORS

Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations.

Dr. Kavita Dhodapkar will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

Dr. Kavita Dhodapkar, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the EMA through Eudravigilance Clinical Trial Module (EVCTM).

Dr. Kavita Dhodapkar will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

Dr. Kavita Dhodapkar will be responsible for the distribution of safety information to Emory IRB:

Emory IRB
1599 Clifton Rd NE, 5th Floor
Atlanta GA 30322
Tel: 404-712-0720
Fax: 404-727-1358

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

Other REPORTS

Investigator will forward a copy of the Publication to Genentech upon completion of the Study.

8.1 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
All secondary malignancies that occur following treatment with an agent under an IND/IDE must be reported through **ONCORE.** Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

8.2 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy).

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

[Clinical Operations Contact Information] rituxan-gsur@gene.com

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

QUERIES

Queries related to the Study will be answered by the Dr. Kavita Dhodapkar or study staff. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. Dr. Kavita Dhodapkar agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech shall have the final say and control over safety crisis management issues relating to the Product. Dr. Kavita Dhodapkar agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech.

COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT / AUDIT

The Parties shall follow their own procedures for adherence to AE reporting timelines.

Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.
In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.
Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

How to file a complaint?
For all Investigator Initiated Studies (interventional and non-interventional):

- For Non-Interventional Investigator Initiated Studies:
  us-acmo-d@gene.com

9. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

9.1 Investigational Agent(s)

Rituxan Hycela:

Mechanism of Action
Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase human increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan. In the doses administered, hyaluronidase human in RITUXAN HYCELA acts locally.

The effects of hyaluronidase human are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

Hyaluronidase human has been shown to increase the absorption rate of a rituximab product into the systemic circulation when given in the subcutis of Göttingen Minipigs.

Rituxan Hycela is given IV Rituximab as first dose followed by rituxan hycela subcutaneously for subsequent doses for those without severe infusion reactions.

DESCRIPTION

RITUXAN HYCELA is a combination of rituximab and hyaluronidase human. Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM. Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium that may contain the antibiotic gentamicin. Gentamicin is not detectable in the final product. Recombinant human hyaluronidase is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). It is a glycosylated single-chain protein with an approximate molecular weight of 61 kD.

RITUXAN HYCELA (rituximab and hyaluronidase human) Injection is a colorless to yellowish, clear to opalescent solution supplied in sterile, preservative-free, single-dose vials for subcutaneous administration.

RITUXAN HYCELA is supplied as 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL in single-dose vials or 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL in single-dose vials. Each mL of solution contains rituximab (120 mg), hyaluronidase human (2,000 Units), L-histidine (0.53 mg), L-histidine hydrochloride monohydrate (3.47 mg), L-methionine (1.49 mg), polysorbate 80 (0.6 mg), α,α-trehalose dihydrate (79.45 mg), and Water for Injection.

9.1.1 Agent Ordering and Agent Accountability

9.1.1.1 Rituxan be requested by the Principal Investigator (or their authorized designee) at Emory.

9.1.1.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents

9.2 *Commercial Agent(s)*

The following commercial agents used to treat melanoma will be utilized as part of standard of care. Please refer to the manufacturer package insert for details.

Nivolumab, commercial supply.

Preparation for Administration
Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.
• Withdraw the required volume of nivolumab and transfer into an intravenous container.
• Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
• Mix diluted solution by gentle inversion. Do not shake.
• Discard partially used vials or empty vials of nivolumab.

Storage of Infusion
The product does not contain a preservative. After preparation, store the nivolumab infusion either:
• at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
• under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation. Do not freeze.

Administration
Administer the infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not coadminister other drugs through the same intravenous line. Flush the intravenous line at end of infusion.

Dosage forms
Injection: 40 mg/4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) and 240mg/24mL (10mg/mL) solution

Ipilimumab, commercial supply.

Preparation for administration
Do not shake product.
• Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles.
• Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
• Withdraw the required volume of ipilimumab and transfer into an intravenous bag.
• Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.

Storage of infusion
• Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).
• Discard partially used vials or empty vials of ipilimumab.

Administration Instructions
• Do not mix ipilimumab with, or administer as an infusion with, other medicinal products.
• Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.
• Administer diluted solution over 90 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

Dosage forms
Injection: 50 mg/10 mL (5 mg/mL)
Injection: 200 mg/40 mL (5 mg/mL)

10. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

This protocol involves extensive correlative studies to gain fundamental insights into the effects of B cell depletion in the setting of immune checkpoint blockade.

Specimens:
Both blood and tissue specimens will be analyzed.

Time-points:
Pre and Post treatment tissue samples
Pre and Post-treatment peripheral blood mononuclear cells.

Assays:
Mass cytometry.
Gene expression, including single cell sequencing.
B and T cell receptor sequencing
Functional assays
Immunohistochemistry
Change cycle below to show nivo being administered on week 13

10.1 Laboratory Correlative Studies

10.1.1 *Title – Peripheral Blood for immune analysis to be drawn any time prior to the cycle of treatment as long as it's the same day as treatment*

10.1.1.1 Collection of Specimen(s): collect 40-60 ml in green top heparin anticoagulant.
10.1.1.2 Handling of Specimens(s): keep at room temperature.
10.1.1.3 Shipping of Specimen(s): call Dhodapkar lab for pickup.
10.1.1.4 Site(s) Performing Correlative Study; Dhodapkar lab

10.1.2 *Title – Tissue for immune analysis*
10.1.2.1 Collection of Specimen(s): Fresh tissue from operating room
10.1.2.2 Handling of Specimens(s): keep at room temperature.
10.1.2.3 Shipping of Specimen(s): call Dhodapkar lab for pickup.
10.1.2.4 Site(s) Performing Correlative Study: Dhodapkar lab.

11. STUDY CALENDAR

Schedules shown in the Study Calendar below are provided as an example and should be modified as appropriate.

Baseline evaluations are to be conducted within 3 weeks prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

All protocol visits have a plus or minus 3 business day window.

Rituxan should be given after ipi/nivo infusion for subjects on Arm B. The timing of Rituxan is 1-2 days (preferably 1 day) following ipi-nivo infusion.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	WK 12	Wk 13	WK 17	WK 21	Off Study
IPI 3mg/kg + Nivo 1mg/kg		X			X			X			X					
Nivo 480mg IV[a]													X	X	X	
Rituxan IV (loading dose)			X													
Rituxan SQ				X	X	X										
Informed consent	X															
Demographics	X															
Medical history	X															
Con Medications	X	X	X	X	X			X			X		X	X	X	X
Physical exam	X	X			X			X			X		X	X	X	X
Vital signs	X	X	X	X	X			X			X		X	X	X	X
Height	X															
Weight	X	X	X	X	X			X			X		X	X	X	X
Performance status	X	X			X			X			X		X			X
CBC w/diff, plts	X	X	X	X	X			X			X		X	X	X	X
Serum chemistry with LDH	X	X	X	X	X			X			X		X	X	X	X
EKG (12-lead)	X															
Adverse Event	X	X	X	X	X			X			X		X	X	X	X
Radiologic Evaluation[b]	X											X				
B-HCG	X															
Hepatitis B (HepB surface antigen and HepB core antibody), Hep C and HIV serology	X															
TSH, Free T, ACTH, cortisol	X				X			X			X		X	X	X	X
Blood correlative	X		X		X						X		X			X
Fresh Tissue Biopsy[c]	X				X											

[a] given every 4 weeks starting at Week 13 for up to 13 doses.
[b] CT scans n/c/a/p with contrast every 12 weeks for the first two years, then every 6 months for five years. MRI brain with contrast should be done at baseline, then every 6 months for patients with no history of CNS mets as per standard of care; every 3 months for those with a history of CNS metastases for two years, then every 6 months. CT head can be used for patients with a contraindication to MRI.
[C] Tissue biopsy before week 4 is optional but encouraged whenever possible.

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect

For the purposes of this study, patients should be re-evaluated for response every 12 weeks. Please see study calendar for details on scan requirements.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with ipilimumab/nivolumab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a

lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of

20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-	No	PR	

	PD/not evaluated			
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death or last follow-up, whichever occurs first.

12.1.7 Response Review

Response will be measured by RECIST criteria.

13. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

13.1.1 Method

Cumulative protocol- and patient-specific data will be submitted electronically into ONCORE monthly.

13.1.2 Responsibility for Data Submission

Study staff are responsible for submitting data and/or data forms in ONCORE per Winship SOP 4.2 Data Completion Metrics. Data completion will be reviewed monthly. In situations where there are significant delays of data completion, the PI may temporarily suspend enrollment. Data entry is to be completed within the designated timeframe, not to exceed 30 days of the subject visit.

Queries will be resolved by the research staff within the time frame specified by the protocol, not to exceed 2 weeks.

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

Endpoints:

Primary:

- Primary endpoint is the rate of CTC (v5.0) grade 3 or greater immune-related adverse events at 6 months of follow up.

Secondary:

- Rate of CTC (v5.0) toxicity related to Rituxan.
- Objective tumor response as assessed by RECIST v1.1 and irRECIST at 12 weeks and every 12 weeks thereafter.
- Rates of overall and progression-free survival at 1 year following initiation of therapy.

14.2 Sample Size/Accrual Rate

This is an open-label, 2-arm phase II clinical trial to study the differential effect in the risk of IRAEs between treatment and control groups. A sample size of 22 patients per arm (44 total) will provide us approximately 80% power to detect a 40% difference in the rates of developing ≥grade 3 IRAE within 6 months follow up between the control and the treatment arm (estimated to be 60% in the control arm, Callahan et al; J Clin Oncol. 2017 Dec 1;35(34):3815-3822). The sample size calculation is based on Fisher's exact test at a one sided significance level of 0.05 under the following assumptions: 1). Patients will be randomized in 1:1 ratio of the treatment to control arm. 2). Approximately 60% patients in the placebo arm will develop ≥ grade 3 IRAE

within 6 months based on our pilot study. 3). The treatment will reduce the rate of ≥ grade 3 IRAE to 20% in the treatment arm. In a recent study, the rate of objective response following combination checkpoint blockade was 42% (Callahan et al; J Clin Oncol. 2017 Dec 1;35(34):3815-3822). In order to monitor potentially adverse impact of Rituxan on checkpoint blockade, we will utilize early stopping rules based on an adaptive design wherein trial will be stopped if we have strong evidence of rates of objective response of <30%. The trial will be stopped early in the unlikely event that less than 2 patients among the first 12 patients treated by Rituxan respond to therapy. If the rate of objective response is > 30%, the probability that at least two out of first twelve patients will achieve an objective response of at least a PR for the first 12 patients is approximately 92%. Hazard ratios and corresponding two-sided 95% confidence intervals will be estimated using Cox-proportional hazards model, with the treatment group as a single covariate. Progression-free and overall survival curves, median with 95% confidence intervals, and progression-free survival rates at 6 months will be estimated with the use of Kaplan-Meier method. Biostatistics support for the study will be provided by biostatistics core resource of Winship Cancer Center.

Newly diagnosed patients as well as patients that have previously received anti-PD-1 therapy in adjuvant setting will be randomized as separate groups equally between the two arms. This will allow us to normalize the ORR between the two groups. ORR will be calculated for every 10 patients enrolled. The trial will be stopped early if there is a difference in ORR of greater than 30% between the two arms.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	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.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.