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EAQ172

Optimizing Immunosuppression for Steroid-Refractory Anti-PD-1/PD-L1 Pneumonitis

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ACTIVATION DATE
June 25, 2020

Addendum #1
Addendum #2
Addendum #3
Addendum #4
Addendum #5

Agents	NSC#	Supply
Infliximab	728729	Commercial
Intravenous immunoglobulin (IVIG)	621996	Commercial

Study Exempt from IND Requirements

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Rev. Add2

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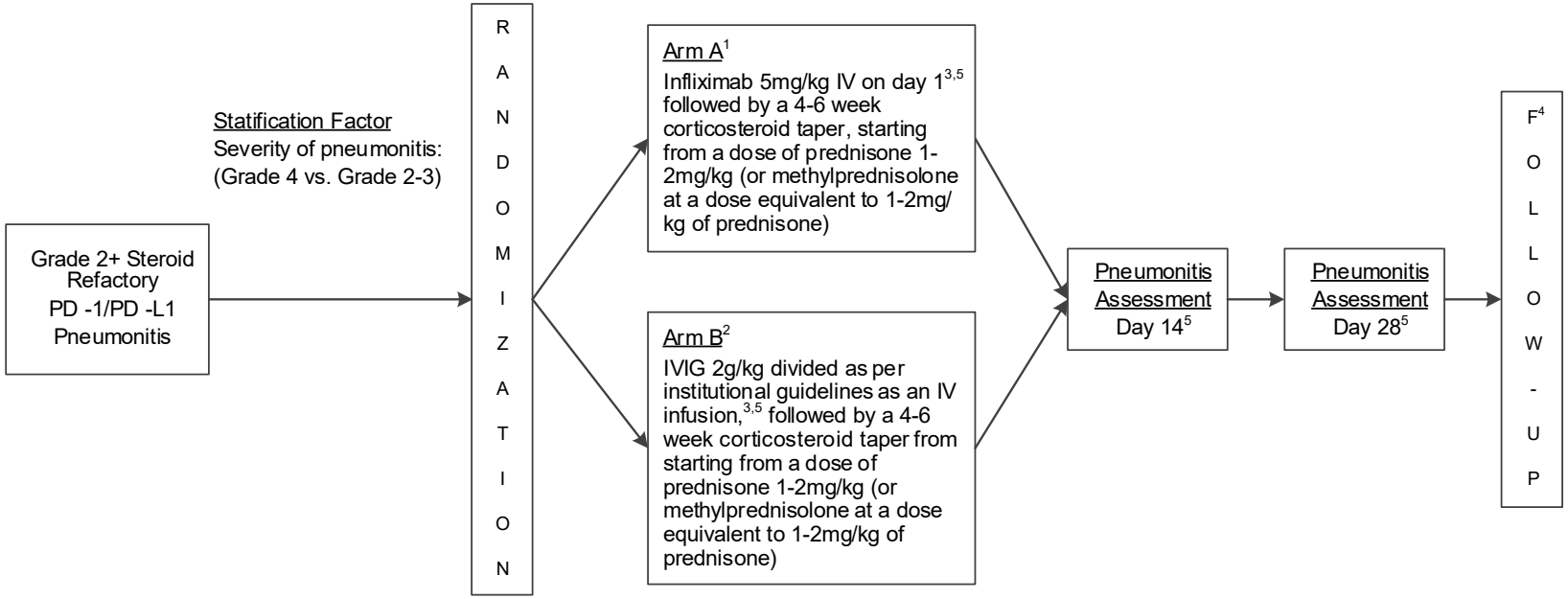
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

Rev. Add2

Schema



Accrual Goal = 36

1. A second dose of infliximab may be delivered 14-days after the first dose as per the treating investigator. If a second dose of infliximab is given, a prednisone taper will be restarted at Day 14.
2. IVIG may be delivered as either Privigen, Gammagard or Gamunex-C as per site standard of care.
3. Either as an inpatient or outpatient.
4. All patients will be followed up on both Days 42 and 56.
5. Required sample submission of 7 green top heparin tubes at Days 1, 14, and 28. Please see Section 7.2 for details.

1. Introduction

1.1 Background

1.1.1 Immune-related Adverse Events

Immune checkpoint inhibitor (ICI) therapy against programmed cell death[1] (PD-1) and its ligand PD-L1 can lead to immune related adverse effects (irAEs).[1] These toxicities have autoimmune etiology and require careful monitoring and specific management strategies. These include immune-related toxicities affecting nearly every organ system in the body, including dermatologic (rash and pruritus), gastrointestinal (diarrhea and colitis, hepatitis), endocrinopathies (hypophysitis and hypothyroidism) and pulmonary (pneumonitis) irAEs. Data regarding the incidence of irAEs comes mainly from large published clinical trials.[2-8] The most common irAE associated with ICIs includes skin rash and/or pruritus. The latter has been reported in 40% of patients treated with nivolumab or pembrolizumab. PD-1 inhibitors have a lower incidence of irAEs compared with other ICIs that block other checkpoint molecules such as cytotoxic T-lymphocyte-4 (CTLA-4), including such as ipilimumab or tremelimumab. Immune-related toxicities from anti-PD-1/PD-L1 ICIs are predominantly grade 1 or 2 in severity, with the incidence of grade 3+ toxicity of < 20% across tumor types.[1] Knowledge of the timing of onset of a suspected irAE may be helpful. For example, dermatological irAEs usually develop during the first few weeks on treatment, whereas diarrhea and colitis tend to occur between weeks 5 and 10, liver toxicity from week 7 to 14, hypophysitis after the 6th week while pneumonitis may occur at anytime during the course of therapy.[9]

Immune-related toxicities improve or resolve if treated promptly and appropriately with immunomodulatory medication. However, high-grade irAEs can result in patient death (occurring in < 2% of cases) if unrecognized, or not appropriately managed. Specific management algorithms have been developed to guide the treatment of irAEs.[1] Treatment consists of immunosuppression, utilizing systemic corticosteroids in most cases. In patients who require a prolonged course of corticosteroids (20mg of prednisone or equivalent daily for more than 4 weeks), appropriate antimicrobial prophylaxis should be considered as per published irAE guidelines.[1,10,11] A multi-disciplinary approach may be important to clarify the diagnosis and determine appropriate management. Other immunomodulatory medications used in specific irAEs include TNF-inhibition with Infliximab (CTLA-4 colitis), mycophenolate mofetil (MMF, hepatitis), intravenous Immunoglobulin (IVIG) or plasmapheresis (neurologic irAEs).[1]

1.1.2 Anti-PD/-PD-L1 Pneumonitis

Pneumonitis is a potentially fatal irAE resulting from therapy with anti-PD-1/PD-L1 affecting the lungs.[1] It occurs in 2-5% of patients treated with PD-1/PD-L1 monotherapy, and up to 10% of patients who receive combinations such as PD-1/CTLA-4. Current recommendations for

the management of anti-PD-1/PD-L1 pneumonitis are based on clinical trial experience, published guidelines and algorithms.

Based on National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) grading of pneumonitis, anti PD-1/ PDL-1 therapy should be withheld (grade 1) and corticosteroids administered (grade 2+).[1-3] In grade 2+ cases, oral steroid treatment includes prednisone 1 to 2-mg/kg daily or methylprednisolone 0.5-10mg/kg daily. Corticosteroid taper should be initiated when the adverse reaction improves to ≤ Grade 1 and should be conducted over 4-6 weeks. For pneumonitis that completely resolves or is grade 2 or less at diagnosis, treatment can be restarted when pneumonitis returns to ≤ Grade 1 and the corticosteroid dose has been reduced to < 10 mg prednisone or equivalent per day. In moderate to severe (grade 2-3+) cases, a routine infectious evaluation is recommended to exclude infectious etiologies before starting immunosuppression. In severe cases (grade 3+), patients should be hospitalized and treatment should consist of high-doses of corticosteroids (i.e. methylprednisolone 1-4mg/kg/day).[1-3]

Patients often improve with corticosteroids, however a significant group (~20%) become steroid-refractory.[1] In published guidelines anti-PD-1/PD-L1, steroid-refractory pneumonitis would have been defined as patients who do not sustain a clinical or functional improvement in pneumonitis, or worsening hypoxemia and clinical or radiographic appearances within 48-72 hours of high-dose corticosteroids.[1-3] Patients with steroid-refractory pneumonitis almost universally die from pneumonitis.[1] Published guidelines suggest that patients with steroid-refractory pneumonitis should be treated with either infliximab, MMF, IVIG or cyclophosphamide after failure of corticosteroids.[2,3] However, there are no published data that demonstrate a benefit in pneumonitis with these agents. Likewise, there are no published data which may establish which agent may lead to the greatest benefit in pneumonitis.

1.1.3 Infliximab or Intravenous Immunoglobulin for Pneumonitis

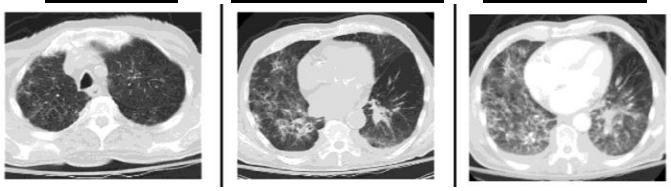


Figure 1: **Radiographic Severity of PD-1/PD-L1 Pneumonitis:** % lung parenchymal involvement describes radiographic pneumonitis severity. Mild= 25% parenchyma involved, Moderate= 25-50%, Severe= >50% involvement.

Infliximab is currently recommended based on its' use in CTLA-4-mediated colitis.[1] However, 3/5 patients with infliximab-treated pneumonitis died from infections related to prolonged immunosuppression, and another from pneumonitis itself, in a published series.[12,13] Intravenous immunoglobulin (IVIG) has benefitted some patients with steroid refractory pneumonitis.[14] In addition, it is a successful treatment for conditions similar to pneumonitis, such as paraneoplastic immune conditions,[15] idiopathic

pulmonary fibrosis,[16] and autoantibody mediated conditions such as idiopathic thrombocytopenia purpura (ITP).[17] Furthermore, IVIG has been used to successfully to treat PD-1induced neurologic irAEs,[18,19] and has minimal infection risk.

When treating pneumonitis, quantitative measures that will help to objectively track clinical responses to immunosuppression are needed. Patient lung function testing may be such a measure, but has not been assessed in previous studies. Radiographically, the appearances of pneumonitis stratifies into 5 subtypes (e.g. cryptogenic-organizing pneumonia-like, ground glass opacities, hypersensitivity type, interstitial type and pneumonitis not otherwise specified).[12,20] The percentage of lung parenchyma involved with pneumonitis at the time of the diagnosis has also been found to be associated with pneumonitis outcomes.[12] In patients with other interstitial lung diseases that are similar to pneumonitis, high attenuation areas on chest CT scans (HAA:-600 - 250HU) are radiographic markers of lung function and inflammation.[21] These quantitative imaging features may correlate with clinical response to immunosuppression in pneumonitis.

The populations of immune cells present in core lung biopsies, obtained from 2 patients with PD-1 pneumonitis demonstrated lymphocytic and macrophage infiltrates, respectively (Fig. 2). Additionally, Johns Hopkins investigators identified that an elevated Th17/T-reg ratio in bronchoalveolar lavage fluid (BAL), is associated with early acute respiratory distress syndrome (ARDS), a similar process to PD-1/PD-L1 pneumonitis.[4]

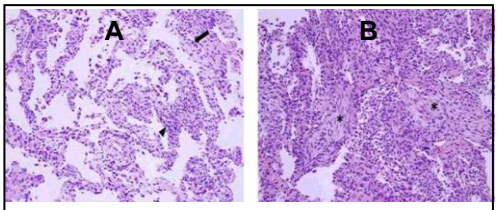


Figure 2: Pathologic Features of Pneumonitis: (A) Lymphocytic infiltrate (B) Macrophages, in pneumonitis lung tissue

The mechanisms that underlie the development of PD-1/PD-L1 pneumonitis are unknown. While autoantibody responses in irAEs have not yet been specifically linked to tumor immunity, autoantibody formation has been identified as a mechanism implicated in CTLA4-mediated hypophysitis[23] and PD-1- thyroiditis.[24] We now have newer tools that allow us to link autoantibody to T-cell responses, through detection of antigen specific T-cell clones by TCR sequencing, in both peripheral blood and tissue.[25,26,27] In support of an autoantibody-mediated mechanism, cytokines (IL-17, IFN-γ, IL-4) are known to support humoral responses via Fc region switching and increased immunoglobulin production,[28,29] and baseline IL17 levels were elevated in melanoma patients who developed CTLA4-colitis, in a neoadjuvant trial.[30]

1.1.4 Preliminary Data and Previous Experience

Thirty-six NSCLC patients at Johns Hopkins University (JHU) developed PD-1/PD-L1 pneumonitis from 2013-2017, 6 of whom were steroid-refractory. Of these patients, we observed two with

radiographic improvement after infliximab, and one with improved oxygenation after IVIG.[5] We evaluated BAL in 5 pneumonitis patients (Fig 3) and baseline sera in 3 pneumonitis patients (Table 1). In BAL, we identified lymphocyte, macrophage, and neutrophil populations (unpublished), and elevations in IL-17, IFN-γ and VEG-F in patient sera vs. non-irAE controls.

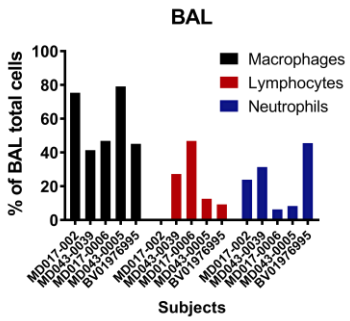


Figure 3: BAL obtained from patients with suspected PD-1 pneumonitis were centrifuged, cytospum and stained for cell differentials (n=5)

Change in cytokine (pg/L)	Pneumonitis (n=3)	Control (n=6)
VEG-F	45.5 (3.4, 55.9)	3.1 (-23.3, 10.3)
IL-6	-0.1 (-0.9, 12.0)	0.7 (0.1, 2.4)
IL-17A	1.2 (0.8, 9.8)	0.8 (0.0, 2.9)
IFN-ɣ	43.7 (7.5, 126.4)	1.7 (-0.6, 3.2)

Table 1: Cytokine profiles in sera from patients with pneumonitis, and controls: Baseline multi-parameter cytokine profiles in 3 pneumonitis patients and 6 control samples of NSCLC patients who did not develop irAEs

Autoantibody discovery platforms have been previously utilized at JHU to describe an autoantibody-mediated link to the development of scleroderma in patients with POL3RA mutant cancers.[6] In these cases, antibodies were identified using a novel immunoprecipitation (IP) assay followed by mass spectroscopy (MS) sequencing, using patient sera pre/post event (present post, absent pre),[7] based on molecular weights in the initial IP step and rigorous candidate autoantigen validation.[7-12] The linkage between antibody and T-cell responses, can then be evaluated through the novel sensitive and specific Functional Expansion of Specific T-cells (FEST) assays, developed at JHU. These assays experimentally and bioinformatically evaluate clonal expansion via next generation T cell receptor (TCR) sequencing of T cells, cultured with peptides representing candidate antigens. This approach has been used in NSCLC patients with acquired resistance to anti-PD-1, to detect peripheral T cell reactivity to mutation-associated neoantigens (MANAs) in resistant tumors, compared to pre-treatment specimens (MANAFEST).[13] MANAFEST

has also been used to detect and monitor antigen-specific immune responses. In patients with colon cancer who responded to pembrolizumab.[14] MANAFEST can be adapted to evaluate CD4+ reactivity to autoantigens (AUTOFEST), together with MANAFEST evaluated CD-8 responses mutant peptides from patients' tumors, identified through genomic sequencing of genes encoding identified autoantigens from tumor DNA.

1.1.5 Pneumonitis from Other Anti-Cancer Agents

Pneumonitis is a rare but potentially lethal complication that may occur as a result of treatment with a number of chemotherapeutic agents.[40] Patients who develop drug induced pneumonitis (or drug-induced interstitial lung disease (DILD)) present clinically with acute or sub-acute breathlessness that is usually accompanied by new pulmonary infiltrates on chest imaging. DILD should be considered in all patients treated with a new anti-cancer therapy who present with acute or sub-acute dyspnea, dry cough, or fever. The diagnosis of DILD depends on a temporal association between the causative agent and the development of respiratory symptoms and signs. Bleomycin,[41] methotrexate,[42] cyclophosphamide,[43] mTOR inhibitors such as everolimus,[44] as well as epidermal growth factor receptor tyrosine kinase inhibitors afatinib,[15] gefitinib[16] and erlotinib[17] are the agents most frequently associated with pneumonitis, with an incidence of 1-10%. Management of DILD in these cases involves withholding of the offending agent, and investigations to exclude competing differential diagnoses, including progressive malignancy in the lung, lung infection or pulmonary embolism. Treatment involves use of high-dose steroids (prednisone 60–100 mg/day) given promptly.[45]

Bleomycin is the drug most commonly studied as a cause of DILD.[41] Larger studies have reported rates of 8-10%. Symptoms may develop earlier than 4 weeks and later than 10 weeks following chemotherapy. Potential risk factors for bleomycin pneumonitis include: age, underlying lung disease, smoking history, cumulative bleomycin dose, renal insufficiency, and prior radiation exposure. Typical radiologic changes include bibasilar infiltrates on chest radiographs and diffuse interstitial and ground glass opacities (GGO) HRCT. Bleomycin induced pneumonitis is thought to be related to the absence of the bleomycin-inactivating enzyme (bleomycin hydrolase) in the lung parenchyma or an excess of free oxygen radicals.[41,46]

Other agents known to cause DILD include: cyclophosphamide, which causes early-onset interstitial lung disease with a low incidence of <1%,[47] and everolimus-induced pneumonitis, which like PD-1/PD-L1 pneumonitis has variable radiographic appearances, but has an incidence of up to 10%.

1.1.6 Clinical Assessment of Pneumonitis

DILD may occur as an adverse event of chemotherapy, targeted therapy, as well as stem cell transplantation.[15,16] The clinical presentation and evaluation of these pneumonitides has provided a framework from which we may begin to approach the characterization of pneumonitis associated with anti–PD-1/PD-L1[17] therapy. A

comprehensive patient history is crucial to establish symptom onset and associated manifestations, which will help to exclude alternative diagnoses such as tumor progression, infection or pulmonary embolism. Symptoms of pneumonitis include non-productive cough, dyspnea, and a low-grade fever. Additionally, patients with PD-1/PD-L1 pneumonitis as with other agents, may be asymptomatic.[1] Usually symptoms may become more pronounced as the pneumonitis worsens, and patients may develop tachypnea, dyspnea at rest, and hypoxia. Physical examination often reveals fine respiratory crackles, rhonchi and/or pleural rubs. Based on data from DILD and interstitial lung disease (ILD), the degree of dyspnea has been linked to disease severity and prognosis.[15]

1.1.7 Radiographic Assessment of Pneumonitis

Radiographic assessment of pneumonitis is essential to diagnose and track the progress of PD-1/ PDL-1-associated pneumonitis during management. Chest imaging characterizes the appearance or pattern of pneumonitis, the severity of pneumonitis (percentage of lung parenchyma involved), the distribution of pneumonitis, and any other associated features.[1] It is also useful to rule out competing diagnosis including progression of cancer, lung infection, pleural effusion or pulmonary embolism. In patients with known ILD and other interstitial lung processes these patients are evaluated radiologically with high resolution non contrast CT (HRCT) imaging of the chest.[18] While chest radiographs may be easier to obtain, these tests may miss interstitial lung processes in a subset of cases. Radiologic features of PD-1/PD-L1 pneumonitis can be classified into five subtypes: (i) consolidative opacities predominantly in a peripheral distribution resembling cryptogenic organizing pneumonia (COP-like) (ii) ground glass opacities (GGO), (iii) interstitial infiltrates; (iv) hypersensitivity pneumonitis, and (v) ground glass opacities with interlobular septal thickening in basilar and peripheral distribution, mimicking nonspecific interstitial pneumonia (NSIP).[1,19] Overall, the most common radiographic changes are GGOs and focal consolidation, predominantly in the lower lobes. Interestingly, HRCT findings have been suggested to reflect histological patterns of pneumonitis, thus predicting the prognosis and determining the most appropriate intervention.[19]

1.1.8 Functional Assessment of Pneumonitis

Assessment of lung function with pulmonary function tests (PFTs) demonstrate a restrictive ventilatory deficit and impaired gas exchange in patients with known DILD or other forms of ILD.[20] In patients who develop chemotherapy-induced pneumonitis (e.g. bleomycin) or those with ILD, diagnostic guidelines recommend PFT to assess respiratory limitations, severity of pneumonitis and monitor disease progression.[20,21] PFTs provide objective, quantitative functional assessments of lung volume, spirometry (e.g., FVC and FEV1), and gas transfer at the alveolar level (DLCO). Specifically, FVC is a widely used measure of disease severity and a common endpoint in clinical trials in patients with idiopathic pulmonary fibrosis (IPF).[22] Longitudinal change in serial FVCs is accepted as a reflection

of disease progression in patients with IPF.[23] Several studies have also identified change in percent-predicted FVC as an independent predictor of mortality in patients with IPF. For example, Du Bois et all studied the reliability and validity of FVC in 1,156 randomized patients in two clinical trials of IFN-G1b, and found that FVC was a robust measure of clinical status in patients with IPF and the change in percent- predicted FVC was found to be highly predictive of mortality.[24] Specifically, a decline in percent-predicted FVC >10% at 24 weeks was associated with a nearly fivefold increase in the risk of mortality. FVC has also been validated by its relationship to other key measures of disease severity including: disease extent on imaging, DLCO, 6MWT, oxygen saturation, symptoms and measures of quality of life (QOL). Both absolute reduction of 10% and relative reduction from 70% to 67% have been shown to confer a worse prognosis.[55] DLCO has also been used a prognostic parameter in patients with chemotherapy-induced pneumonitis, and strong correlated with changes in FVC.[26]

PFTs are completed as a standard assessment for patients with suspected bleomycin induced pneumonitis. Zhao et al suggested that PFTs were a more sensitive measurement that could be used to diagnose bleomycin-induced pneumonitis, compared with respiratory symptoms or chest radiographs. Similarly, a 5-year cohort study of bleomycin-induced pneumonitis was performed in patients with testicular cancer, where PFTs were obtained in 565 patients before and after treatment with bleomycin. A significant proportion of patients discontinued therapy based on bleomycin induced pneumonitis (10%). The DLCO threshold used to determine discontinuation of treatment, was a 25% reduction in DLCO compared with pretreatment values.

Even though PFTs can provide useful clinical and prognostic information, the feasibility to perform these studies is challenging in critically ill patients who have limited respiratory effort due to sedation, mechanical ventilation or prolonged critical care stay.[36] Other limitations of using FVC include: 1) difficulty handling missing data since a proportion of patients will not be able to perform serial FVC measurements because of cough, worsening respiratory failure or inter-current infection. 2), a proportion of patients can have stable FVC prior to death and 3) measurement variation can be as much as 5-9% between readings.

1.1.9 Functional Assessment of Pneumonitis: PaO2/FiO2 Ratio on Arterial Blood Gas Assessment

The ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2/FiO2 ratio) is a measure that represents patient oxygenation. This ratio is calculated from an arterial blood gas assessment obtained either from an arterial puncture or an arterial catheter to obtain a PaO2 result, and by the fraction of inspired oxygen (FIO2) the patient is receiving. For example, the FiO2 is 0.21 if a patient is breathing room air, where the oxygen concentration is 21%. The PaO2/FiO2 ratio is calculated by dividing the PaO2 by the FiO2. This is a practical, bedside test that can represent a patient's arterial oxygenation.[27,28] Higher ratios (from high PaO2 or lower FiO2)

represent easier oxygenation, whereas lower ratios represent difficulty in achieving arterial oxygenation. This measure has been widely used to monitor and predict mortality in patients with acute respiratory distress syndrome (ARDS), a clinical condition characterized by acute pulmonary inflammation that may be caused by a wide variety of clinical conditions, and is similar in clinical and radiologic appearance to PD-1/PD-L1 pneumonitis. The Berlin Definition for ARDS was a consensus definition developed in 2012 that focused on the feasibility, validity, reliability and reproducibility of defining and monitoring ARDS, and also represented the mortality risk from ARDS29.

The initial draft definition proposed 3 mutually exclusive categories of ARDS based on the degree of patient hypoxemia: mild (PaO2/FIO2= 201-300 mm Hg), moderate (PaO2/FIO2= 101-200 mm Hg), and severe (PaO2/FIO2 ≤ 100 mm Hg).[29] The Berlin Definition was empirically evaluated using patient-level meta-analysis of 4188 patients with ARDS from 4 multicenter clinical datasets, as well as 269 patients with ARDS from 3 single-center datasets. Using this definition, the stages of mild, moderate, and severe ARDS were associated with increased mortality (27%; 95% CI, 24%-30%; 32%; 95% CI, 29%-34%; and 45%; 95% CI, 42%-48%, respectively; p=0.001).

Other potential measures of patient oxygenation have been proposed in ARDS and related literature. The measure of PaO2/FiO2 has been found to correlate with simple ambulatory oxygen saturation values (pulse oximetry) in studies with patients who have idiopathic pulmonary fibrosis (IPF).[30] However, pulse oximetry values may not accurately measure patient oxygenation, as patient and procedural factors such as positioning, recent exertion, cold extremities, skin pigmentation, and receipt of vasopressor medications may alter this measurement.[31] Similarly, the ratio of pulse oximetry to FiO2 (SpO2/FiO2) has been explored as a measure of patient oxygenation. However, the relationship between SpO2 and PaO2 has been found to be non-linear, therefore this may not represent an accurate measure of patient oxygenation.[31]

The PaO2/FiO2 measure has also been used as a primary outcome variable to assess benefit in acute lung injury in patients who require mechanical ventilation.[32] To maximize reproducibility and interpretation of PaO2/FiO2 ratio in clinical trials, methods of oxygen delivery be standardized to minimize room air contamination (or entrainment) of oxygen. In addition, in patients who are being treated with mechanical ventilation, it is recommended to use standardized ventilator settings and a pulse oximetry goal of 90%.[33]

Rev. Add4

1.1.10 Laboratory Tests as an Assessment of Pneumonitis

Although there are no specific laboratory tests that are pathognomonic for the diagnosis of pneumonitis, patients being assessed for pneumonitis according to standard algorithms,[34] undergo routine complete blood cell count with differential, platelet count, erythrocyte sedimentation rate (ESR); and determination of serum

electrolyte levels, including calcium, serum urea nitrogen, and creatinine, liver function tests.

1.1.11 Patient-Reported Outcome Assessment of Pneumonitis

The utility of health-related quality of life (HRQOL) assessments has been studied in patients with ILD such as IPF.[50.51] This is of importance since a patient's functional status and life expectancy is affected by interstitial processes such as pneumonitis. Several prospective clinical trials in the field of IPF have thus incorporated HR-QOL measures as secondary endpoints in these studies. Several instruments have been designed to capture the effect of dyspnea on patients with lung disease. Among patients with ILD, HRQOL measures capture patient-reported dyspnea on physical inactivity, de-conditioning, loss of independence, impaired emotional well-being and overall QOL. Questionnaires that assess dyspnea have not previously been used in clinical practice or as a research endpoint in studies for drug-induced pneumonitis.[49,52,53]

A systemic review examining measures of breathlessness in patients with lung cancer, included 31 studies and examined 18 outcome measures.[54] FACT-L was the most commonly used assessment.[55] This consists of a 36 item, self-assessment tool, developed to measure a lung cancer patient's QOL over the last 7-day period, using a 0 to 4 Likert scale. The four sub-sections assess: emotional, functional, physical, and social /family well-being. The fifth sub scale queries the patient's additional concerns.

Measuring dyspnea intensity associated provides insights into dyspnea-limited exercise capacity, and it's a fundamental tool used to evaluate treatment outcomes for various pulmonary conditions in several clinical trials. The most widely used instrument to measure perceived exertion or exercise intensity is the Borg scale which was initially described in 1982.[56] Since then, several modifications have been made. The American Thoracic Society (ATS)/American College of Chest Physicians (ACCP)[57] recommends the use of modified Borg Scale (MBS) for quantifying dyspnea in several pulmonary conditions including ILD, COPD and asthma. Research on this scale has focused on how it relates to a variety of physiological measures (e.g. heart rate, ventilatory drive, blood lactate concentration, creatine) and psychologic perception of wellbeing.[57] This is 0 to 10 rated scale which has been used in several clinical trials. Moreover, the MBS has been shown to be feasible, reliable and valid in patients with dyspnea.

1.1.12 Rationale for the Proposed Study

Immune checkpoint blockade is now standard therapy for patients with multiple malignancies However, in 5% of patients treated with anti-PD-1/PD-L1 monotherapy, and up to 10% with anti-PD-1/PD-L1-based combinations, pneumonitis will occur.[1-3] In 20% of these cases, pneumonitis that develops is refractory to corticosteroids, and can result in death from pneumonitis itself, or infections in the context of prolonged/profound immunosuppression.[2,4] While the incidence may seem low, the absolute numbers of patients with solid tumors treated with anti-PD-1/PD-L1 alone or in combination, either as standard-of-

care or on clinical trials, is high. There is thus an unmet clinical need to identify efficacious immunosuppression for these patients, and improve our understanding of the underlying mechanisms of this toxicity. So far, no standard immunosuppressive agent beyond steroids has proved efficacious for anti-PD-1/PD-L1 pneumonitis, and biospecimens from these patients are not routinely obtained. We aim to identify an efficacious immunosuppressive agent for steroid-refractory anti-PD-1/PD-L1 pneumonitis, by completing a randomized study of infliximab vs. IVIG, two promising therapies for this phenomenon. We will collect pre and post-immunosuppression clinical, radiologic, functional parameters and biospecimens with the goal of characterizing the mechanisms of this phenomenon.

2. Objectives

2.1 Primary Objective

2.1.1 To assess pneumonitis response to additional immunosuppression (infliximab or IVIG) in patients with steroid-refractory pneumonitis at 28-days.

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2.2 Secondary Objectives

2.2.1 To assess functional parameters of steroid-refractory pneumonitis on Days 1, 14, and 28 of receipt of additional immunosuppression (infliximab or IVIG).

2.2.2 To assess radiologic parameters of steroid-refractory pneumonitis on Days 1, 14, and 28 of receipt of additional immunosuppression (infliximab or IVIG).

2.2.3 To assess patient-reported outcomes of steroid-refractory pneumonitis on Days 1, 14, and 28 of receipt of additional immunosuppression (infliximab or IVIG).

2.2.4 To assess death in the 28-day period after additional immunosuppression.

2.2.5 To assess the rate of infections after additional immunosuppression.

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2.3 Exploratory Objectives

2.3.1 To examine serial blood samples in patients who develop steroid-refractory pneumonitis.

2.3.2 To evaluate associations between pneumonitis and autoantibodies, T-cell expansion, and baseline cytokines in the blood.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The randomization of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

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3.1 Eligibility Criteria

_____ 3.1.1 Patient must be ≥ 18 years of age.

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_____ 3.1.2 Patient must be English-speaking and have the ability to understand and the willingness to sign a written informed consent document. Patients with impaired decision-making capacity (IDMC) who have a legally authorized representative (LAR) or caregiver and/or family member available will also be considered eligible.

English Speaking? _____ (Yes or No)

Date of Written Informed Consent: _____

_____ 3.1.3 Patient must be willing and able to undergo arterial blood gas assessment as per the treating investigator. Patient must not have contraindication for arterial blood gas assessment.

_____ 3.1.4 Women must not be pregnant or breast-feeding due to the potential risk to the fetus with infliximab or IVIG.

All females of childbearing potential must have a blood test or urine test within 14 days prior to randomization to rule out pregnancy.

A female of childbearing potential is defined as any woman, regardless of sexual orientation or whether they have undergone tubal

ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of child bearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.5 Women of childbearing potential and sexually active males must not conceive or father children by using accepted and effective method(s) of contraception or to abstain from sexual intercourse for a minimum of 56 days (the duration of their participation in the study).

_____ 3.1.6 Patient must have an ECOG Performance Status of 0-3. Please see Appendix III.

PS: _____ (0, 1, 2, or 3)

_____ 3.1.7 Patient with any solid tumor or hematologic malignancy is eligible.

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NOTE: Patient may have received any number of lines of prior systemic therapy.

_____ 3.1.8 Patient must have received treatment with an anti-PD-1/PD-L1 agent either alone or in combination with another anti-cancer agent, as their most recent therapy prior to development of pneumonitis.

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NOTE: Patient may have received anti-PD-1/PD-L1 therapy as standard-of-care or part of a clinical trial.

Prior Anti-PD-1 or PD-L1: _____ (Yes or No)

If yes, list agent and date of last dose: _____

_____ 3.1.9 Patient must not be receiving anti-PD-1/PD-L1 agent in combination with any of the following anti-cancer agents: docetaxel, cyclophosphamide, gefitinib, erlotinib, osimertinib, crizotinib, bleomycin, afatinib.

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_____ 3.1.10 Patient must have steroid-refractory pneumonitis defined as:

- Grade 2 pneumonitis that has not improved by a CTCAE grade in greater than 72 hours or maximum of 21 days or

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- Grade 3 or higher pneumonitis that has not clinically improved by a CTCAE grade in greater than 48 hours or maximum of 21 days with high dose corticosteroids (methylprednisolone or prednisone 1-4mg/kg/equivalent) as their most recent treatment for pneumonitis, as determined by the treating investigator.

_____ 3.1.11 Patient must have had pathogen-negative infectious diagnostic evaluation within 21 days prior to randomization, and at a minimum these should include: blood culture, urine culture, sputum culture, and viral panel: rapid flu and RSV (respiratory syncytial virus). Empiric antibiotics for culture negative infections are not an exclusion for study entry.

Date of pathogen-negative infectious diagnostic evaluation: _____

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_____ 3.1.12 Patient must not have clinical evidence of cardiac dysfunction (as determined by the treating investigator) as an alternative diagnosis to steroid-refractory pneumonitis.

_____ 3.1.13 Patient must not be receiving concurrent radiation therapy to the chest.

Concurrent radiation therapy: _____ (Yes or No)

If yes, provide site(s): _____

_____ 3.1.14 Patient must not be deemed to have radiation pneumonitis. Patients with a history of stable radiation pneumonitis not requiring corticosteroid therapy within the last 3 months prior to randomization will be allowed on study.

Date of last corticosteroid therapy: _____

_____ 3.1.15 Patient must not have pre-existing interstitial lung disease or pneumonitis requiring corticosteroid therapy from any other cause, as determined by the treating investigator.

_____ 3.1.16 Patient must not have an absolute contraindication to IVIG or infliximab, including: clinical history of severe hypersensitivity reaction, selective IgA deficiency, active hepatitis B, active tuberculosis, active human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) where a study subject has a CD4 count of ≤ 200 at screening, or drug interaction as detailed in Section 8.1.8 and 8.2.9.

_____ 3.1.17 Patient must have a negative tuberculosis assessment (TB spot test, quantiferon gold or tuberculin skin test) within 21days prior to randomization and either negative or low clinical suspicion.

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Date of negative TB test: _____

_____ 3.1.18 Patient must have chest CT scan with or without contrast performed ≤14 days before randomization. Patient must not have a contraindication for CT.

Date of CT chest: _____

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Rev. Add2 **4. Registration and Randomization Procedures**

Cancer Therapy Evaluation Program Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at (https://ctepcore.nci.nih.gov/rcr).

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as site primary contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

In addition, all investigators act as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization. Additional

information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR ***Help Desk*** by email at <RCRHelpDesk@nih.gov>.

CTSU Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents

- Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below. Log in to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
  - Enter the protocol # in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand then select ECOG-ACRIN and protocol number EAQ172.
  - Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

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Protocol Specific Requirements for EAQ172 Site Registration

- Site-designated personnel must attest to the below requirements by signing the Site Registration Attestation Form submitted via the CTSU Regulatory Submission Portal.
- Sites must be able to comply with the below requirements as part of the patient's standard of care:
  - Have a medical oncology co-PI at each site to provide oversight of study procedures.
  - IVIG must be available in the treating institution.

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB
- Full protocol title and number
- Version Date
- Type of review (full board vs. expedited)
- Date of review.
- Signature of IRB official

3. Site Certification Form (See Section □□□)

Checking Your Site's Registration Status:

Site's registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of your screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

NOTE: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol treatment prior to randomization.

Treatment must start within seven days after randomization.

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Patient Registration

The following information is to be provided at time of registration.

4.1.1 Protocol Number

4.1.2 Site/Investigator Identification

- Institution CTEP ID
- Treating Investigator
- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Sex
- Birth date (mm/dd/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- Method of payment
- Country of residence

4.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.3 Stratification Factors

Severity of pneumonitis: (Grade 4 vs. Grade 2-3)

4.4 Additional Requirements

4.4.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.4.2 Biospecimens are to be submitted as indicated in Section 7.2 and Section 10

4.4.3 Site Requirements

- Site-designated personnel must attest to the below requirements by signing the Site Registration Attestation Form submitted via the CTSU Regulatory Submission Portal.
- Sites must be able to comply with the below requirements as part of the patient's standard of care:

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  - Have a medical oncology co-PI at each site to provide oversight of study procedures.
  - IVIG must be available in the treating institution.

4.4.4 Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the relevant LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
  - Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
  - Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their

account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.4.5 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

NOTE: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

4.4.6 Digital Radiation Therapy (RT) Data Submission Using Transfer of Radiation Images and Data (TRIAD)

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid CTEP-IAM account.
- Registration and Credential Repository (RCR) registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

- All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installations:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email at TRIAD-Support@acr.org or 1-703-390-9858.

4.5 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EAQ172 Forms Completion Guidelines.

5. Treatment Plan

5.1 Administration Schedule

Patients will be randomized to one of two possible immunosuppressive treatments as per the study schema. These will include:

5.1.1 Arm A Treatment

Infliximab 5mg/kg IV on day 1 followed by a 4-6 week corticosteroid taper, starting from a dose of prednisone 1-2mg/kg (or methylprednisolone at a dose equivalent to 1-2mg/kg of prednisone) either orally or intravenously in divided doses, and determined by the treating investigator. The date of commencement of the corticosteroid taper will be from Day 1 of the first infliximab dose. A second dose of infliximab may be delivered 14-days after the first dose as per the treating investigator. If a second infliximab dose is administered, corticosteroid taper will be restarted from a dose of prednisone 1-2mg/kg either orally or intravenously in divided doses at Day 14, at the discretion of the treating investigator. Dosing will be based on actual patient body weight. Treatment may be delivered either as an outpatient or an inpatient at the discretion of the treating investigator. Patient may receive infliximab as per locally obtainable formulation. Patient should be under assessment for latent or active tuberculosis as per local institutional guidelines. (Appendix VI)

5.1.2 Arm B Treatment

IVIG 2g/kg divided as per institutional guidelines as an IV infusion, followed by a 4-6 week corticosteroid taper, starting from a dose of prednisone 1-2mg/kg (or methylprednisolone at a dose equivalent to 1-2mg/kg of prednisone) either orally or intravenously in divided doses, determined by the treating investigator. The date of commencement of the corticosteroid taper will be from Day 1 of the first IVIG dose. Dosing will be based on actual patient body weight. Treatment may be delivered either as an outpatient or an inpatient at the discretion of the treating investigator. (Appendix VII)

5.1.3 Corticosteroids and Pill Calendar

Patients will keep a pill calendar as per Appendix VIII to record administration of corticosteroids after receipt of study therapy, if given orally. Corticosteroids will be tapered over a 4-6 week period as deemed appropriate by the treating investigator. Administration of corticosteroids will be confirmed at days 14 and 28 visits as per the study calendar in Section 7. Patients in both Arm A and Arm B will need this pill calendar.

5.1.4 Recommendations for chest CT[58-60]

All patients will undergo a chest CT during study screening, and days 1, 14 and 28.

5.1.4.1 Chest CT Techniques

- Diagnostic chest CT taken in a spine position at end-inspiration (as routinely done for clinical chest CT).

- Contiguous axial slices with slice thickness of 3 mm or less
- Reconstructed with 1) lung algorithm and 2) mediastinum/soft tissue algorithm
- IV contrast is not necessary to diagnose pneumonitis, but OK to be present if clinically indicated.
- Use the same techniques on the serial scans in the same patient as much as possible.

5.1.4.2 Assessment of Pneumonitis on CT

- Assessment is done primarily using the contiguous axial images reconstructed with lung algorithm displayed on a lung window setting.
- Other image series (soft tissue reconstructions, coronal/sagittal images if available) can be reviewed if necessary to differentiate pneumonitis and other findings.

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5.1.4.3 Assessment of Chest CT scan at each timepoint (study screening, days 1, 14, and 28 of study therapy administration)

- Assessment is done primarily using the contiguous axial images reconstructed with lung algorithm displayed on a lung window setting.
- Other image series (soft tissue reconstructions, coronal/sagittal images if available) can be reviewed if necessary to differentiate pneumonitis and other findings.

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Abnormal pulmonary as consistent with the published Fleischner criteria outlined in Johkoh et al, Radiology 2021 and Chest 2021. Abnormal findings indicative pneumonitis are evaluated for:

1) Extent in upper, middle and lower lungs using a 6-point scale;

   1a) Upper lung: 0: none, 1: 1-5%, 2: 6-25%, 3: 26-50%, 4: 51%-75%, 5: 76-100%

   1b) Middle lung: 0: none, 1: 1-5%, 2: 6-25%, 3: 26-50%, 4: 51%-75%, 5: 76-100%

   1c) Lower lung: 0: none, 1: 1-5%, 2: 6-25%, 3: 26-50%, 4: 51%-75%, 5: 76-100%

   NOTE: Visually evaluate the extent of pneumonitis involvement in upper, middle, and lower lungs. “Upper” is from the apices to the level of carina, “middle” is from the level of carina to the level of inferior pulmonary veins (at the junction with atrium), and “lower” is below the level of inferior pulmonary veins. Assess both lungs together, on contiguous

axial slices. For example, there is diffuse GGO all over in all or most slices in the upper lung, that is 5 (76-100%) for the upper lung. Note this is a qualitative score based on visual assessments, and no quantification image processing necessary.

2) Distributions in terms of (pick one each for 2a and 2b; based on the predominant distribution of the abnormalities of pneumonitis):

   2a) peripheral, diffuse, central, mixed*

   2b) upper, lower, diffuse, multifocal, focal

   * Two or more of the other three patterns co-exist without definite predominance

3) Lobar involvement (involved/not involved):
   - Right upper lobe (RUL)
   - Right middle lobe (RML)
   - Right lower lobe (RLL)
   - Left upper lobe (LUL)
   - Lingula
   - Left lower lobe (LLL)

4) Specific CT findings (present/absent):
   - Traction bronchiectasis
   - Consolidation
   - Reticular opacities
   - Ground glass opacities (GGOs)
   - Centrilobular nodularity
   - Honeycombing

   NOTE: Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008 Mar;246(3):697-722.

5) Lung volumes (qualitative assessment by visual evaluation, in references to what is expected in normal cases, paying attention to the entire lung volume and expansions, as well as the presence of traction bronchiectasis)

   1: Definitely decreased,

   2: Probably decreased,

   3: Within expected normal range,

   4: Probably increased,

   5: Definitely increased

5.1.4.4 Chest CT scans at days 14 and 28 are additionally assessed for the following in comparison with the prior scans*:

1) Overall findings of pneumonitis:

1: Definitely decreased,

2: Probably decreased,

3: No significant change,

4: Probably increased,

5: Definitely increased

2) Lung volumes (qualitative assessment by visual evaluation)

1: Definitely decreased,

2: Probably decreased,

3: No significant change,

4: Probably increased,

5: Definitely increased

* Day 14 scan compared with day 1 scan

* Day 28 scan compared with pre-therapy/baseline scan and with 14-day scan (two assessments)

5.1.4.5 Data Collection

CT scans are to be submitted. Please refer to Section 4.4.5 for digital RT data submission using TRIAD.

5.2 Adverse Event Reporting Requirements

All toxicity grades described throughout this protocol and all reportable adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

5.2.2 Routine Reporting of Adverse Events (Medidata Rave)

Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to Section 4 of the protocol for more information on how to access the Medidata Rave system and the EAQ172 forms

packet for instructions on where, when and what adverse events are to be reported routinely on this protocol.

5.2.3 Expedited Reporting of Adverse Events (CTEP-AERS)

In addition to routine reporting, certain adverse events must be also reported in an expedited manner for timelier monitoring of patient safety and care. The remainder of this section provides information and instructions regarding expedited adverse event reporting.

5.2.4 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans, whether or not considered agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment (Arm A or Arm B), using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment administered in Arm A or B.
Unlikely	The AE is *doubtfully related* to treatment administered in Arm A or B.
Possible	The AE *may be related* to treatment administered in Arm A or B.
Probable	The AE is *likely related* to treatment administered in Arm A or B.
Definite	The AE is *clearly related* to treatment administered in Arm A or B.

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol or drug package insert.
- **Life Threatening Adverse Event:** Any AE that places the patient at immediate risk of death from the AE as it occurred.

5.2.5 Expedited Adverse Event Reporting Procedure

Adverse events requiring expedited adverse event reporting will use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov, so

that ECOG-ACRIN and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900)
- the FDA (1-800-FDA-1088)

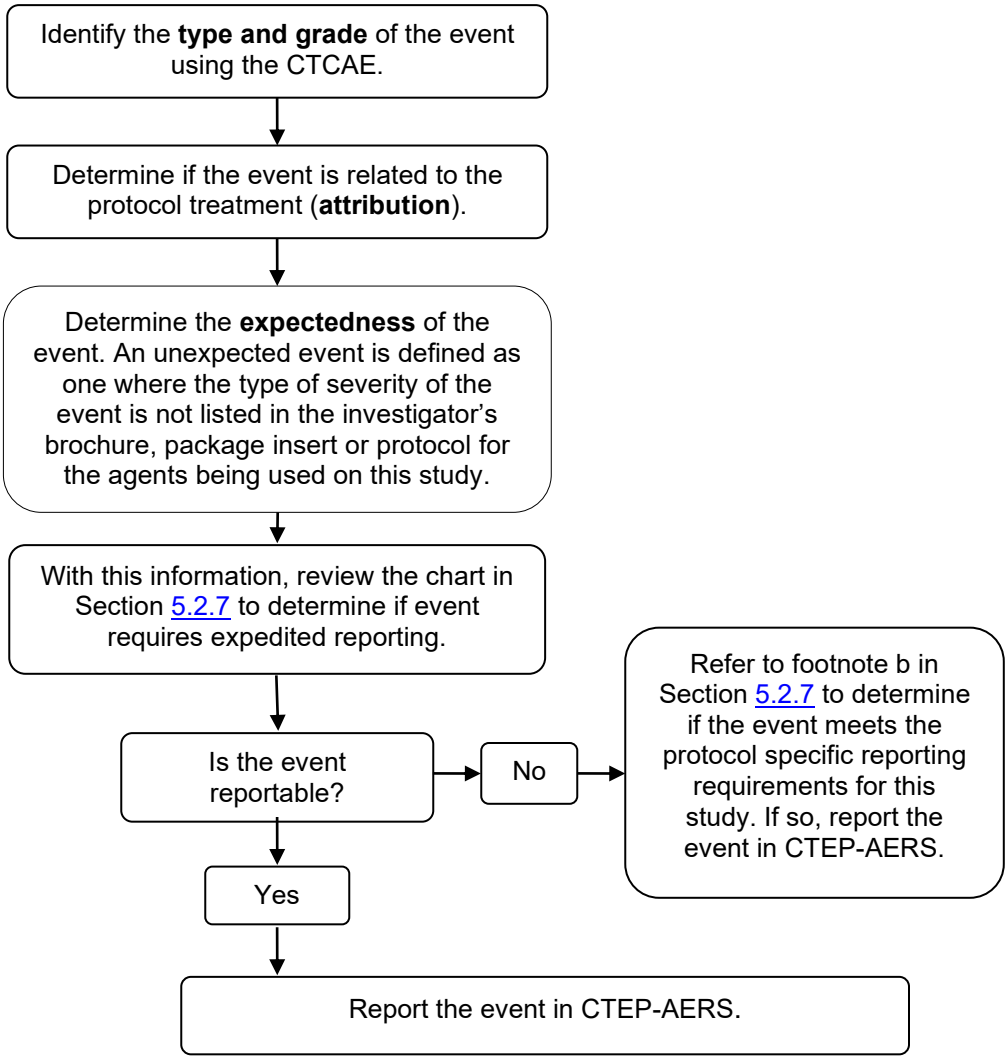
An electronic CTEP-AERS report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

Many factors determine the requirements for expedited reporting of adverse events on each individual protocol. The instructions and tables in the following sections have been customized for protocol EAQ172 and outline the specific expedited adverse event reporting requirements for study EAQ172.

5.2.6 Steps to determine if an event is to be reported in an expedited manner



5.2.7 Expedited Reporting Requirements on protocol EAQ172

Commercial Agents: Infliximab and Intravenous Immunoglobulin (IVIG)

Expedited reporting requirements for adverse events experienced by patients on protocol EAQ172

Attribution	**Grade 4**		**Grade 5[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

NOTE: Any death that occurs > 30 days after the last dose of treatment on this study and is attributed possibly, probably, or definitely to the treatment on this study must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported in CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events in CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

5.2.8 Other recipients of adverse event reports and supplemental data.

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.3 Dose Modifications

There are no dose modifications of study agents in this study. If a dose of study medication is missed at the time of administration specified in Section 5.1 and/or Appendices VI-VII, this will be recorded and considered missed. Study treatment will not be made up at a later date.

5.4 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

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5.5 Duration of Therapy

Patients will receive protocol therapy unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EAQ172 Forms Completion Guidelines, accessible under the Case Report Forms tab of the EAQ172 page on the CTSU website.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity deemed related to or possibly-related to study therapy.
- Patient develops progressive cancer during the study time period and this is deemed to be of greater clinical significance than pneumonitis and requiring cancer therapy. (Patient will be replaced with a new one in this case).
- Patient develops worsening pneumonitis, defined as worsening pneumonitis symptoms despite protocol-directed therapy, or an escalation in the level of clinical care for pneumonitis, as deemed by the treating investigator.
- Non-protocol therapies are administered.

5.6 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed until day 28 for pneumonitis response, and up to day 56 for other assessments (refer to table in Section 7.1).

6. Measurement of Effect

For the purposes of this study, patients will be re-evaluated for response to protocol-directed therapy at Days 14 and 28, compared with an assessment at Day 1 of study therapy administration.

Evaluation of response in patients with pneumonitis will be assessed by PaO2/FiO2 ratio at Days 1, 14 and 28 of the study period. For the purposes of evaluating the primary objective of the study, pneumonitis response will be defined as an improvement of ≥20% in PaO2/FiO2 ratio, at Day 28 compared with Day 1.

6.1 Methods for Evaluation

All measurements should be taken and recorded using mmHg for PaO2 on an arterial blood gas assessment as in Section 6.1.1. FiO2 will be calculated based on patient inspired oxygen as per Section 6.1.2.

- All Day 1 evaluations should be performed as closely as possible to the administration of study therapy (+/-5 days of commencement of study therapy as per Study Calendar).
- All Day 14 evaluations will be done on day 14 (+/-5 days) after the day of administration of study therapy.
- All Day 28 evaluations will be done on day 28 (+/-5 days) after the day of administration of study therapy.

To the extent that is possible, the same method of assessment, same machine and the same technique should be used to evaluate each patient at each timepoint.

6.1.1 PaO2 calculation

An arterial blood gas assessment will be performed as outlined in Appendix IV.

6.1.2 FiO2 calculation

FiO2 will be calculated as per the fraction of inspired oxygen the patient is receiving, to maintain their pulse oximetry reading at 92-94%. This will be calculated based on if a patient is receiving oxygen either by: 1. room air, 2. supplemental oxygen delivery (facemask or mouthpiece with nose clip, only), 3. non-invasive ventilation, or 4. invasive ventilation. Patients who are receiving supplemental oxygen by nasal cannula or who cannot maintain oxygen saturations (SpO2) of 92-94% on room air for 20 minutes, will be switched to receiving oxygen delivered either by facemask or mouthpiece/nose clip for 20-30 minutes, to ensure accuracy of the FiO2 measurement, as defined in Appendix IV.

Examples:

1. Room air: 21% oxygen on room air: FiO2= 0.21
2. High-flow humidified oxygen by facemask (e.g. 60% oxygen delivered to maintain SpO2 of 92-94%): FiO2= 0.60
3. 100% Oxygen delivered by mouthpiece with one-way valve and nose clip (100% oxygen delivered to maintain SpO2 of 92-94%): FiO2=1.0

4. Oxygen delivery by non-invasive ventilation (e.g. 60% oxygen delivered to maintain SpO2 of 92-94%): FiO2= 0.6
5. Oxygen by mechanical ventilation (e.g. 80% oxygen delivered to maintain SpO2 of 92-94%): FiO2= 0.80

The fraction of inspired oxygen (FiO2) will be recorded by a member of the study team as outlined in Appendix V. The oxygen saturation will also be recorded at the time the supplemental oxygen liter volume is recorded.

6.1.3 Measurement of Infection

The proportion of patients who develop a confirmed bacterial, viral or fungal infection after immunosuppression, using standard infective evaluation as per the treating investigator.

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6.2 Patient Reported Outcome Measurement

6.2.1 Quality of Life Instruments to be Administered

Improvement in pneumonitis symptoms will be assessed using the FACT-L scale and the Borg Dyspnea Score.

6.2.2 Quality of Life Assessment Schedule

Patients will be assessed according to the following schedule:

1) Day 1 (up to 5 days before Day 1 or on Day 1, as per study calendar)

2) Day 14 (+/- 5 days, as per study calendar)

3) Day 28 (+/- 5 days as per study calendar)

These patient-reported outcome assessment time points correspond to standard clinic office visits of routine care to minimize participant burden.

PRO	Baseline (up to 5 days before Day 1 or on Day 1)	Day 14 (+/- 5 days)	Day 28 (+/- 5 days)
FACT-L Questionnaire	X	X	X
Borg Dyspnea Score	X	X	X

6.2.3 Quality of Life Administration Instructions

6.2.3.1 The questionnaires must be administered at the time points listed above. The patient should be instructed to respond to the questionnaires in terms of their experience during the timeframe specified on each questionnaire.

6.2.3.2 The baseline questionnaire (up to 5 days before Day 1 or on Day 1) must be completed prior to administration of study treatment.

6.2.3.3 The patient should be asked to read the instructions at the beginning of each questionnaire and complete all the items.

6.2.3.4 The questionnaires must be reviewed by the protocol nurse or research coordinator as soon as the patient completes them to ensure all items were marked appropriately. If more than one answer was marked, the patient should be asked to choose the answer which best reflects how they are feeling. If a question was not answered, the patient should be asked if they would like to answer it. The patient should always have the option to refuse. If the patient refuses, it should be indicated on the questionnaire that they declined to answer the item.

6.2.3.5 If the patient cannot complete a questionnaire, or if the patient refuses to complete the questionnaire, the reason should be noted according to the instructions in the EAQ172 Forms Completion Guidelines.

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7. Study Parameters

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7.1 Therapeutic Parameters

1. Pre-treatment Standard of Care CT scans must be done ≤14 days before randomization
2. Pre-study CBC (with differential and platelet count) should be done ≤ 14 days before randomization
3. All required pre-study chemistries should be done ≤ 14 days before randomization

Study Calendar

Trial Period	**Study Screening (Prior to Randomization)[10]**	**Treatment Phase**			**Follow-Up**
Treatment Day	≤21 days before randomization	Day 1[10]	Day 14	Day 28	Days 42 and 56
Scheduling Window (days)		+/-5	+/-5	+/-5	+/-5
Clinical Procedures/Assessments					
Patient demographics/Age	X				
Medical and Surgical History	X				
Pregnancy test[1]	X				
Prior and concomitant medications	X	X	X	X	X
Review of Adverse Events	X	X	X	X	X
Full Physical Examination	X	X	X	X	X
Vital Signs[2]	X	X	X	X	X
Supplemental Oxygen Use[3]	X	X	X	X	
ECOG Performance Status	X	X	X	X	X
Weight/BMI	X	X	X	X	X
Height	X				
EKG	X[13]	X	X	X	
Infliximab or IVIG administration		X	X		
Corticosteroids Administration		X	X	X	
Arterial Blood Gas (PaO2/FiO2 ratio)[3]		X	X	X	

Trial Period	Study Screening (Prior to Randomization)[10]	Treatment Phase			Follow-Up
Treatment Day	≤21 days before randomization	Day 1[10]	Day 14	Day 28	Days 42 and 56
Scheduling Window (days)		+/-5	+/-5	+/-5	+/-5
Clinical Procedures/Assessments					
Pill counts			X	X	X[7]
Laboratory Procedures/Assessments					
Hematology labs[12]	X	X	X	X	X
Serum chemistries, Liver function tests[12]	X	X	X	X	X
Coagulation Profile (PT, INR)	X[9]				
ESR (erythrocyte sedimentation rate)		X	X	X	X
Pulmonary Function Tests[4]	X	X	X	X	
Tuberculosis test[8]	X				
Hepatitis B serology	X				
Blood culture	X[9]				
Urine culture	X[9]				
Viral Panel including rapid flu and RSV	X[9]				
Sputum Culture	X[9]				
Radiologic Assessments					
CT chest with or without contrast[11]	X	X	X	X	
Patient-Reported Outcome Assessments					
FACT-L Questionnaire		X[14]	X	X	
Borg scale		X[14]	X	X	
Biological Sample Submissions: See Sections 7.2 and 10					

1. All females of childbearing potential must have a negative blood test or urine test within 14 days prior to randomization to rule out pregnancy.
2. Vital signs include: blood pressure, heart rate (pulse), respiratory rate, oxygen saturation on room air.

3. Response Assessment will be performed by assessment of PaO2/FiO2 ratio. To calculate this, patients will need an arterial blood gas assessment obtained from an arterial puncture or an indwelling arterial catheter, and a recording of the fraction of inspired oxygen received, as outlined in Appendices IV and V.
4. Pulmonary Function Tests include: FVC, FEV1, DLCO, Total Lung Capacity (TLC) and Flow-volume loops without bronchodilator use. These only need to be completed if the patient is clinically able to complete this assessment. Selected patients (such as those on a ventilator) may not be able to complete this test. Raw values and the percent predicted for FEV1, FVC, DLCO and TLC should be collected.
5. **Arm A:** If corticosteroids taper is given for 6 weeks or is re-commenced for another 4-6 weeks after day 14 administration of infliximab.
6. Tuberculosis test must be completed as per local practices, and may refer to either: TB spot test, quantiferon gold or tuberculin skin test as per eligibility criteria. Patient must have a negative tuberculosis assessment within 21 days of randomization and either negative or low clinical suspicion.

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7. Patients must have pathogen-negative infectious diagnostic evaluation within 21 days of randomization, at a minimum these should include: blood culture, sputum culture, and viral panel (including rapid flu and RSV). Perform urine culture and coagulation profile as clinically indicated.
8. All study screening assessments must be completed within ≤21 days prior to randomization. If screening tests are done within 5 days of day 1, assessments that are also required on day 1 do not need to be repeated.
9. IV contrast is not necessary to diagnose pneumonitis, but OK to be present if clinically indicated. Please refer to Section 5.1.4 for imaging guidelines and Section 4.4.6 for digital RT data submission using TRIAD.
10. Hematology tests are to include a CBC with differential (i.e., WBC, ANC, platelet, Hgb, Hct). Serum chemistry tests are to include: sodium, potassium, calcium, magnesium, glucose (non-fasting), creatinine, creatinine clearance (CrCl; calculated with the Crockcroft-Gault formula), bilirubin, alkaline phosphatase, aspartate aminotransferase (AST or SGOT), alanine aminotransferase (ALT or SGPT), blood urea nitrogen (BUN).
11. Perform screening EKG as clinically indicated.
12. Patient-reported outcome assessments should be completed up to 5 days before Day 1 or on Day 1

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7.2 Biological Sample Submissions

Biospecimens are to be submitted for research studies as outlined in Section 10. The submission of biospecimens is mandatory for use in the correlative studies described in Section 11.

All samples submitted must be logged and tracked in the ECOG-ACRIN Sample Tracking System (STS).

Material	Pre-Study	Day 1[3]	Day 14[3]	Day 28[3]	**Ship To:**
MANDATORY					
Peripheral blood, 7 Heparin tubes[3]		X	X	X	D'Alessio Laboratory Johns Hopkins
Per Participant Consent: If collected, these will be submitted from patients who answer "Yes" to "*I agree that my samples and related health information may be used for the laboratory studies described above*."					
Tumor Tissue, FFPE[2]	X				

1. Tissue collected during previous standard of care (SOC) procedures prior to trial entry are requested to be submitted to the Central Biorepository and Pathology Facility (CBPF) – MDACC Life Sciences Plaza as outlined in Section 10 with 4 weeks following randomization. The associated pathology and related reports are to be submitted with all tissue submissions.
2. Blood is to be collected within +/- 5 days of the timepoints indicated. Research blood samples are not to be collected or shipped on Fridays or a day before a holiday, as the receiving laboratory is closed on Saturdays and holidays. Samples must be shipped the day of collection as they are required to be processed within 36 hours of sample collection. To order kits, please see Appendix X. Kit supplies are limited and are available for US and Canadian sites only. Institutional supplies are requested to be used if kits are not available.

8. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees. Biosimilars and other formulations of infliximab or IVIG not stated below, will not be permitted.

8.1 Infliximab

8.1.1 Other Names

Infliximab is also known as Remicade (Janssen Biotech Inc., PA).

8.1.2 Classification

Infliximab neutralized the biologic activity of TNF-alpha, by binding with high affinity to the soluble and transmembrane forms of TNF alpha, and inhibits blocking of TNFalpha with its receptions. Infliximab is an FDA-approved treatment for a number of immunologic conditions, including but not limited to: ulcerative colitis, Crohn's disease, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis.

8.1.3 Mode of Action

Infliximab is a chimeric monoclonal antibody that inhibits binding of the inflammatory cytokine tumor necrosis factor alpha (TNF-a) to its receptor. Infliximab is an FDA-approved tumor necrosis factor (TNF) modifier marketed in the U.S. targeted against tumor necrosis factor-alpha (TNF-alpha). Biological activities attributed to TNFalpha include induction of pro-inflammatory cytokines such as interleukin (IL)-1 and IL-6; enhancement of leukocyte migration by increasing endothelial layer permeability; expression of adhesion molecules by endothelial cells and leukocytes; activation of neutrophil and eosinophil functional activity; fibroblast proliferation; synthesis of prostaglandins; and induction of acute phase and other liver proteins. Preclinical studies have implicated TNF-alpha as an important effector molecule in the development of lung injury. This has led to the application of TNF-alpha inhibitors in different clinical scenarios. For example, etanercept has been used (46) in idiopathic pneumonia syndrome (IPS), which like PDL-1 induced pneumonitis is triggered by immunologic factors. Specifically, murine IPS models have suggested that the lung is a target of distinct immune-mediated injury pathways that include soluble inflammatory effectors such as TNF-alpha and antigen specific T-cell which synergize to cause inflammation, cellular injury and pulmonary dysfunction. Based on infliximab use in CTLA 4-mediated colitis, prior studies have used infliximab in steroid refractory pneumonitis.[57] However, infliximab may be implicated in the development of infections leading to poor outcomes in these patients and more recently the number of reported cases of ILD triggered by anti TNF-alpha agents is increasing. Given that infliximab may be implicated in the development of severe infections (renal and hepatic), other alternatives have been explored for the treatment of anti PD1/PDL-1 related pneumonitis.

8.1.4 Storage and Stability

Store unopened infliximab vials in a refrigerator at 2-8°C. Do not use infliximab beyond the expiration date on the carton or vial. This product contains no preservatives. Unopened vials may be stored up to 30°C for a single period for up to 6 months, but not exceeding the expiration date.

8.1.5 Dose Specifics

Refer to Section 5.1.1.

8.1.6 Preparation

Infliximab is a chimeric IgGk monoclonal antibody composed of human constant and murine variable regions specific to human tumor necrosis factor-alpha (TNFalpha). Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

Infliximab is supplied as a sterile white lypholized powder for intravenous infusion. Following reconstitution with 10ml of sterile water for injection, the resulting pH is 7.2.

8.1.7 Route of Administration

Infliximab is administered intravenously. It is predominantly distributed within the vascular compartment. The elimination half-life of infliximab is 8-9.5 days. When single infusions of infliximab 1 - 20 mg/kg are given, a linear relationship exists between the dose administered and the Cmax and AUC. A single infusion of 5 mg/kg IV results in a median Cmax of 118 mcg/m. The standard recommended dose for PD-1/PDL1 pneumonitis is 5mg/kg.

Prior to initiating infliximab therapy, patients must be evaluated for latent tuberculosis as per institutional policies (tuberculin skin test, TB spot test, or Quantiferon test). Prior to IV infusion, infliximab will be administered as outlined in Appendix VI.

- The IV infusion should begin within 3 hours of reconstitution and dilution.
- Do not administer the solution if visibly opaque particles, discoloration, or other foreign particles are observed.
- Do not infuse the infliximab solution concomitantly in the same intravenous line with other agents.
- Infuse IV over a period of not less than 2 hours. Use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 microns or less). Discard any unused portion.

Laboratory monitoring should include:

- CBC with differential
- Hepatitis B serology
- Assessment for Active/Latent Tuberculosis (as per local guidelines)

- Cytochrome p450 (CYP450) substrates: advised to monitor drug concentrations or the effects of drugs that are known to be CYP450 substrates such as warfarin, cyclosporine and theophylline.

Treatment of Infliximab infusion reactions

Infusion reactions may occur within 2 hours of an infliximab infusion in up to 20% of patients. Infusion-related reactions include flushing (9%), headache (18%), and rash (10%). Among infliximab infusions in reported clinical trials, 3% were accompanied by non-specific symptoms such as fever or chills, and 1% were accompanied by cardiopulmonary reactions such as chest pain (unspecified), hypotension, hypertension, or dyspnea. Less than 1% were accompanied by itching, urticaria, or the combined symptoms of itching/urticaria and cardiopulmonary reactions. Serious acute infusion related reactions including anaphylactic shock, convulsions, erythematous rash, and hypotension occurred in < 1% of adults treated during clinical trials.

If infusion reactions occur, sites should follow local institutional protocols for management of infusion reactions. For example, mild to moderate infusion reactions should prompt slowing of infusion rate or temporary discontinuation of the infusion. Upon resolution of the reaction, reinitiate administration at a lower infusion rate and/or the prescriber may order treatment with antihistamines, acetaminophen, and/or corticosteroids, in accordance with local infusion reaction guidelines For patients that do not tolerate the infusion following these interventions, infliximab should be discontinued. Infliximab would be discontinued if severe hypersensitivity reactions occur. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a serious reaction.

8.1.8 Incompatibilities

Contraindications

Infliximab at doses >5mg/kg should not be administered to patients with moderate to severe heart failure. Infliximab should not be re-administered to patients who have experienced a severe hypersensitivity reaction to infliximab. Additionally, patients should not receive infliximab if they have known hypersensitivity to any components of the product or murine proteins.

Drug Interactions:

- Anakinra or Abatacept: Increased risk of serious infections were seen in clinical studies of these agents with infliximab.
- Tocilizumab: this combination should be avoided due to increased risk of infection or immunosuppression.
- Methotrexate: concomitant use my increase infliximab concentrations
- Live vaccines: These should not be given concurrently with infliximab.

Pregnancy

It is not known whether infliximab may cause fetal harm. Patients will be strongly encouraged to use contraception during this study, if of child-bearing potential. Infliximab should not be given to breastfeeding mothers as the penetration of the agent into breast milk is unknown.

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8.1.9 Availability

The drug will be provided by the treating investigator at the study site. Infliximab is included in national guidelines (American Society of Clinical Oncology (ASCO), Society for Immunotherapy of Cancer (SITC), and National Comprehensive Cancer Network (NCCN)), and will be billed to the patient's insurance. This study will not be conducted under an IND.

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8.1.10 Side Effects

Common AEs include: rash (10%), abdominal pain (12%), nausea (21%), headache (18%), cough 12%, pharyngitis (12%), sinusitis (14%), upper respiratory infection (32%), fatigue (9%).

Side effects by organ system are annotated below:

- Cardiovascular: Hypertension (5%), Acute coronary syndrome, Bradyarrhythmia (≥ 0.2%), Hypotension, Heart failure, Systemic vasculitis (Rare)
- Dermatologic: Pruritis (7%), Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis
- Gastrointestinal: Abdominal pain (12%), Diarrhea (12%), Dyspepsia (10%), Bowel obstruction (≥ 0.2%)
- Hematologic: Hemolytic anemia (≥ 0.2%), Leukopenia (Adult, ≥ 0.2%; pediatric, 9%), Neutropenia (Pediatric, 7%), Pancytopenia (≥ 0.2%), Thrombocytopenia (≥ 0.2%)
- Hepatic: Autoimmune hepatitis (Rare), Hepatic failure, acute (Rare), Hepatitis (≥ 0.2%), Hepatotoxicity (Rare)
- Immunologic: Allergic reaction (≥ 0.2%), Anaphylaxis, Hepatosplenic T-cell lymphoma (Rare), Hypersensitivity reaction, Malignant lymphoma, Sarcoidosis (≥ 0.2%)
- Infectious: Infliximab-associated infection ranges from 5.3 -56% in incidence. The infections most frequently reported include: upper respiratory tract infections (32%), e.g. sinusitis (14%), pharyngitis (12%), bronchitis (10%) urinary tract infections (8%). Reported serious infections: pneumonia (0.2%), cellulitis (0.2%), sepsis (0.2%), skin ulcer, abscess, bacterial infections.
- Neurologic: Demyelinating disease of central nervous system, Change in vision (Rare)
- Respiratory: Dyspnea (1%), Pulmonary edema (≥ 0.2%), Tuberculosis (0.4%)
- Other: Cancer, Histoplasmosis, Infectious disease (Adult, 36-50%; pediatric, 38-74%), Infusion reaction (Adult, < 20%; pediatric, 13-18%), Mycosis fungoides.

8.1.11 Nursing/Patient Implications

Advise the patient to read the FDA-approved packaging information/labelling for this agent (medication guide). Patients and caregivers should be advised of the potential risks and side effects of this agent. Patients should be informed that infliximab may lower the effects of their immune system, and the ability to fight infection. Patients should be counselled on an increased risk of lymphoma and other malignancies. Advise patients to report any new or worsening heart failure, neurologic disease or autoimmune toxicity.

8.1.12 References

Remicade (Infliximab) package insert 2013.

Janssen Biotech, Inc.

Horsham, PS 19044

8.2 Intravenous Immunoglobulin (IVIG)

8.2.1 Other Names

Intravenous immunoglobulin (IVIG) may also be known by a number of commercial names/brands. For the purposes of this study, the following IVIG formulations may be used: Privigen (CSL Beyring AG, Bern, Switzerland), Gammagard Liquid (Baxalta Us Inc, Westlake Village, CA, USA). Gamunex-C (Grifols USA, Research Triangle Park, NC, USA) may be used as an alternative IVIG formulation in the event either Privigen or Gammagard are not available from the manufacturer due to production shortages.

8.2.2 Classification

IVIG is an intravenous solution composed primarily of human immunoglobulin G (IgG), with trace amounts of IgA and IgM. IVIG is derived from the pooled human plasma of thousands of donors, ensuring a diversified collection of antibodies with variable antigen binding regions. All samples undergo human immunodeficiency virus (HIV), hepatitis B, and hepatitis C testing. IVIG is an FDA-approved treatment for a number of immunologic conditions, including but not limited to: primary humoral immunodeficiency, chronic immune thrombocytopenia purpura ITP), chronic inflammatory demyelinating polyneuropathy (CIDP).

8.2.3 Mode of Action

IVIG is a well-established anti-inflammatory and immunomodulatory agent that primarily contains intact monomeric IgG with only trace amounts of IgA, IgM, and IgE. IVIG exerts its effects through multiple mechanisms: modulation of macrophage Fc receptor expression and function; alteration of T cell and B cell function; inhibition of pathogenic autoantibodies; inhibition of inflammatory cytokines and inhibition of complement activation.

Within 24 hours, up to 30% of a dose may be removed by catabolism and distribution. IVIG appears to distribute throughout intravascular (60%) and extravascular (40%) spaces. The exact fate of IVIG is not

well defined, but the serum half-life is that of immune globulin (IgG), approximately 21 to 29 days. High variability exists for the half-life of IgG. Fever, infection, or high IgG concentrations appear to coincide with a shortened half-life whereas immunodeficiency appears to be associated with a longer half-life of IgG. For example, the apparent half-life of IgG after Octagam is approximately 40 days (range, 23 to 84 days) in immunosuppressed patients. Peak serum concentrations occur immediately after IV injection and are dose-related. Following infusion, IVIG products show a biphasic decay curve. The initial phase is characterized by an immediate post-infusion peak in serum IgG and is followed by rapid decay due to equilibration between the plasma and extravascular fluid compartments. The second phase is characterized by a slower and constant rate of decay. After receipt of 300 to 450 mg/kg of IVIG every 4 weeks, the mean total IgG serum concentration decreased approximately 47% to 55% over 28 days. The mean trough total IgG concentration after 6 or 7 infusions of Octagam was 766 to 871 mg/dL. The concentrations were similar to the patient's baseline trough total concentrations (883 to 986 mg/dL) on other IVIG products (59).

The use of IVIG for the treatment of ILD is limited to case series, exploratory trials and anecdotal reports. As such, it has been used primarily as salvage therapy when traditional immunosuppression has either failed or been poorly tolerated. IVIG is a known therapy for multiple autoimmune, paraneoplastic immune conditions, steroid-resistant polymyositis and severe idiopathic pulmonary fibrosis (IPF) (59). Donahoe and colleagues reported that patients who received IVIG in addition to rituximab and plasma exchange had a more durable response in terms of mortality and improvement in PFTs compared to rituximab and plasma exchange alone(60).

8.2.4 Storage and Stability

Privigen, Gammagard Liquid and Gamunex-C are supplied in a single-use tamper-evident vial containing a labelled amount of functionally active IVIG. Packing components are not made with rubber latex. Privigen, Gammagard Liquid and Gamunex-C should be kept in its original carton to protect it from light. Each vial has an integral suspension band and a label with two peel off strips showing product name, lot number and expiration date. When stored at room temperature (up to 25°C, or 77°F). Privigen is stable for up to 36 months and Gammagard is stable for up to 24 months respectively. Gamunex-C may be stored under refrigeration for up to 36 months at 2-8° C (36-46° F).

8.2.5 Dose Specifics

Refer to Section 5.1.2. *The dose of IVIG varies depending on the condition it is being administered.* For patients receiving privigen as part of this study: patients will be treated with 2g/kg per day in divided doses, and the initial infusion rate will commence as outlined in Appendix VII. For patients receiving Gammagard Liquid and Gamunex-C as part of this study: patients will be treated with 2g/kg in

divided doses, and the initial infusion rate will commence as outlined in Appendix VII.

8.2.6 Preparation

Do not mix immune globulin products of different formulations or from different manufacturers. Do not shake vials to avoid excessive foaming. Do not use IVIG (products beyond their expiration date on the label). Privigen, Gammagard Liquid and Gamunex-C vials are for single-use only and contain no preservative. Discard any partially used vials or unused product according to institutional requirements. If large doses are to be administered several vials can be pooled using aseptic technique. IVIG products can be diluted with D5W only, do not use NS to further dilute. May flush the infusion line with NS or D5W for either IVIG product.

8.2.7 Dosage Forms and Description

IVIG is ready-to-use sterile 10% protein liquid preparation of polyvalent human immunoglobulin G (IgG) for intravenous use Privigen and Gammagard Liquid has a purity of at least 98% IgG consisting primarily of monomers. Privigen contains 250mmol/L (range 210-290) of L proline as a stabilizer and trace amounts of sodium. Gammagard Liquid contains 250mmol/L of glycine as a stabilizer and buffering agent. Privigen and Gammagard Liquid contain no carbohydrate stabilizers or preservatives. Privigen, Gammagard Liquid and Gamunex-C are supplied in single-use tamper-evident vials containing a labelled amount of functionally active IVIG. Packing components are not made with rubber latex.

8.2.8 Route of Administration

IVIG is administered intravenously, and will be administered as outlined in Appendix VII.

Severe adverse events may be related to infusion rate; it is important to follow recommendations closely. Administer at the minimum infusion rate possible for patients at risk for renal dysfunction or thromboembolic events**.** Thrombotic events have been associated with the administration of IVIG, particularly in patients with renal dysfunction. Therefore, the investigators must ensure adequate hydration prior to infusion, particularly in patients with preexisting renal insufficiency or those at risk of thrombosis.

The following laboratory parameters, should be monitored daily before and after initiation of IVIG:

- Evaluate for signs and symptoms of thrombotic events during administration
- Assess renal function, including BUN and serum creatinine
- Monitor glucose levels in patients with diabetes
- Consider assessing baseline blood viscosity in patients at risk for hyperviscosity, including those patients with cryoglobulins, fasting chylomicronemia/markedly high triglycerides, monoclonal gammopathies or polycythemia

- Hemoglobin and hematocrit, given risk of hemolysis after the infusion and within 36 to 96 hours post-infusion
- If transfusion-related acute lung injury (TRALI) is suspected, conduct appropriate tests to check for anti-neutrophil antibodies and anti-HLA antibodies in both the product and patient's serum
- Conduct cerebrospinal fluid studies if symptoms of meningitis occur.

The following signs and symptoms should be monitored during, and after infusion:

- Signs and symptoms of thrombotic events
- Urine output periodically in patients with an increased risk of acute renal failure (i.e., preexisting renal dysfunction, diabetes mellitus, volume depletion, sepsis, paraproteinemia, age ≥65 years, and those receiving concomitant nephrotoxic agents)
- Signs of infusion reaction, including fever, chills, nausea, and vomiting,
- Signs and symptoms of hemolysis
- Pulmonary adverse reactions. If transfusion-related acute lung injury (TRALI) is suspected, conduct appropriate tests to check for anti-neutrophil antibodies and anti-HLA antibodies in both the product and patient's serum
- Monitor vital signs during the IV infusion
- Monitor for signs and symptoms of volume overload
- Perform a neurological exam if meningitis symptoms occur

Diagnosis and Treatment of IVIG -Related Infusion Reactions

Infusion reactions generally appear 30 minutes to 1 hour after initiation of the infusion and might also be associated with flushing of the face, tightness in the chest, chills, fever, dizziness, nausea, vomiting, diaphoresis, and hypotension or hypertension. The investigators will closely monitor for adverse reactions throughout the infusion. IVIG may cause a precipitous fall in blood pressure and clinical manifestations of anaphylaxis, which appear to be related to the rate of IVIG infusion; do not exceed the recommended rate of infusion.

If infusion reactions occur, sites should follow local institutional protocols for management of infusion reactions. For example, if flushing and changes in blood pressure, temperature or pulse occur with the infusion, slow or temporarily stop the infusion. In some cases, when symptoms subside the infusion may be resumed at a rate that is comfortable for the patient. The infusion will be stopped immediately if anaphylaxis or other severe reactions occur. Immediate AEs can be treated by the slowing or temporary discontinuation of the infusion and symptomatic therapy with analgesics, nonsteroidal anti-inflammatory drugs, antihistamines, and glucocorticoids in more severe reactions. Slow infusion rate of low concentration of IVIG products and

hydration, especially in high-risk patients, may prevent renal failure, thromboembolic events, and aseptic meningitis.

Risk of Transmissible Agents with IVIG:

IVIG is a derivative of human blood. As with other products derived from or purified with human blood components, the remote possibility of contamination with bacterial or viral infection, including hepatitis, or Creutzfeldt-Jakob disease (CJD) exists in patients receiving IVIG. Screening plasma donors for prior exposure to certain viruses, testing for the presence of viruses, and inactivating and/or reducing viruses has reduced the risk of transmission of infectious agents; however, none of the processes are completely effective. Some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate.

8.2.9 Incompatibilities

Contraindications:

IVIG should not be administered to patients with a history of anaphylaxis or severe systemic reaction to human immune globulin. This agent is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline. Privigen, Gammagard Liquid and Gamunex-C are contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

- Drug Interactions:
- Hypersensitivity: As outlined above, if this occurs stop IVIG and institute appropriate supportive treatment

Pregnancy

It is not known whether IVIG may cause fetal harm. Patients will be strongly encouraged to use contraception during this study, if of child-bearing potential. IVIG should not be given to breastfeeding mothers as the penetration of the agent into breastmilk is unknown.

8.2.10 Availability

The drug will be provided by the treating investigator at the study site. IVIG is included in national guidelines (ASCO, SITC, and NCCN), and will be billed to the patient's insurance. This study will not be conducted under an IND.

8.2.11 Side Effects

Adverse reactions have been reported in approximately 2-25% of all IVIG infusions, in reported clinical studies and post-marketing evaluations. The majority of adverse reactions associated with IVIG are minor, transient, and infusion-related. However, serious systemic reactions affecting renal, cardiovascular, central nervous system, integumentary, and hematological systems have been reported. Potential risk factors affecting the risk and intensity of adverse events include the underlying condition and pre-existing cardiovascular or renal disease, as well as IVIG formulation, lot number, dose, concentration, and rate of infusion. Conservative product-specific infusion rates should be initiated and patients should be monitored

closely throughout each infusion. Particular care should be taken when patients are IVIG-naïve.

Adverse events following IVIG infusions may be classified as immediate (occurring during the infusion itself) or delayed (occurring after the infusion has ceased). The rate of IVIG infusions should be low at the beginning and increased every 15-30 min, based on the patient's tolerance.

Common adverse effects of IVIG include: hypertension (6-8%), hypotension (11%), increased heart rate (11-22%), edema (8.2%), injection site reaction (5-98%), pruritus (6-8%), rash (4.1-7.8%), urticaria (5-8.2%), increased body temperature (2-4%), diarrhea (6-28%), nausea (5- 26%), vomiting (7- 23%), arthralgia (3.9-13%), myalgia (5-20%), limb pain (6.4-11.5%), asthenia (5-10%), dizziness (< 13.1%), headache (8-64.9%), otalgia (6.4-18%), asthma (8.5-29%), cough (6-26%), nasal congestion (13-15%), throat pain (6.4-6.8%).

Reported serious side effects of IVIG by organ system include:

- Cardiovascular: Chest discomfort (5-9%), Chest pain (5-11%), Myocardial infarction, Tachycardia (5% - 22%)
- Endocrine metabolic: Hyponatremia
- Hematologic: Hemolysis, Hemolytic anemia, Thrombosis (Primary humoral immunodeficiency, 2%; immune thrombocytopenic purpura, 22%)
- Hepatic: Hepatitis C
- Immunologic: Anaphylaxis/Hypersensitivity reactions
- Musculoskeletal: Backache (3.9-28%)
- Neurologic: Aseptic meningitis (0.02%)
- Renal: Acute renal failure, Hypokalemic nephropathy
- Respiratory: Pulmonary embolism (0.9%), Transfusion-related acute lung injury

8.2.12 Nursing/Patient Implications

Patients should be informed that IVIG is made from human blood and may contain infectious agents that can cause disease, such as viruses and CJD. Explain that the risk of transmission of an infection through Privigen, Gammagard Liquid and Gamunex-C have been reduced by screening plasma donors and testing donated plasma. Patients should be informed that IVIG may interfere with a response to live vaccines.

8.2.13 References

Privigen package insert

CSL Behring AG, Bern, Switzerland.

Gammagard Liquid package insert

Baxalta US Inc., Westlake, CA, USA

Gamunex-C package insert

Grifols USA, Research Triangle Park, NC, USA

8.3 Prednisone

8.3.1 Other Names

Deltasone, Orasone, Medicorten, Panasol-S, Liquid-Pred, others

8.3.2 Classification

Adrenal corticosteroid.

8.3.3 Mode of Action

Prednisone is a potent synthetic glucocorticoid that affects almost every body system. It has anti-inflammatory, immunosuppressant, and minimal mineralocorticoid activity, and antineoplastic properties. As an antineoplastic agent, prednisone may bind to specific proteins (receptors) within the cell forming a steroid-receptor complex. Binding of the receptor-steroid complex with nuclear chromatin alters mRNA and protein synthesis within the cell.

8.3.4 Storage and Stability

The drug is stored at room temperature in a dry place. Refer to the package insert from the manufacturer for storage specifics.

8.3.5 Dose Specifics

4-6 week corticosteroid taper, starting from a dose of prednisone 1-2mg/kg either orally or intravenously in divided doses, and determined by the treating investigator.

8.3.6 Administration

Prednisone is taken orally (with food or a meal) or intravenously in divided doses, as determined by the treating investigator. A pill calendar will be provided to patients. See Appendix VIII.

8.3.7 Availability

Commercially available in 1, 2.5, 5, 10, 20, 25 and 50 mg tablets. Also available as a 1 mg/ml oral solution or syrup and as a 5 mg/mL oral solution.

8.3.8 Side Effects

1. Gastrointestinal: Nausea, vomiting, anorexia; increased appetite and weight gain; peptic ulceration.
2. Dermatologic: Rash; skin atrophy; facial hair growth, acne, facial erythema; ecchymoses.
3. Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities), urinary frequency.
4. Neurologic: Insomnia; muscle weakness; euphoria, psychosis, depression; headache, vertigo, seizures.
5. Cardiovascular: Fluid retention and edema; hypertension.
6. Ocular: Cataracts; increased intraocular pressure; exophthalmos.

7. Metabolic: Hyperglycemia; decreased glucose tolerance; aggravation or precipitation of diabetes mellitus; adrenal suppression; Cushingoid features; hypokalemia.
8. Hematologic: Leukocytosis.
9. Other: Osteoporosis (and resulting back pain); serious infections including herpes zoster, varicella zoster, fungal infections, pneumocystis carinii, tuberculosis; muscle wasting; delayed wound healing; suppression of reactions to skin tests.

8.3.9 Nursing Implications

1. Instruct patients to take prednisone after meals. Should not be taken too close to bedtime to avoid insomnia. A mild sedative may be required.
2. GI symptoms should be treated symptomatically.
3. Monitor blood glucose levels.
4. Educate patient concerning potential mood swings.

NOTE: Please refer to the commercially-available package labeling for more information.

8.3.10 References

1. Pickup ME: Clinical pharmacokinetics of prednisone and prednisolone. Clin Pharmacokinet 4:111-128, 1979.
2. The Boston Collaborative Drug Surveillance Program: Acute reactions to prednisone in relation to dosage. J Clin Pharmacol 13:694-698, 1972.
3. Ling MHM, Perry PJ, Tsuang MT: Side effects of corticosteroid therapy: Psychiatric aspects. Arch Gen Psychiatry 38:471-477, 1981.

8.4 Methylprednisolone

Rev. Add2

8.4.1 Other Names

Methylprednisolone sodium succinate (Solu-Medrol), methylprednisolone acetate (Depo-Medrol), Methylprednisolone (Medrol), others.

8.4.2 Classification

Adrenal corticosteroid

8.4.3 Mode of Action

Methylprednisolone is a potent synthetic glucocorticoid that affects almost every body system. It has anti-inflammatory, immunosuppressant, and minimal mineralocorticoid activity, and antineoplastic properties. As an antineoplastic agent, methylprednisolone may bind to specific proteins (receptors) within the cell forming a steroid-receptor complex. Binding of the receptor-steroid complex with nuclear chromatin alters mRNS and protein synthesis within the cell.

8.4.4 Storage and Stability

The intact vials are stored at room temperature. After reconstitution, the solution is stable for 48 hours at room temperature. When further diluted in dextrose 5% or normal saline, concentrations of < 0.25 mg/ml are stable for 24 hours when refrigerated; concentrations > 0.25 mg/ml are stable for 4 hours when refrigerated.

8.4.5 Dose Specifics

4-6 week corticosteroid taper, starting from a dose of methylprednisolone at a dose equivalent to 1-2mg/kg of prednisone either orally or intravenously in divided doses, and determined by the treating investigator. Methylprednisolone 0.8mg/kg either orally or intravenously is the equivalent of 1mg/kg of prednisone.

8.4.6 Preparation

The 40 mg vial of methylprednisolone sodium succinate is reconstituted with 1 ml of the provided diluent or bacteriostatic water, resulting in a concentration of 40 mg/ml. The 125 mg, 500 mg, and 1 gm vials are reconstituted with 2, 8, and 16 ml, resulting in a concentration of 62.5 mg/ml. The 2 gm vials are reconstituted with 30 ml, resulting in a concentration of 65.3 mg/ml.

Rev. Add2

8.4.7 Route of Administration

Methylprednisolone sodium succinate is administered intravenously over one to several minutes or intramuscularly. Methylprednisolone sodium succinate is administered intramuscularly, intra-articularly, or intralesionally. Methylprednisolone may also be administered orally taken with food or a meal.

8.4.8 Incompatibilities

Stability with intravenous fluids and additives varies with concentration; consult your pharmacist for specific information. Drugs that induce hepatic microsomal enzymes (phenytoin, barbiturates, rifampin) accelerate the metabolism of methylprednisolone.

Rev. Add2

8.4.9 Availability

The sodium succinate salt is commercially available as a powder for injection with provided diluent in 40, 125, 500, 1000, and 2000 mg vials. The acetate salt is available in 20, 40, and 80 mg/ml vials. Oral methylprednisolone is available in 2, 4, 8, 16, and 32 mg tablets.

8.4.10 Side Effects

1. Hematologic Leukocytosis
2. Gastrointestinal: Nausea, vomiting, anorexia; increased appetite and weight gain; peptic ulceration.
3. Dermatologic: Rash; skin atrophy; facial hair growth, acne, facial erythema; ecchymoses.
4. Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities).

5. Neurologic: Insomnia; muscle weakness; euphoria, psychosis, depression; headache, vertigo, seizures.
6. Cardiovascular: Fluid retention and edema; hypertension; hypokalemia.
7. Ocular: Cataracts; increased intraocular pressure; exophthalmos.
8. Metabolic: Hyperglycemia; decreased glucose tolerance; aggravation or precipitation of diabetes mellitus; adrenal suppression; redistribution of body fat (truncal obesity, moon facies, cervical fat deposition).
9. Musculoskeletal: Muscle wasting, osteoporosis (and resulting back pain).
10. Other: Serious infections including herpes zoster, varicella zoster, fungal infections, pneumocystis carinii, tuberculosis; muscle wasting; delayed wound healing.

8.4.11 Nursing Implications

1. GI symptoms should be treated symptomatically.
2. Monitor blood glucose levels and blood pressure.
3. Educate patient concerning potential mood swings.
4. If used longer than 1-2 weeks, educate patient about long-term side effects.
5. If used longer than 1-2 weeks, doses should be tapered prior to withdrawal.

8.4.12 References

1. Derendorf H et al. Kinetics of methylprednisolone and its hemisuccinate ester. Clin Pharmacol Ther 37:502-7, 1985.
2. The Boston Collaborative Drug Surveillance Program. Acute reactions to prednisone in relation to dosage. J Clin Pharmacol 13:694-698, 1972.
3. Ling MHM, Perry PJ, Tsuang MT. Side effects of corticosteroid therapy: psychiatric aspects. Arch Gen Psychiatry 38:471-477, 1981.

9. Statistical Considerations

This is a study with 1-step registration and two randomized arms. The main interest of this study is to assess pneumonitis response to an additional immunosuppressive agent (either infliximab or IVIG) in patients with steroid-refractory pneumonitis in order to inform future more definitive research. This study is not designed to compare infliximab vs. IVIG due to the rarity of the patient population, however a randomized design will ensure balance between patients enrolled in each arm.

The primary outcome, pneumonitis response, is defined as an improvement of ≥ 20% in the PaO2/FiO2 ratio at Day 28 compared to Day 1 of the protocol treatment. This is assessed as in Section 6.1. This is measured by arterial blood gas assessment (obtained by arterial puncture, or from an indwelling arterial catheter), and recording of the fraction of inspired oxygen the patient is receiving. For the assessment of the primary outcome of the study, this ratio will be calculated at Day 28 after receipt of additional immunosuppression (infliximab or IVIG), and compared with the PaO2/FiO2 calculated on Day 1 of receipt of additional immunosuppression. Secondary outcome include radiologic and functional measurement of pneumonitis, patient-reported outcome, death, and infection. Exploratory outcomes include blood/serum biomarkers for steroid-refractory pneumonitis.

Rev. Add4

9.1 Study Design

For either immunosuppression arm, 16 patients will be needed in order to detect an improvement in pneumonitis response from 5% to 25%, using one sample exact binomial test with type I error (one-sided) of 4.3% for the null and power of 80.3% for the alternative. Assuming a 10% ineligibility rate, 18 patients will be enrolled into each arm. If at least three patients are reported with pneumonitis response on Day 28 after the initiation of study treatment among the 16 eligible and treated patients, the new agent will be considered promising.

9.2 Accrual Goal and Rate

For either arm, 18 patients will be enrolled, leading to the accrual of 36 patients in total for this study. With the expectation of approximately 1-2 patients per month to this trial, it is estimated that the accrual for this study will take approximately 24 months.

9.3 Analysis Plan

The analysis plan described below will be performed on eligible and treated patients only unless specified otherwise.

9.3.1 Primary Objective

The primary outcome of this study is pneumonitis response to infliximab or IVIG therapy. In all enrolled patients, pneumonitis response will be defined as an improvement in PaO2/FiO2 of ≥20% measured by arterial blood gas assessment (PaO2) and recording of the fraction of inspired oxygen (FiO2) received by the patient at the time of the arterial blood gas assessment, on Day 28 compared with Day 1. In patients who discontinue protocol therapy early or cannot complete an arterial blood gas assessment on either Day 1 or Day 28, this will be deemed as a failed event. However, if a patient develops progressive cancer during the study time period and this is deemed to be of greater clinical significance than pneumonitis and requiring

discontinuation from the protocol therapy for cancer therapy, this patient will be replaced and excluded from the primary objective analysis. This response rate will be reported with a proportion and its 90% confidence interval for each treatment arm. A comparison on the pneumonitis response rate between the two arms (infliximab vs. IVIG) will be performed using Fisher's exact test. However, this comparison will be exploratory as steroid-refractory pneumonitis is a rare phenomenon and the current study is not designed to detect any significant difference between arms.

9.3.2 Secondary Objectives

Radiologic features of steroid-refractory pneumonitis will be assessed by the extent and distributions of the parenchymal abnormalities and the qualitative assessment of the lung volumes on CT. These outcomes will be assessed three times – first at Day 1 of study treatment, second Day 14 after initiation of study treatment, and the last on Day 28 after the initiation of study treatment. On review of the scans taken on Day 14 and Day 28, comparisons will be made between the current scan and the on from Day 1. The pneumonitis and lung volume will be graded "Definitely decreased", "Probably decreased", "No significant change", "Probably increased" and "Definitely increased". Response to study therapy will be defined by combining the categories "Definitely decreased" and "Probably decreased". The response rate will be compared between the arms using Fisher's exact test.

Functional features and patient-reported outcomes of pneumonitis will be assessed three times as well - first at baseline (Day 1 of study treatment), second on Day 14 after the initiation of study treatment, and the last on Day 28 after the initiation of study treatment. Functional features of pneumonitis will be assessed by spirometry (FVC, FEV1), diffusion capacity of the lung (DLCO) and oxygen saturation on room air at rest, collected as part of the vital signs; These quantitative measures will be reported descriptively (by median, mean, and range) by timepoints and treatment arms. Pneumonitis improvement (from Day 1 to Day 14 and from Day 1 to Day 28) by each measure will be evaluated using the Wilcoxon signed-rank tests, by arm, without statistical adjustments.

Patient-reported outcomes of pneumonitis will be measured by questionnaires (FACT-L (version 4) and the Borg scale). FACT-L consists of 5 subscales - physical well-being (PWB, 7 items), social/family welling-being (EWB, 7 items), emotional well-being (EWB, 6 items), functional well-being (FWB, 7 items), and additional concerns (10 items, but subscale score is computed based on the 7 symptom items only). Each FACT-L subscale score will be computed separately (per the guidelines posted at https://www.facit.org). The primary outcome from FACT-L is the Trial Outcome Index (TOI), which is the sum of the scores from PWB, FWB, and lung-symptom (7 items) Subscales. The lung-symptom subscale score is the sum of 7 symptom items from the Additional Concerns Subscale, excluding the ones related with hair loss and smoking). All FACT-L questions (except for the smoke history, no vs. yes) are rated on a five-point

Likert scale (ranging from 0 “not at all” to 4 “very much”). Negatively worded items will be reversely scored. The TOI score will thus range from 0-84, with higher scores representing better QOL. The one-item Borg Dyspnea score is ranging from 0 “Nothing at all” to 10 “maximal”, with higher rating signifying more intensity or severity of breathlessness. These quantitative measures will be reported descriptively (by median, mean, and range) by timepoints and treatment arms. Pneumonitis improvement (from Day 1 to Day 14 and from Day 1 to Day 28) by each measure will be evaluated using the Wilcoxon signed-rank tests, by arm, without statistical adjustments.

Death reported in the 28-day period after additional immunosuppression will be tabulated by treatment arm, and classified as pneumonitis-related, immunosuppression-related, disease-related or other.

The number and severity of treatment-related adverse events from infections in any organ system by the CTCAE reported in the 28-day period after additional immunosuppression, will be tabulated by treatment arm. This analysis will include all patients starting protocol therapy regardless of eligibility.

Rev. Add4

9.3.3 Correlative Objectives

Potential blood/serum biomarkers for pneumonitis will be assessed from serially collected blood/serum in accrued patients (on Days 1, 14 and 28 after study treatment) and controls, whose blood/serum will be obtained as part of a parallel tissue-collection protocol. Assays for these samples will include: cytokine assays, autoantibody assays, MANAFEST assay and AUTOFEST assay. Autoantibodies, T-cell expansions (negative/positive), and cytokine levels (e.g., IFN-ɣ, IL-17, and VEG-F) will be summarized descriptively in patients with pneumonitis vs. controls, by timepoint and treatment arm (when appropriate). Fisher’s exact test will be used to evaluate associations of pneumonitis (Yes/No) with autoantibodies, T-cell expansions (negative/positive), and baseline cytokines (dichotomized by the median of each cytokine).

Given the phenomenon of steroid-refractory pneumonitis is rare and a small number of these patients will be accrued to this trial, all the correlative analyses performed in this study will be explorative in nature.

9.4 Monitoring Plan

Study Progress and Safety Reports are prepared twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2.

9.5 Gender and Ethnicity

The anticipated accrual in subgroups defined by race, ethnicity and gender is as follows:

Racial Categories	Not Hispanic/Latino		Hispanic/Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	1	2	0	0	3
White	15	17	0	1	33
Total	16	19	0	1	36

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

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10. Specimen Submissions

Representative original diagnostic tumor, and blood specimens are to be submitted for use in the research studies outlined in Section 11.

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KITS: Kits are available only for US and Canadian sites for the submission of the blood samples to the D'Alessio Laboratory. Kit supplies are limited, therefore starter kits are not to be ordered. It is requested that kits be ordered after patient has consented to participate in the trial and has been determined to be eligible to register. To order kits follow the instructions outlined in Appendix X of the protocol. Kits will arrive within 3-5 working days from when the order is placed. Institutional supplies are requested to be utilized if kits are not available.

All specimens must be labeled with the ECOG-ACRIN protocol number, the patient's initials and ECOG-ACRIN sequence number, the collection date, and the type of sample. For pathology materials, it is strongly recommended that full patient names be provided.

All specimens must be logged and tracked via the ECOG-ACRIN Sample Tracking System (STS) Web Application (Section 10.3) and submitted with an STS-generated shipping manifest. Specimens not available for submission are to be indicated in STS as well.

10.1 Tissue Submissions to the ECOG-ACRIN Central Biopathology and Pathology Facility

Submit from patients who answer "Yes" to "I agree that my samples and related health information may be used for the laboratory studies described above."

Guidelines for pathologists are provided in Appendix I.

10.1.1 Tissue Submission Requirements

Formalin-fixed paraffin-embedded tumor tissue block(s) are to be submitted.

a. Pre-trial diagnostic FFPE Tumor tissue: the optimal block is 70% tumor tissue with preferred specimen size as follows:
   - Surface area: 25mm^2 is optimal. Minimum is 5mm^2
   - Volume: 1mm^3 optimal. Minimum volume is 0.2mm^3

NOTE: If blocks are not available for submission, the following alternative is to be submitted, in the indicated order of availability:
- 1 H&E (from the source block),
- 20 unstained slides. The optimal quantity of tissue requested should be equivalent to the amount indicated above. Slides and H&E must be numbered in the order cut.
- 1-2 tissue core punches

The relevant pathology and surgical reports must accompany all tissue submissions:
- Copy of the diagnostic or surgical Pathology Report
- Other Immunologic and cytologic reports
- STS generated shipping manifest for all submitted tissue.

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10.1.2 Shipping Procedures

Tissue samples are to be shipped at ambient (use a cool pack in warm weather). Shipping manifest generated from the ECOG-ACRIN STS system must accompany the samples.

Shipments to the MD Anderson Life Sciences Plaza may be done using the ECOG-ACRIN Central Biorepository and Pathology Facility (EA-CBPF) FedEx account. This account may NOT be used for shipment of materials to any other facility. Access to the shipping account for specimen shipments to the ECOG-ACRIN CBPF at MD Anderson can now only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

Ship to:

MD Anderson Cancer Center CBPF
Mike Balco
Life Science Plaza – Suite 910
2130 West Holcombe Blvd, LSP9.4227
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506

10.2 Submissions to the D'Alessio Laboratory

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10.2.1 **Blood Submissions (MANDATORY)**

Peripheral blood samples must be shipped the day they are drawn. If you have any questions concerning collection and shipment please contact the Johns Hopkins and Asthma & Allergy Center, Attention Dr. D'Alessio or Andres Villabona-Rueba at email: avillab1@jhmi.edu or phone: 410-550-2612.

NOTE: Local processing instructions are provided in Section 10.2.1.2 below if blood is collected on Fridays or a day before a holiday by a US site and for all specimens collected by an international site.

10.2.1.1 Sample Preparation Guidelines

Please completely fill all blood tubes as full as possible and collect the correct number and tube type as outlined below.

Peripheral blood samples are to be collected:

- Day 1 (+/- 5 days)
- Day 14 (+/-5 days)
- Day 28 (+/-5 days)

At **each** time point please submit the following:

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- Seven (7) FULL 10cc green top heparin tubes

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10.2.1.2 Guidelines for Local Blood Processing

The following instructions are for International sites and for sites who cannot avoid collecting samples on a Friday or day before a holiday.

Local supplies are to be utilized to process, store and submit blood specimens that are processed locally. No kits, no supplies, and no additional funding support are available for locally processed research blood specimens. It is essential that all samples be labeled with the protocol number, patient caseID, specimen type, and timepoint/date of collection.

Materials

Abbreviation	Name
PBS	Phosphate-buffered saline
ACK	ACK lysing buffer
RLT buffer	Qiagen Buffer RLT lysis buffer
2-ME	2-Mercaptoethanol
Freezing media	BAMBANKER
Cell strainer	Cell strainer 70um

Processing Protocol:

1. Read the directions and label the vials with the buffer/freezing medium and cell count. Provide the information in STS.
2. Spin down the cells at 350g for 6 min at 4° C.
3. Remove and SAVE all supernatant.
   a. The first 5mL should be aliquoted out in 1mL cryogenic vials.
   b. The remaining supernatant can be stored in 15 mL conical tubes (10mL per tube).
4. Re-suspend cells in PBS according the pellet size (for good size pellet we use 5mL).
   a. If there is an exceptional amount of mucus present which does not allow to do cell count: filter the sample using a 70um cell strainer and wash the filter with 5mL PBS twice.
   b. If presence of red blood cells use ACK. The volume of ACK to use depends on the pellet size. (We usually do 3mL for 3mins in good size pellet)
5. Do cell count.
6. Aliquot small cell amount for Cytospin (50,000 to 150,000 cells).
   a. Cytospin is done when having high cell counts.
7. Spin down the cells at 350g for 6 min at 4° C.

8. Remove supernatant and re-suspend in freezing media according to cell count
   a. 2x106/tube in freezing medium for future FACS.
   b. 5x105 cell in 350uL RLT buffer and 3.3uL 2-ME.
   c. 1x105 cell/tube in freezing medium for TCR.
9. Store the cells below -80° C. Ship on dry ice within one week of collection.

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Ship to:

Johns Hopkins Asthma & Allergy Center
Asthma and Allergy Building, Room 4A.44
Johns Hopkins Bayview
5501 Hopkins Bayview Circle
Baltimore, MD, 21224
Email: avillab1@jhmi.edu
Phone: 410-550-2612

10.3 ECOG-ACRIN Sample Tracking System

It is **required** (barring special circumstances) that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). Samples which are not available for submission are also to be noted within STS.

The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest must be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu .

Study Specific Notes:

If the STS is unavailable, the Generic Specimen Submission Form (#2981) is to be used as a substitute for the STS shipping manifest. The completed form is to be faxed to the receiving laboratory the day the samples are shipped. Indicate the appropriate Lab on the submission form:

- Johns Hopkins Asthma & Allergy Center

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- MDACC Life Sciences Plaza

Retroactively enter all specimen collection and shipping information when STS is available.

10.4 Use of Specimens in Research

Materials will be processed and distributed to investigators for analysis for the research studies defined in Section 11.

Specimens from patients who consented to allow their specimens to be used for undefined future ECOG-ACRIN approved research studies, including residuals from the mandatory diagnostic review, will be retained in an ECOG-ACRIN designated central repository.

For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility.

Specimens submitted will be processed to maximize their utility for current and future research projects. Tissue processing may include, but not limited to, extraction of DNA and RNA and construction of tissue microarrays (TMAs). DNA, RNA, serum, and plasma (if appropriate) will be isolated from the submitted peripheral blood specimens.

Any residual blocks will be available for purposes of individual patient management on specific written request.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future research study. Pathology materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository.

10.5 Sample Inventory Submission Guidelines

Inventories of all samples submitted will be tracked via the ECOG-ACRIN STS and receipt and\ usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized will be submitted by the laboratory to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

Rev. Add4 **11. Specimen Analyses: Diagnostic Review and Research Studies**

Rev. Add4 11.1 Blood: MANAFEST and AUTOFEST

With increasing appreciation that mutation-associated neoantigens (MANA) are an important target of anti-tumor T cell immunity and potential immune toxicity, simple and sensitive assays are critical to assess the broad repertoire of functional MANA-specific T cells in cancer patients. MANAFEST (Mutation Associated NeoAntigen Functional Expansion of Specific T-cells),[14] integrates predicted MANAs identified through large-scale genomic sequencing (Section 11.3) and computational modeling with single short term in vitro stimulation and deep sequencing of CDR3 regions to identify the repertoire of MANA-specific T cells in cancer patients based on antigen-specific clonal expansion. Each CDR3 from expanded clones can then be used as a molecular barcode to identify and quantitate MANA-specific T cells in tumor sections and blood. To evaluate linkage between antibody (Section 11.4) and T-cell responses, the FEST assay, used previously in NSCLC patients with acquired resistance to anti-PD-1, to detect peripheral T-cell reactivity to mutation-associated neoantigens (MANAs) in resistant tumors, can also be used to evaluate CD-4 responses. In this study, this assay will also be used to evaluate CD4+ reactivity to autoantigens (AUTOFEST), together with MANAFEST-evaluated CD 8 responses to mutant peptides from patients' tumors, and if detected, assessment for possible cross-reactivity to wild-type peptide resulting in irAE. In this proposal, we would identify autoantibody hits to possible tumor mutations using pneumonitis patient sera and controls, and perform genomic sequencing of genes encoding identified autoantigens, using available tumor DNA. These assessments will be conducted by Kellie N. Smith, PhD and Drew M Pardoll, M.D., PhD, Department of Immunology at Johns Hopkins University.

Sample Acquisition and Processing

Blood samples will be taken as in Figure 1 (Section 11), and from patients enrolled in a JHU specimen collection study who did not develop irAEs, these patients will act as pre/post-PD-1 controls and will be matched as closely as possible for clinical and treatment characteristics. Blood will be shipped from participating study sites to JHU for processing.

Methodology, Equipment and Reagents

DNA will be extracted from peptide-stimulated T cells, archival tumor tissue, and pre- and post-treatment PBMC using a Qiagen DNA FFPE kit, DNA blood kit, or DNA blood mini kit (Qiagen). TCR Vb CDR3 sequencing will be performed using the survey (tissue and cultured cells) or deep (PBMC) resolution Immunoseq platforms (Adaptive Biotechnologies, Seattle, WA).[46] Bioinformatic and biostatistical analysis of productive clones will be performed to assess the dynamics of peripheral T cells and to identify antigen-specific expansions. We will measure MANA-specific TCR expansions in stimulated cultures of autologous T cells. To assess T cell responses to autoantigens, candidate MHC class I and class II restricted epitopes respectively will be predicted from serologically identified autoantigens in (a) and analyzed by AUTOFEST. For MHCII restricted $CD4^+$ responses, peptide epitopes (20-mers overlapping by 10 amino acids) will be synthesized and used to stimulate autologous pre- and post-treatment $CD4^+$ T cells cultured for 10-days in the presence of cytokines. For $CD8^+$ responses, NetMHCpan-predicted peptides matched to patient HLA-A and

–B alleles, will be tested. On day 10, we will isolate $CD4^+$ T-cells and $CD8^+$ T-cells respectively using negative bead selection, and assess functionality. TCR Vβ deep sequencing will be performed on FFPE. This will allow us to match intratumoral TCR Vβ sequences with autoantigen specificity identified above. These will allow us to evaluate dynamic immunologic responses in pneumonitis.

Quantification of Results

We will present graphical representations of the genomic landscape pre-treatment tumor tissue, and candidate MANAs detected in pre-treatment tumor tissue following after implementation of the neoantigen prediction pipeline. Epitope-specific expansion of each T cell clone detected in a culture will be compared to expansion of that clone in culture that did not undergo peptide stimulation and to every other peptide-stimulated culture. T-cell reactivity to a given epitope will be considered positive if there is at least 1 T-cell clone with significant expansion to the relevant peptide and every other peptide tested at a significance of <0.01 and an odds ratio of >5 to allow for sensitive, and specific antigen recognition. Autoantibodies, T-cell expansion, and cytokine levels will be summarized descriptively in pneumonitis vs. controls, by timepoint and treatment arm.

11.2 Blood: Autoantibody Analyses (MANDATORY)

Autoantibody formation has been identified as a mechanism implicated in selected irAEs including CTLA4-mediated hypophysitis,[47] and PD-1- thyroiditis.[48] These clinical observations have been made based on routine ELISA assays. We now have newer tools that allow us to link autoantibody to T-cell responses, through detection of antigen specific T-cell clones by TCR sequencing (outlines in Section 11.4), in both peripheral blood and tissue.[25,26,27] We will leverage expertise in antibody discovery at JHU, as previously described in scleroderma patients with POL3RA-mutant cancers.[6] In these cases, antibodies were identified using a novel immunoprecipitation (IP) assay followed by mass spectrometry sequencing, using patient sera pre/post event (present post, absent pre),[32] based on molecular weights in the initial IP step and rigorous candidate autoantigen validation.[7-12] We will also evaluate the linkage between antibody and T-cell responses, through AUTOFEST, as outlined above. These studies will be conducted by Kellie N. Smith, PhD. Department of Immunology and Livia Casciola-Rosen. Department of Rheumatology at Johns Hopkins University.

Sample Acquisition and Processing

Blood samples will be taken as in Figure 1 (Section 11), and from patients enrolled in a JHU specimen collection study who did not develop irAEs, these patients will act as pre/post-PD-1 controls and will be matched as closely as possible for clinical and treatment characteristics.

11.3 Blood: Cytokine Analyses (MANDATORY)

It is postulated that irAEs may be an autoantibody-mediated condition, and that baseline and on-treatment elevations of certain cytokines may support this mechanism. Baseline IL17 levels have been elevated in melanoma patients who developed CTLA4-colitis. Cytokines such as 1L-17, IFN-γ and IL-4 are known to support humoral responses, via Fc region switching and increased immunoglobulin production.[24,25] Moreover, colleagues at JHU identified that an elevated Th17/T-reg ratio has been associated with early acute respiratory

distress syndrome (ARDS), a similar diffuse alveolar damage process to PD-1/PD-L1 pneumonitis.[26] Thus, we propose that pneumonitis may be an autoantibody mediated process against tumor and/or self-antigens, identification of which could identify tumor-related biomarkers, or specific pneumonitis treatments (IVIG, IL17 mAb). These studies will be conducted by Kellie N. Smith, PhD. and Drew M. Pardoll, MD PhD. Department of Immunology at Johns Hopkins University.

Sample Acquisition and Processing

Blood samples will be taken as in Figure 1 (Section 11), and from patients enrolled in a JHU specimen collection study who did not develop irAEs, these patients will act as pre/post-PD-1 controls and will be matched as closely as possible for clinical and treatment characteristics.

Methodology, Equipment and Reagents

Positive peptides identified by AUTOFEST will be used in ELISpot and ICS assays to assess cytokine production at pre/post immunosuppression/PD-1, and in controls.

11.4 Sample Inventory Submission Guidelines

Inventories of all samples submitted will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for the will be submitted by the laboratory to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

11.5 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operations Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator. The quarterly cut-off dates are March 31, June 30, September 30, and December 31. Data is due at the ECOG-ACRIN Operations Office - Boston 1 week after these cut-off dates.

12. Electronic Data Capture

Please refer to the **EAQ172** Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for EAQ172
4. ECOG-ACRIN Generic Specimen Submission Form (#2981)

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Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG Pathology Coordinating Office:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- ECOG-ACRIN Sample Tracking System (STS)-Generated Shipping Manifest

Instructions:

5. Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, will expedite any required communications with the institution (including site pathologists).
6. List required path materials for each specified timepoint separately, as per below

   b) Tumor tissue: Block. If block cannot be submit one H&E and at least 10 slides (number the slides in the order sectioned). Provide the Type of sample (cytology, core biopsy, resection specimen) and Source of tissue (e.g., lung, liver)
7. Since blocks are being used for laboratory studies, the materials may potentially be exhausted. It is important that the site retains what they need for purposes of patient care and management.
8. Keep a copy of the STS-manifest or Submission Form for your records.
9. Double-check that ALL required forms, reports and pathology samples are included in the package.

Pathology specimens submitted WILL NOT be processed by the Pathology Coordinating Office until all necessary items are received.

Mail pathology materials to:

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MD Anderson Cancer Center CBPF
Mike Balco
Life Science Plaza - Suite 910
2130 West Holcombe Boulevard, LSP9.4227
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility.

ECOG-ACRIN cancer research group
Reshaping the future of patient care

Operations Office

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Edmund Lattime, PhD, Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: Submission of Pathology Materials for EAQ172

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for laboratory studies.

Keep a copy of the submission for your records and return any relevant completed forms, the surgical pathology report(s), the slides and/or blocks and any other required material (see List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF).

Pathology materials submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies per patient consent. Paraffin blocks will be returned upon request for purposes of patient management.

Please note: Since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at (1-844-744-2420 (713-745-4440 Local or International Sites) or email: pillei1@jhmi.edu.

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address: _____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

Optimizing Immunosuppression for Steroid-Refractory Anti-PD-1/PD-L1 Pneumonitis

Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Appendix III

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Optimizing Immunosuppression for Steroid-Refractory Anti-PD-1/PD-L1 Pneumonitis

Appendix IV

Calculation of PaO2/FiO2 Ratio

Guidelines for assessment of PaO2/FiO2 ratio

- PaO2/FiO2 ratio is the ratio derived from dividing the partial pressure of arterial oxygen (PaO2), by the FiO2, or fraction of inspired oxygen that a study subject is receiving.
- The PaO2/FiO2 is a measurement of oxygenation that is commonly used in mechanically ventilated patients.
- A normal PaO2/FiO2 ratio is 300-500. Values that are lower than <300 are considered abnormal and reflect abnormal gas exchange in the lung, while values below 200 are associated with significant hypoxemia.
- The PaO2/FiO2 will be calculated from an arterial blood gas assessment obtained after 20-30 minutes of stable oxygen requirements/supplemental oxygen use, during which time the study subject can maintain Sp02 of 92-94%.
- The arterial blood gas assessment will be obtained either through arterial puncture, or by acquisition of a sample through an indwelling arterial catheter, if the study subject already has one in place.
- The FiO2 will be calculated depending on the fraction of inspired oxygen the study subject is receiving, as outlined below.
- The study subject's oxygenation by pulse oximetry, respiratory rate, and method of oxygen delivery at the time of the AGB assessment, will also be recorded by the study team in Appendix V.
- An institutional pulse oximeter device will be used to record pulse oximetry.

a) **Assessment of FIO2 (fraction of inspired oxygen)**

- Hospitalized study subjects will lie in a supine position for 20-30 minutes before FiO2 is recorded.
- Study subjects in the outpatient setting may be either seated or supine for 20-30 minutes before FiO2 is recorded.
- For patients who are on room air at the time of PaO2/FiO2 calculation:
  - FiO2 will be 0.21 (21% of room air is estimated to contain oxygen).
- For patients receiving high-flow, humidified, supplemental oxygen by facemask:
  - High-flow oxygen will be delivered at a rate of 50L/minute to minimize room air entrainment.
  - High-flow Oxygen will be delivered through a humidifier for patient comfort.
  - FiO2 setting on the high-flow machine will start at 30%, and will be titrated until the study subject maintains an SpO2 of 92-94% for 20-30 minutes.
  - Study subjects receiving supplemental oxygen by nasal cannula may be switched to high-flow oxygen by facemask as detailed above, to minimize room air entrainment. The choice to switch to facemask or mouthpiece with nasal clip (below) will be at the discretion of the treating investigator and the availability of equipment and resources at the study site.

- For patients receiving 100% supplemental oxygen through a mouthpiece with one-way valve and nose clip:
  - Study subjects receiving supplemental oxygen by nasal cannula, may be switched to 100% supplemental oxygen through a mouthpiece with one-way valve and nose clip, to minimize room air entrainment. The choice to switch to facemask or mouthpiece with nasal clip (below) will be at the discretion of the treating investigator and the availability of equipment and resources at the study site.
  - FiO2 will be 1.0
- For patients receiving supplemental oxygen through a non-invasive ventilation device (e.g. CPAP, BiPAP):
  - FiO2 settings on the non-invasive ventilation device will be titrated until the study subject maintains an SpO2 of 92-94% for 20-30 minutes.
- For patients receiving supplemental oxygen through invasive ventilation (intubation):
  - FiO2 settings on invasive ventilation will be titrated until the study subject maintains an SpO2 of 92-94% for 20-30 minutes.
  - The PEEP (positive end expiratory pressure) on the ventilator will be set at ≥ 5mmHg.
  - The tidal volume will be set at 6-8ml/kg of predicted body weight.
- The FiO2 will be recorded by the study team as outlined in Appendix V.

b) **Assessment of PaO2: Arterial Blood Gas assessment**

- The ABG (arterial blood gas assessment) will be obtained after the study subject has received 20-30 minutes of stable oxygen requirement/use and the FiO2 has been recorded, as outlined above.
- The ABG will be obtained by either arterial puncture, or acquisition of a sample from an indwelling arterial catheter.
- Study subjects who are hospitalized will lie flat in a supine position while this assessment is completed.
- Study subjects who are in the outpatient setting may be either be in a seated or supine position while this assessment is completed.
- For study subjects undergoing an arterial puncture for ABG assessment:
  - The area for acquisition of the sample (skin overlying radial artery) will be cleaned with an alcohol wipe.
  - The arterial blood gas assessment will be obtained using aseptic technique.
  - The sample will be obtained by local study staff.
  - The sample will be processed through a local ABG machine immediately, to yield a PaO2 result.
  - The PaO2 result will be recorded in the study case report form.
- For study subjects undergoing ABG assessment from an existing indwelling arterial catheter:
  - The tip of the arterial catheter will be cleaned with an alcohol wipe.
  - A sample of arterial blood will be obtained from the indwelling catheter, using aseptic technique.
  - The sample will be obtained by local study staff.

- The sample will be processed through a local ABG machine immediately, to yield a PaO2 result.
- The PaO2 result will be recorded in the study case report form.

Optimizing Immunosuppression for Steroid-Refractory Anti-PD-1/PD-L1 Pneumonitis

Appendix V

PaO2/FiO2 Recording Form

NOTE: The PF ratio will be measured without a bronchodilator.

_____	PaO2 (mmHg)	FiO2 (fraction)	PaO2/ FiO2 _____	Respiratory Rate	SpO2	Method of oxygen delivery (Please circle)	Method of ABG assessment (Please circle)
Day 1	_____	_____	_____	_____	_____	1. Room air 2. High-flow oxygen (facemask) 3. Oxygen (mouthpiece + nose clip) 4. Non-invasive ventilation 5. Invasive Ventilation	1. Arterial puncture 2. Arterial catheter
Day 14	_____	_____	_____	_____	_____	1. Room air 2. High-flow oxygen 3. Oxygen (mouthpiece + nose clip) 4. Non-invasive ventilation 5. Invasive Ventilation	1. Arterial puncture 2. Arterial catheter
Day 28	_____		_____	_____	_____	1. Room air 2. High-flow oxygen 3. Oxygen (mouthpiece + nose clip) 4. Non-invasive ventilation 5. Invasive Ventilation	1. Arterial puncture 2. Arterial catheter

Optimizing Immunosuppression for Steroid-Refractory Anti-PD-1/PD-L1 Pneumonitis

Appendix VI

Guidelines for Infliximab Administration

*Biosimilars and other formulations of infliximab not stated below, will not be permitted.

1. Calculate the dose, total volume of reconstituted Infliximab solution required and the number of Infliximab vials needed. Each Infliximab vial contains 100 mg of the infliximab antibody.
2. Reconstitute each Infliximab vial with 10 mL of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle as follows: Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if the lyophilized cake has not fully dissolved or if opaque particles, discoloration, or other foreign particles are present.
3. Dilute the total volume of the reconstituted Infliximab solution dose to 250 mL with sterile 0.9% Sodium Chloride Injection, USP, by withdrawing a volume equal to the volume of reconstituted Infliximab from the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag. Do not dilute the reconstituted Infliximab solution with any other diluent. Slowly add the total volume of reconstituted Infliximab solution to the 250 mL infusion bottle or bag. Gently mix. The resulting infusion concentration should range between 0.4 mg/mL and 4 mg/mL.
4. The Infliximab infusion should begin within 3 hours of reconstitution and dilution. The infusion must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less). The vials do not contain antibacterial preservatives. Therefore, any unused portion of the infusion solution should not be stored for reuse.
5. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of Infliximab with other agents. Infliximab should not be infused concomitantly in the same intravenous line with other agents.
6. Parenteral drug products should be inspected visually before and after reconstitution for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.

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Appendix VII

Instructions for IVIG Administration

*Biosimilars and other formulations of IVIG not stated below, will not be permitted.

Ordering Immunoglobulin Products:

1. Orders for immunoglobulin products must be calculated according to the patient's weight. For patients with BMI greater than 30 Kg/m^2, use adjusted body weight with 40% correction factor to determine dose.

Dispensing Immunoglobulin Products:

Immunoglobulin should be prepared and dispensed in accordance with the local Pharmacy policy and policies on drug preparation, labeling and checking.

Assessment:

1. Obtain patient's baseline height and weight on every admission.
2. For all inpatients, assess temperature, pulse, blood pressure and respiratory rate
   a. Prior to start of infusion.
   b. Every 15 minutes X 2.
   c. Then every 2 hours for the duration of the infusion.
3. Perform a visual/verbal assessment of the patient, refer to the Infusion Reaction Form, with each rate change to detect symptoms of adverse effects.
4. Maintain strict I&O (input and output) in high risk patients (e.g., pre-existing heart failure and renal failure).

Administration and Monitoring of IVIG:

1. Infuse IVIG via infusion pump or syringe pump for all areas.
2. IVIG IS NOT COMPATIBLE WITH ANY OTHER DRUG. No other medication should be concurrently administered through the IV line. Flush with D5W or NS if emergency use of the line is necessary. Privigen, Gammagard Liquid and Gamunex-C cannot be diluted or mixed with NSS. If a flush or interruption of the line is needed, D5W or NS can be used the flush the infusion line.
3. DO NOT AGITATE THE BOTTLE. TREAT IT GENTLY. Drug should not be turbid. Do not transport via the pneumatic tube.
4. It is recommended that immunoglobulin to be administered 2 hours post blood product administration.
5. Gammagard Liquid, and Gamunex-C and Privigen do not require a filter. EXCEPTION: Gammagard S/D® ONLY, must have a 0.22 micron in-line filter to be added to the IV tubing.
6. Infusion rates are weight based. Refer to section B below: IVIG Infusion Rates for Privigen, Gammagard Liquid and Gamunex-C for infusion rates or refer to product-specific prescribing information. Titrate as follows:
   a. Start infusion slowly, at a rate of 0.5 mL/kg/hr for the first 30 minutes.
   b. IVIG Infusion Rates for Privigen, Gamunex-C, and Gammagard Liquid: Advance rate if no adverse reaction observed.

i. 0.5 mL/kg/hr (0.8 mg/kg/min) for 30 minutes.
ii. 1 mL/kg/hr (1.7 mg/kg/min) for 31-60 minutes.
iii. 2 mL/kg/hr (3.3 mg/kg/min) for 61-90 minutes. Maximum rate for patients with documented renal failure, creatinine clearance less than 60ml/min
iv. 5 mL/kg/hr 8.3 mg/kg/min) for 90 minutes to completion of infusion minutes.
v. 5 mL/kg/hr maximum rate for remainder of infusion for all IVIG indications.

7. For patients with documented renal failure (creatinine clearance less than 60ml/min) or at risk for renal failure, start at the minimum infusion rate of 0.5 mL/kg/hr for 30 minutes of the infusion (note: this applies to both Privigen, Gammagard, and Gamunex-C). The rate may then be increased according to the above protocol until a maximum rate of 2ml/kg/hr is reached or based on patient tolerability if lower.
8. If the patient experiences minor symptoms such as fever (temp greater than 38ºC), headache, chills or flu-like symptoms:
   a. Stop the infusion and notify prescriber.
   b. Obtain vital signs.
   c. Once symptoms have resolved, advanced practitioner (RN, NP, or MD) will determine if the infusion may be restarted.
   d. Rate should be restarted at the next lowest rate from when it was stopped.
9. In case of hypotension, urticaria, signs/symptoms of fluid overload or other symptoms of anaphylaxis:
   a. Discontinue IVIG infusion and IMMEDIATELY notify the AP.
   b. With AP's order, start oxygen at 6 Liters per minute by facemask if indicated for adults. For pediatric patients, provide oxygen as appropriate if indicated.
   c. Obtain vital signs.

Optimizing Immunosuppression for Steroid-Refractory Anti-PD-1/PD-L1 Pneumonitis

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Appendix VIII

Patient Pill Calendar

This is a calendar on which you are to record the time and number of tablets of oral corticosteroids you take each day (these include either: prednisone or methylprednisolone). You should take your scheduled dose of each pill. Pills should be taken with food. Note the times and the number of corticosteroid tablets that you take each day. If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits. Since the corticosteroid dose is based on a patient's weight, the specific corticosteroid taper schedule will depend on patient weight. A reduction in corticosteroid dose by 20-25% per week until stop will yield a 4-6 week taper. You could be on the steroid for up to 56 days.*

Patient Initials: _____ Patient Study ID: _____

DAY	Date			Time pills taken		Number of pills taken		Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year	AM	PM	AM	PM	
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								

DAY	Date			Time pills taken		Number of pills taken		Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year	AM	PM	AM	PM	
19								
20								
21								
22								
23								
24								
25								
26								
27								
28								
29								
30								
31								
32								
33								
34								
35								
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								
48								
49								
50								

DAY	Date			Time pills taken		Number of pills taken		Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year	AM	PM	AM	PM	
51								
52								
53								
54								
55								
56								

*Prednisone 1mg/kg is the equivalent of methylprednisolone 0.8mg/kg orally or intravenously.

Patient Signature: _____ **Date:** _____

Reviewing Staff Signature: _____ **Date:** _____

Optimizing Immunosuppression for Steroid-Refractory Anti-PD-1/PD-L1 Pneumonitis

Appendix IX

Patient Clinical Trial Wallet Card

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: EAQ172

Study Drug(S): Infliximab, Intravenous immunoglobulin (IVIG)

Version: *February 2020*

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

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Appendix X

EAQ172 Collection and Shipping Kit Order Instructions

Specimen Collection/Shipping Kits are being provided by CENETRON CENTRAL LABORATORIES for US and Canadian sites only and are to be ordered ONLINE.

Kit supplies are limited and starter kits are not to be requested. Kit requests should be made after patient has consented to participate in the trial. If kits are not available, sites are requested to utilize institutional supplies to collect and submit the blood specimens.

Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000.

Ordering Process:

- Following randomization of the patient to the trial, go to the website www.cenetron.com and click on the 'Order Kits' button at the top right. It is recommended that kits be ordered same day as patient randomization.
- The order form is not study specific and can be used for any study. Complete the online form as follows:
  - **Sponsor (REQUIRED):** ECOG-ACRIN
  - **Contact Name (REQUIRED):** Name of the institution kit contact.
  - **Protocol Number (REQUIRED):** EAQ172
  - **Phone Number (REQUIRED):** Phone number of the kit contact. Please ensure that this is a number that can be reached from an external caller
  - **Site Number (REQUIRED):** Institution NCI Site ID
  - **FAX Number:** Fax number of the kit contact
  - **Investigator:** Last name of the kit contact is adequate
  - **Email (REQUIRED):** Email of the institution kit contact. Must be entered twice to confirm
  - **Date Supplies Needed (REQUIRED):** Add three (3) business days or more to order date. (Reminder that weekends and holidays must also be considered in this timeline)
  - **KIT NAME (REQUIRED):** EAQ172 Collection Kit
  - **Quantity:** 1
  - **Comments:** Provide EAQ172 Patient Case ID# and full shipping address
    - Patient Case ID =' #####
    - *Ship Kit to*' name of the individual to whom the kit is being shipped. (May be different than the kit contact provided above)
    - Full street address, town, state and zip code
  - Answer the security question

Please complete this form correctly, including the valid ECOG-ACRIN patient case number and complete shipping address. If information is missing the kit processing will be delayed.