**NCI Protocol #:** Not applicable

**DF/HCC Protocol #: 19-817**

**TITLE: A Phase I/II Study of the Safety and Efficacy of Cemiplimab (PD-1 blockade) in Selected Organ Transplant Recipients with Advanced Cutaneous Squamous Cell Carcinoma (CONTRAC)**


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**Agent:** Cemiplimab
**Other Agents:** Everolimus, Sirolimus, Prednisone

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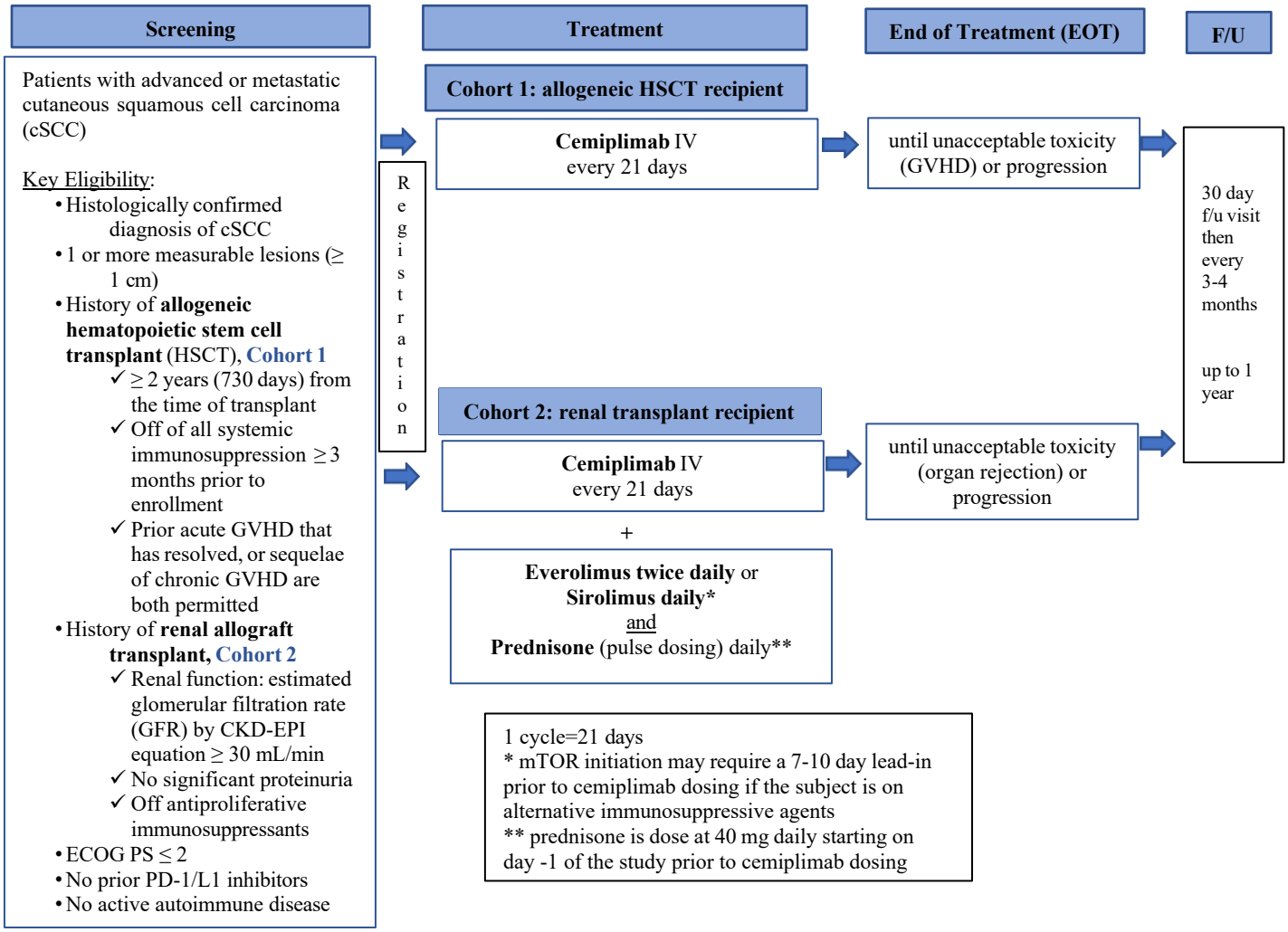
**SCHEMA**


Screening
Treatment
End of Treatment (EOT)
F/U
Patients with advanced or metastatic cutaneous squamous cell carcinoma (cSCC)
Key Eligibility:
• Histologically confirmed diagnosis of cSCC
• 1 or more measurable lesions (≥ 1 cm)
• History of allogeneic hematopoietic stem cell transplant (HSCT), Cohort 1
✓ ≥ 2 years (730 days) from the time of transplant
✓ Off of all systemic immunosuppression ≥ 3 months prior to enrollment
✓ Prior acute GVHD that has resolved, or sequelae of chronic GVHD are both permitted
• History of renal allograft transplant, Cohort 2
✓ Renal function: estimated glomerular filtration rate (GFR) by CKD-EPI equation ≥ 30 mL/min
✓ No significant proteinuria
✓ Off antiproliferative immunosuppressants
• ECOG PS ≤ 2
• No prior PD-1/L1 inhibitors
• No active autoimmune disease
Registration
Cohort 1: allogeneic HSCT recipient
Cemiplimab IV every 21 days
until unacceptable toxicity (GVHD) or progression
Cohort 2: renal transplant recipient
Cemiplimab IV every 21 days
+
Everolimus twice daily or Sirolimus daily*
and
Prednisone (pulse dosing) daily**
until unacceptable toxicity (organ rejection) or progression
30 day f/u visit then every 3-4 months
up to 1 year
1 cycle=21 days
* mTOR initiation may require a 7-10 day lead-in prior to cemiplimab dosing if the subject is on alternative immunosuppressive agents
** prednisone is dose at 40 mg daily starting on day -1 of the study prior to cemiplimab dosing

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# 1. OBJECTIVES

## 1.1 Study Design

This is an open-label, two cohort, phase I/II study of immune checkpoint blockade with cemiplimab in patients with advanced cutaneous squamous cell carcinoma (cSCC) who have previously undergone an allogeneic hematopoietic stem cell transplant (HSCT) or renal allograft transplantation. Patients are divided into two cohorts based on their history of prior HSCT for a lymphoproliferative disorder or hematologic malignancy (**Cohort 1**), and a history of prior renal transplantation (**Cohort 2**). In the rare event that a patient has a history of both prior HSCT and prior renal transplantation, the patient would be included in Cohort 2. Following biopsy, screening, and enrollment, participants in **Cohort 1** receive cemiplimab at standard dosing (350 mg IV every 21 days) until disease progression or unacceptable toxicity (including graft-versus-host disease [GVHD]), whichever occurs first. **Cohort 2** mandates that the patient follow a standard immunosuppressive regimen that includes: everolimus or sirolimus with monitored trough levels to ensure therapeutic levels, in addition to prednisone pulse dosing corresponding to each dose of cemiplimab (prednisone 40 mg daily 1 day prior to cemiplimab, followed by 40 mg daily on the day of and up to 2 additional days after dosing, then 20 mg for 3 days, followed by 10 mg daily thereafter until the day prior to redosing of cemiplimab when the prednisone cycle repeats). Prophylactic antibiotics are permitted at the discretion of the treating physician while the patient is on immunosuppression and for the duration of the study. Treatment continues in **Cohort 2** with cemiplimab at standard dosing (350 mg IV every 21 days) until unacceptable toxicity (acute allograft rejection) or disease progression. Our aim is to evaluate the safety and efficacy of cemiplimab in this high-risk but in-need population, and utilize a standard, augmented immunosuppression regimen to minimize the risk of immune-related toxicity, specifically organ transplant rejection.

## 1.2 Primary Objectives

To determine the safety and toxicity of immunotherapy in advanced cutaneous squamous cell carcinoma (cSCC) patients having undergone prior hematopoietic stem cell or renal transplant.

## 1.3 Secondary Objectives

To evaluate the anti-tumor activity and survival benefit in advanced cSCC patients receiving immunotherapy despite a history of transplant:

- To estimate progression-free survival (PFS) and overall survival (OS)
- To estimate overall response rate (ORR)
- To estimate duration of therapeutic response
- To estimate the propensity for secondary infection on treatment

## 2. BACKGROUND

### 2.1 Study Disease(s)

Cutaneous squamous cell carcinoma (cSCC) is diagnosed in hundreds of thousands of patients each year in the United States and continues to increase due to our aging and sun-exposed population [1]. Risk factors for cSCC include sun or ultraviolet (UV) radiation exposure, advanced age, and immunosuppression [2]. The vast majority of cases are localized to the skin and treatment is with curative intent but, compared with other non-melanomatous skin cancers cSCC in immunosuppressed populations, can result in a greater propensity for aggressive recurrence and metastatic involvement [3]. Standard treatments involve surgery with the goal of oncologic resection (including sizeable excisional margins) with a role for adjuvant radiotherapy favored among patients with intermediate-to-high risk features such as nodal involvement, perineural invasion, significant depth of invasion, and large tumor size – with 5-year survival estimated at 73% in those receiving radiation vs. surgery alone (54%), and mitigating locoregional recurrence rates (20% vs. 43%) in this scenario [4]. Host factors such as the immunocompetence of the patient and whether the lesion in question represents a recurrence are other important considerations when considering adjuvant radiation to prevent locoregional relapse.

When unresectable or advanced, metastatic cSCC develops, prior to 2018 there had previously been no standard systemic regimen when considering platinum-based chemotherapy and epidermal growth factor receptor (EGFR) targeting antibodies due to a lack of robust safety and efficacy data in large, prospective, multicenter trials. Rather, single-arm studies often reported benefit among a heterogeneous cSCC population with much extrapolation from head and neck SCC data. Cisplatin and 5-fluorouracil-based regimens have shown some efficacy but with notable rates of toxicity (76% of cSCC patients with grade 3+ adverse events) [5]. The EGFR inhibitor cetuximab has demonstrated a 28% overall response rate with a median OS of 8 months [6], and a similar antibody (panitumumab) demonstrated 31% response rates [7]. Across the board, response rates for systemic cytotoxic and antibody-directed therapies in advanced cSCC have ranged from 17-50% and seem to be muted in patients with more widespread disease [8].

Until 2018, no systemic therapies were approved for the treatment of advanced cSCC, as mentioned above. Because of a robust UV driven mutational burden and the link with immunosuppression, there was a strong interest in exploring immunotherapies in this disease. Cancer medicine has been revolutionized by the advent of immune checkpoint blockade agents that serve to block T cell inhibitory signaling and thereby promote T cell activation through receptors like programmed cell death-protein 1 (PD-1) and its ligand (PD-L1) on tumor and surrounding immune cells [9]. Recently, a landmark phase I/II study demonstrated that the highly potent PD-1 inhibitor cemiplimab (formerly REGN2810) resulted in 47-50% overall response rates among advanced cSCC patients; with the duration of response exceeding 6 months in more than half of patients [10]. Neither median PFS nor OS had been reached at that time of reporting, but the estimated PFS at 1-year was 53% and 1-year OS 81%. Adverse events were manageable with 15% of patients experiencing immune-mediated side effects such as rash, diarrhea, and fatigue. These data led to Food and Drug Administration (FDA) approval of cemiplimab in September 2018.

Despite the success of immune checkpoint blockade in advanced cSCC, there are some important groups excluded from immunotherapy trials in general. Non-melanomatous skins cancers, particularly cSCC, represents a major cause of morbidity following organ transplantation – with SCC representing the most common cutaneous malignancy in this setting with a 65-100 fold greater incidence among organ transplant recipients compared with the general population [11]. Because of their ongoing need for some component of long-term immunosuppression, their competing medical issues, and the concern for off-target immune toxicity jeopardizing their transplanted organ, these patients have been excluded from immunotherapy trials despite the devastation and mortality of advanced cSCC in these transplant survivors – where 3-year disease-specific survival may only approach 50% [12].

## 2.2 IND Agents

### 2.2.1 Cemiplimab

#### 2.2.1.1 Mechanism of action and pharmacology

Cemiplimab-rwlc is a recombinant human IgG4 monoclonal antibody that inhibits programmed death-1 (PD-1) activity by binding to PD-1 and blocking the interactions with the ligands PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of immune response, including anti-tumor response. PD-1 ligand upregulation may occur in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Blocking PD-1 activity has resulted in decreased tumor growth. Cemiplimab has a volume of distribution of 5.3L and a half-life elimination of 19 days with renal clearance (first dose: 0.32 L/day, steady state: 0.21 L/day).

#### 2.2.1.2 Clinical safety

Cemiplimab was investigated in a phase I/II open-label trial in advanced cSCC patients where the most common adverse events were diarrhea (27% of patients), fatigue (24%), nausea (17%), constipation (15%), and skin rash (15%) [10]. Four patients (7% of the initial study) discontinued therapy due to adverse events. Grade 3 toxicity or higher events that occurred in >1 patient included cellulitis, pneumonitis, hypercalcemia, pleural effusion, and death. Overall there were 11 deaths in the original phase I/II study, 8 attributed to disease progression, and 3 from adverse events.

In terms of safety after allogeneic hematopoietic stem cell transplantation (allo-HSCT), Herbaux and colleagues reported on 20 relapsed Hodgkin lymphoma (HL) patients treated with another PD-1 inhibitor, nivolumab [13] (**Table 1**, *below*). GVHD occurred in 6 patients (30%) after nivolumab initiation, but all had a prior history of acute GVHD. Overall response rate was 95% and the 1-year PFS was 58% and OS 79%. All cases of PD-1 triggered acute GVHD occurred within 1 week of the first dose. There were no reported cases of chronic GVHD among the cohort. Time between allo-HSCT and nivolumab treatment was significantly shorter in patients with PD-1 triggered GVHD (median of 8.5 months). All patients were successfully managed with standard GVHD treatments. In another study evaluating relapsed lymphoma patients post-

allo-HSCT, Haverkos and colleagues reported anti-PD-1 inhibitor use in 31 patients with a response rate of 77% overall but n = 8/31 (26%) developed significant GVHD after anti-PD-1 dosing, with an onset between 1-2 doses [14]. The majority of cases were among those with prior acute GVHD or active chronic GVHD.

There is also emerging data about allo-HSCT patients who have previously received immune checkpoint blockade for lymphoma after autologous HSCT. A report of 39 patients with lymphoma who had prior PD-1 inhibition before allo-HSCT showed that at a median of 12 month follow-up, 1-year cumulative rates of grade 3-4 GVHD were 23%, but the overall survival at 1-year was excellent at 89% [15].

**Table 1. Retrospective studies using PD-1 blockade after allogeneic HSCT**

| Study | Diagnosis/ Treatment | # | Therapy | +GVHD Post-PD-1 | Prior aGVHD | Prior cGVHD | Time between allo-HSCT and PD-1i |
|---|---|---|---|---|---|---|---|
| Haverkos BM, et al. **2017** | Lymphoma; allo-SCT with relapse | 31 | Nivolumab, pembrolizumab | 17 (55%)[A] | 3 (18%) | 9 (53%) | -- |
| Herbaux C, et al. **2017** | Hodgkin lymphoma, allo-SCT with relapse | 20 | Nivolumab | 6 (30%) | 6 (100%) | 1 (17%) | 8.5 months[B] |

[A] all GVHD occurred after ≤ 2 PD-1 inhibitor doses except in 1/17 patients; GVHD occurred most often in matched sibling donor transplant cases;
[B] median time from allo-HSCT to PD-1 blockade among those patients who did not experience GVHD was 28.5 months

In terms of PD-1 blockade in organ transplantation recipients, data is limited to case reports to-date given the concern for acute organ rejection and ongoing immunosuppression needs. Herz and colleagues reported a renal transplant recipient treated with tacrolimus and prednisolone who received the anti-cytotoxic T lymphocyte associated antigen-4 (CTLA-4) antibody ipilimumab, another immune checkpoint inhibitor, and later received PD-1 blockade with single-agent nivolumab [16]. Neither PD-1 or CTLA-4 inhibition triggered renal allograft rejection and the patient had clinical benefit from the therapy. Several studies summarized in **Table 2** *below* have reported success and failure with allograft tolerance following checkpoint inhibitor use, but the actual rates of rejection are not known. An important observation among these reports is that in two series (Lesouhaitier, et al. 2018; Barnett, et al. 2017) [17, 18], all of the patients in the anti-PD-1 use post-renal transplant group who did not experience organ rejection had been on mechanistic target of rapamycin (mTOR) inhibition as part of immunosuppression. Abdel-Wahab and colleagues recently published the largest series to date of 23 renal transplant recipients who received various checkpoint inhibitors (PD-1/CTLA-4 directed, or both) and 11/23 (48%) experienced acute kidney rejection within a median of 21 days (range: 5-60 days) from transplantation [19]. Of note, the immunosuppressive regimen was quite variable among this retrospective group and included steroids, mTOR inhibitors, CNIs, and combinations of these agents without standardization.

**Table 2. Case reports and series using immune checkpoint blockade after kidney transplant**

| Report | Diagnosis | # | Therapy | Kidney Rejection Post-PD-1 | IS agents | Median Time between kidney transplant and PD-1i |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| Ong, et al. 2016 | Melanoma | 1 | Nivolumab | Yes | Tacrolimus, prednisone, MMF (tapered prior to PD-1i) | 10 years |
| Herz, et al. 2016 | Melanoma | 1 | Ipilimumab, Nivolumab | No | Tacrolimus + prednisone | -- |
| Spain, et al. 2016 | Melanoma | 1 | Nivolumab (after ipilimumab) | Yes | Prednisolone | 12 years |
| Kwatra, et al 2017 | Melanoma | 1 | Pembrolizumab | Yes | Tacrolimus + MMF | 13 years |
| Barnett, et al. 2017 | Renal cell carcinoma | 1 | Nivolumab | No | Everolimus + prednisone | -- |
| Lesouhaitier, et al. 2018 | NSCLC, Melanoma, Merkel cell | 7 | Nivolumab, Ipilimumab, Pembrolizumab, or Avelumab | Yes = 3<br>No = 4 | Steroids, MMF, mTORi (4 non-GVHD); tacrolimus, MMF, cyclosporine (3 with GVHD) | 1-3 months |
| Tio, et al. 2018 | Melanoma | 5 | Pembrolizumab, Nivolumab, Ipilimumab | Yes = 1<br>No = 4 | Steroids, MMF, tacrolimus, mTORi (4 non-GVHD); tacro, steroid (1 with GVHD) | -- |
| Abdel-Wahab, et al. 2019 | Solid tumors | 23 | Pembrolizumab, Nivolumab, Ipilimumab | Yes = 4<br>No = 19 | mTOR inhibitor (n = 11), steroids (n = 23), Tacrolimus, cyclosporin (n = 19) | 9 years (0.3-32 years) |

#### 2.2.1.3 Clinical efficacy

In the pivotal phase I/II trial of cemiplimab in advanced or metastatic cSCC patients the overall response rate was 47% and the rate of durable disease control was 61% with 4 complete responses and 24 partial responses [10]. Median time to an observed response was 1.9 months (range, 1.7-6.0 months), and the median duration of response had not been reached at the time of reporting. However, 57% of patients with a response had a duration of benefit that exceeded 6 months in their analysis. Only 3 patients had subsequent disease progression following confirmed response, and at the time of data cutoff 82% of responders continued to benefit and continued on PD-1 blockade. Both median PFS and OS were not reached at the time of analysis but the estimated 1-year PFS was 53% (95% confidence interval [CI], 37-66%) and 1-year OS was 81% (95% CI, 68-89%). In subgroup analysis, similar efficacy was observed in patients with either regional or distant metastatic disease involvement (43 vs. 49% response rate, respectively).

Several trials are ongoing which utilize PD-1 antibodies in the HSCT setting. A study of the PD-1 inhibitor pembrolizumab as maintenance after autologous HSCT is enrolling in diffuse large B-cell lymphoma (DLBCL), classical HL, and T cell non-HL (NCT02362997). In addition, studies are enrolling using nivolumab after autologous HSCT in multiple myeloma (NCT03292263) and evaluating the PD-L1 antibody durvalumab for DLBCL (NCT03241017). PD-1 blockade has a track record of clinical benefit in post-HSCT patients: a report of 3 classical HL patients who relapsed after allo-HSCT all had objective responses to the PD-1 inhibitor nivolumab [20]. Haverkos and colleagues treated classical HL patients who relapsed after allo-HSCT with PD-1 blockade as well and noted an overall response rate of 77% (15 complete and 8 partial responses among 30 patients) [14]. Herbaux and colleagues reported a 95% response rate with a 1-year PFS of 58% and 79% 1-year OS among 20 classical HL patients treated with nivolumab after relapse following allo-HSCT [13].

Anti-tumor response rates among post-renal allograft transplant patients with advanced

malignancies has not uniformly been reported – as the literature is comprised of cases reports and a few series. That said, complete and partial responses in this setting have been observed [21].

### 2.2.2 Mechanistic target of rapamycin (mTOR) inhibition: Everolimus and Sirolimus

#### 2.2.2.1 Mechanism of action and pharmacology

**Everolimus** is a macrolide immunosuppressant and a mechanistic target of rapamycin (mTOR) inhibitor which has antiproliferative and antiangiogenic properties. It reduces protein synthesis and cell proliferation by binding to the FK binding protein-12 (FKBP-12), an intracellular protein, to form a complex that inhibits activation of mTOR (mechanistic target of rapamycin) serine-threonine kinase activity. It also reduces angiogenesis by inhibiting vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF-1) expression.

Everolimus is rapidly absorbed with a volume of distribution of 128-589L and is 74% protein bound. The drug is extensively metabolized in the liver by CYP3A4 and yields six weak metabolites [22]. The tablet form is 30% bioavailable and this is reduced by 22% with a high-fate meal and by 32% with a light-fat meal. The tablet for suspension form has an area under the curve (AUC) equivalent to tablets although peak concentrations are 20-36% lower and steady state concentrations are similar [23]. Systemic exposure is reduced by 12% with a high-fat meal and 30% with a low-fat meal. The half-life of elimination is about 30 hours and the time to peak plasma concentration is about 1-2 hours. Fecal excretion is about 80% with around 5% urinary excretion [24].

**Sirolimus** inhibits T-lymphocyte activation and proliferation in response to antigenic and cytokine stimulation and inhibits antibody production. Its mechanism differs from other immunosuppressants. Sirolimus binds to FKBP-12, an intracellular protein, to form an immunosuppressive complex which inhibits the regulatory kinase, mTOR. This inhibition suppresses cytokine mediated T-cell proliferation, halting progression from the G1 to the S phase of the cell cycle.

Sirolimus is rapidly absorbed with a volume of distribution of 12L/kg and is about 92% protein bound to albumin primarily. The drug is extensively metabolized in the intestinal wall via P-glycoprotein and hepatic CYP3A4 enzymes to seven major metabolites. The oral solution form is 14% bioavailable where the oral tablet form is 27% higher relative to the oral solution bioavailability. Half-life of elimination is on average 62 hours (range: 46-78 hours) and extended up to 113 hours in those with hepatic impairment. Time to peak concentration is 1-3 hours for the oral solution and 1-6 hours for the oral tablet. Fecal excretion is about 91% due to the P-glycoprotein-mediated efflux into the gut lumen, and 2% urinary excretion [25].

#### 2.2.2.2 Clinical safety

The dose and schedule of everolimus for clinical use was established in a study of 55 advanced solid tumor patients using a dose escalation scheme whereby dose limiting toxicity (DLT) of stomatitis, neutropenia, and hyperglycemia yielded a recommended 10 mg daily dose for further

development [24]. Everolimus has established safety in patients with advanced renal cell carcinoma (RCC) where a phase II study utilized a 10 mg daily oral dose without interruption with permitted dose modifications for toxicity among 39 patients. Common toxicities included: nausea (38% of patients), anorexia (38%), diarrhea (31%), stomatitis (31%), pneumonitis (31%), and skin rash (10%). Grade 3-4 adverse events included pneumonitis (18%) transaminase elevations (10%), thrombocytopenia, hyperglycemia, and alkaline phosphatase elevations (8% each), and hyperlipidemia (5%) [26]. In a phase III, randomized trial, everolimus and exemestane (endocrine hormone therapy) was compared in 724 post-menopausal hormone-receptor positive breast cancer patients with similar expected toxicities as noted in RCC. In addition, grade 3-4 adverse events included: stomatitis (8%), anemia (6%), dyspnea (4%), hyperglycemia (4%), fatigue (4%), and pneumonitis (3%) in the hormone and mTOR combination arm [27].

Outside of treatment for malignancy, mTOR inhibition also has an established role as immunosuppression alone or in combination for kidney transplant recipients to prevent organ rejection. In the multicenter, open-label ZEUS study of everolimus-based, calcineurin-inhibitor (CNI)-free immunosuppression for recipients of de-novo kidney transplants, 155 patients received an everolimus-based regimen based on trough concentrations (6-10 ng/mL) with a primary objective of showing favorable renal function at 1-year post-transplant [28]. In the mTOR inhibition arm, 76% (118 patients) completed therapy with rates of biopsy-proven acute renal rejection being around 10% (n = 15/154). Adverse events included elevated lipid concentrations, mildly elevated urine protein excretion, and lower hemoglobin concentrations in the everolimus-based arm. Thrombocytopenia, aphthous stomatitis, and diarrhea also were notable in the mTOR inhibition arm. Similarly, a multinational comparative, randomized trial using sirolimus 1-5 mg/day adjusted to a trough concentration of 8-15 ng/mL at the time of conversion to the agent (and 7-15 ng/mL thereafter) in 57 patients post-cardiac transplantation compared with a CNI was reported [29]. The most common adverse events in the sirolimus arm were diarrhea (28%), skin rash (28%), and infection (47%). Everolimus also has established immunosuppressive safety in pediatric transplant recipients: a phase I trial examined single dose everolimus in combination with cyclosporin A and steroids with and without azathioprine. Nineteen children enrolled at 1.2 mg/m$^2$ per day which was safe and well tolerated. There was no increase in infection rates [23].

#### 2.2.2.3 Clinical efficacy

Everolimus has demonstrated efficacy as immunosuppression following de-novo lung transplantation as noted in an investigator-sponsored, single institution study from Germany in 2016 [30]. Forty-three patients were randomized to everolimus (over mycophenolate mofetil [MMF]) and the everolimus group had less rates of acute organ rejection, lower rates of cytomegalovirus (CMV) infection, and lower rates of respiratory tract infection. In addition, rates of bronchiolitis obliterans syndrome (BOS) were lower (1/43 patients) compared with the MMF group (p=0.04). There was a notable dropout rate in the mTOR inhibition group due to drug-related side effects, which are discussed above. Among de-novo kidney transplant recipients in the ZEUS trial, mTOR inhibition demonstrated somewhat higher rates of acute kidney rejection (10%) compared with 3% in the CNI group [28]. Sirolimus had numerically higher acute rejection rates compared with MMF in a post-cardiac transplant group, but overall

rates of rejection were low, comparatively [29].

#### 2.2.3 Combining Cemiplimab and mTOR inhibition

##### 2.2.3.1 Preclinical efficacy

While no data have yet reported the safety or efficacy of PD-1/L1 blockade used in combination with everolimus or mTOR inhibition, therapeutic efficacy in the early preclinical setting suggests that combining these agents could offer enhanced anti-tumor effect [31]. Hirayama and colleagues treated immunocompetent mice with RCC with anti-PD-L1 therapy and everolimus and showed a significant decrease in tumor burden as compared with anti-PD-L1 and placebo alone groups. They also noted increased tumor-infiltrating lymphocytes (TILs) and a higher ratio of CD8+ cytotoxic T cells compared to TILs in the combination arm. **It is important to acknowledge that a serious and overlapping toxicity shared by both anti-PD-1/L1 and mTOR inhibitors is pneumonitis, and it is unknown whether combined use increases the likelihood of lung inflammation as compared with either agent alone. Nonetheless, we are excluding patients with significant renal dysfunction which have been associated with the highest risk of pneumonitis on mTOR inhibitors [32].**

## 2.3 Rationale

Until 2018 there were no systemic therapies approved for the treatment of advanced or metastatic cSCC, despite its significant cosmetic and functional morbidity and overall poor prognosis. However, UV radiation leading to a rich mutational burden in this disease proved a promising attribute when considering the influx of novel immunotherapies in cancer medicine. Immune checkpoint inhibitors targeting PD-1 work to remove the inhibitory break signal on surrounding T cells to enhance tumor killing potential [33]. Cemiplimab, an anti-PD-1 antibody, demonstrated a nearly 50% durable response rate in advanced cSCC with a favorable toxicity profile – leading to regulatory approval of this agent for an otherwise devastating disease [10].

Despite the success of solid organ and hematopoietic stem cell transplantation (HSCT) in the last decade, transplant recipients remain at high-risk for second cancers given their altered immune systems and immunosuppressive needs [34] – with cSCC representing the most common new malignancy with a nearly 100-fold risk increase in this population [11]. When the cSCC becomes advanced or metastatic post-transplant, the treating physician is left with minimizing systemic immunosuppression or offering cytotoxic chemotherapy to palliate the disease. Of note, mTOR inhibitors (namely everolimus and sirolimus) are generally the preferred immunosuppressive agent after transplant to prevent future malignancies [35]. While immune checkpoint inhibitors have revolutionized the cancer landscape, trials have excluded this high-risk, but in-need population for fear of precipitating transplant rejection by stimulating a broad immune response – a scenario that has been reported of late [34, 36, 37]. In addition, including post-HSCT patients brings concern about the recrudescence of GVHD. Recent studies have shown that rates of acute GVHD exceed 45-50% when a patient is challenged with PD-1 blockade for relapse >3 months out from their prior HSCT and when they have a prior history of acute GVHD [13, 38]. While acute GVHD can occur in post-HSCT patients exposed to PD-1 blockade even in the absence of prior GVHD, a shorter time from HSCT increases the risk significantly – therefore we expect the

risk to be lower given the requirement that patients enrolled to this study be ≥2 years out from HSCT.

While the hazards of immune checkpoint therapy in HSCT and renal transplant recipients is important to recognize, advanced cSCC patients post-transplant are often left with no further therapeutic options and the prospect of morbidity and death. It is not known whether response rates to PD-1 blockade are similar in prior transplant recipients with cSCC, moreover the actual rate of allograft rejection or GVHD has not been elucidated in this population. A uniform and aggressive approach to immunomodulation using dynamic immunosuppression (as not to impair the anti-tumor response) has not been applied to these patients to further understand the role of PD-1 blockade in this critical population. Barnett and colleagues reported the use of a dynamic immunosuppression regimen (combining pulsed steroids before, concurrent, and rapidly tapering after PD-1 blockade with mTOR inhibition) in a single patient with microsatellite unstable duodenal adenocarcinoma having undergone kidney transplantation and receiving nivolumab – with no evidence organ rejection nearly a year out from therapy [18]. Similarly, small series have demonstrated success with mTOR inhibition as the backbone of immunosuppression to prevent organ rejection when also a patient with concomitant immune checkpoint blockade [17, 21].

Here we plan to investigate PD-1 blockade with cemiplimab in post-allo-HSCT and post-renal allograft transplant populations to better understand anti-tumor activity and to potentially mitigate the risk of acute rejection by using a dynamic mTOR-based immunosuppression regimen in our renal transplant recipients.

### 2.4 Correlative Studies Background

Clinical trial administration of immune checkpoint blockade among prior transplant recipients with a modified immunosuppressive regimen will provide a unique opportunity to understand immunology within this high-risk and vulnerable population. Peripheral blood and tumor tissue biopsy samples will be required before (at baseline) and after (after 30 days or 2 cycles of therapy) anti-PD-1 therapy, with an additional required tissue biopsy at the time of organ rejection or the development of GVHD to assess the off-target immunologic effects of treatment.

*Phenotypic analysis of immune cells in the blood and tumor microenvironment*. Incubation of peripheral blood and tumor biopsy samples with monoclonal antibodies specific for different cell markers will be used to identify immune cell subsets and tumor cells. After incubation of cells with monoclonal antibodies, individual subsets are then enumerated by flow cytometry (and immunohistochemistry [IHC]/multiplexed immunofluorescence [MIF] where applicable). These studies will allow us to measure quantitative changes of individual cell populations that occur as a result of anti-PD-1 treatment. Mass cytometry (CyTOF) allows for high throughput analysis of single cells for a large number of parameters, and has recently been used to deeply immunophenotype and track the inhibitory and activating receptor diversity of human immune cells [39].

*Plasma cytokines and chemokines*. ELISA or other relevant assays will be used to measure levels of key cytokines (including IL-2, IFN-γ etc.), chemokines (such as CXCL2, CXCL5 etc.) and soluble ligands in plasma samples.

*Functional assays*. To assess the functional capacity of cytotoxic T cells that expand in vivo in response to treatment, selected samples will be used to assess their cytokine and cytotoxicity responses after re-stimulation with cytokines and tumor target cells.

*DNA analyses*. Additional genetic analyses (e.g., short term tandem repeats [STRs]) will be considered to assess clearance of measurable disease and underlying tumor subclones and banked DNA and cell samples would be accessed for such analyses.

## 3. PARTICIPANT SELECTION

### 3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed, advanced or metastatic cutaneous squamous cell carcinoma (cSCC) with 1 or more measurable lesions (greater than or equal to 1 cm).

3.1.2 A history of either **(Cohort 1)** *allogeneic hematopoietic stem cell transplant (allo-HSCT)* and ≥ 2 years or 730 days from day 0 of their HSCT with adequate bone marrow function (see *Section 3.1.6*) and off of all systemic immunosuppression (topical agents permitted) for at least 3 months prior to enrollment; sequelae of chronic GVHD is permitted (i.e. chronic dry eyes, sclerodermatous skin changes, etc.) if the patient is *not* on systemic immunosuppression, or **(Cohort 2)** a *renal transplant* with a functioning allograft (at least 6 months from allograft transplant) as determined by estimated glomerular filtration (GFR) rate (CKD-EPI equation 1 [40], *Appendix A*) ≥ 30 mL/min, baseline proteinuria lower than 0.5 g/day (spot urine protein-creatinine ratio), and off antiproliferative immunosuppressive medications.

3.1.3 Willing to provide blood and tissue from diagnostic biopsies.

3.1.4 Age 18 years or older.

3.1.5 ECOG performance status ≤ 2 (Karnofsky ≥ 60%, see *Appendix B*).

3.1.6 Participants must have adequate organ and marrow function as defined below:

- leukocytes ≥ 2,200/mcL
- absolute neutrophil count ≥ 1,000/mcL
- platelets ≥ 90,000/mcL
- total bilirubin within normal institutional limits (except in cases where Gilbert syndrome is known or suspected, where total bilirubin should be < 3 mg/dL)
- AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional upper limit of normal
- creatinine ≤ 1.5 × institutional upper limit of normal

OR

- estimated GFR ≥ 30 mL/min/1.73 $m^2$ for participants with creatinine levels above

institutional normal (CKD-EPI equation).

- urine protein/creatinine ratio < 0.5 (equal to less than 500 mg of proteinuria per day)

3.1.7 Ability to understand and the willingness to sign a written informed consent document.

3.1.8 A prior history of *acute* GVHD that has resolved, or sequelae of *chronic* GVHD following allo-HSCT is permitted. Active *acute* GVHD patients are excluded.

3.1.9 Women of childbearing potential (WOCBP) must agree to use at least 1 highly effective form of contraception (refer to *Appendix C* for examples). WOCBP should plan to use an adequate method to avoid pregnancy for up to 7 months (30 days plus the time required for cemiplimab to undergo five half-lives) after the last dose of investigational drug.

"Women of childbearing potential (WOCBP)" is defined as any female who has experienced menarche, who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy), who is not postmenopausal, who is sexually active with a male partner. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL.

3.1.10 Women of childbearing potential, as defined above, must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of cemiplimab.

3.1.11 Men who are sexually active with WOCBP must agree to use any contraceptive method with a failure rate of less than 1% per year. Men who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational product. Women who are not of childbearing potential as defined above, and azoospermic men) do not require contraception. See *Appendix C* for further guidance on contraception.

### 3.2 Exclusion Criteria

Participants who have had chemotherapy or radiotherapy within 1 week prior to entering the study or those who have unresolved toxicities from prior anti-cancer therapy more than 2 weeks earlier, defined as not resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 5.0), grade 0 or 1.

3.2.1 Participants who are receiving any other investigational agents.

3.2.2 For **Cohort 1** allo-HSCT patients enrolling to the study, corticosteroid doses > 10 mg of prednisone daily or equivalent within 4 weeks of the first dose of PD-1 inhibitor are prohibited. For **Cohort 2** renal transplant patients enrolling to the study, corticosteroid use is permitted if used as part of their immunosuppressive regimen for graft protection prior to enrollment.

3.2.3 Existing significant autoimmune conditions. Patients with a history of Hashimoto thyroiditis who are stable on replacement hormone therapy are not excluded.

3.2.4 Known human immunodeficiency virus carrier or a diagnosis of immunodeficiency. Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, e.g., Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

3.2.5 Kidney transplant recipients with active acute rejection.

3.2.6 Allergy to cemiplimab or any of its components.

3.2.7 *Any* prior exposure to the phosphoinositide 3-kinase inhibitor idelalisib.

3.2.8 Subject who has been treated with immunotherapy. This includes prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways (including chimeric antigen receptor [CAR] T cell therapies). Prior topical or intralesional immunotherapies (e.g. imiquimod, talimogene laherperepvec) are allowed.

3.2.9 Subject with known and untreated brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. However, baseline brain imaging is not required prior to enrollment in the study if patients are asymptomatic. Patients at least 4 weeks out from metastatic central nervous system (CNS) treatment are permitted to enroll, if they are asymptomatic, radiographically stable per the investigator, and on stable doses of anti-epileptic drugs (AEDs) and oral corticosteroids (for **Cohort 1** only, the patient must be on 10 mg of prednisone daily equivalent dosing or less, see 3.2.2) at the time of enrollment.

3.2.10 Participants receiving any medications or substances that are strong inhibitors or inducers of *CYP3A4* are ineligible. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.11 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

3.2.12 Known non-infectious pneumonitis or any history of interstitial lung disease.

### 3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

## 4. REGISTRATION PROCEDURES

### 4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

### 4.1 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

## 5. TREATMENT PLAN

While accrual is expected to be slow, we will approve **two** patients to enroll into to each cohort at a time to monitor toxicity appropriately.

Eligibility and exclusion criteria are provided in *Section 3*. These criteria will be assessed within 14 days prior to study registration to establish eligibility and baseline values.

Informed consent will be obtained after the study has been fully explained to the subject and before the conduct of any screening procedures or assessments.

Demographic information and baseline characteristics will be collected at the Screening Visit. Standard demographic parameters include age, sex, and race/ethnicity (recorded in accordance with prevailing regulations). Baseline characteristics will include ECOG PS (*Appendix B*),

disease status, and medical histories.

### 5.1 Treatment Regimen

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy during the course of treatment. Treatment cycles will be **21 days** throughout the protocol. Patients are assigned to one of two predetermined Cohorts based on their prior transplant history: **Cohort 1** (prior allogeneic hematopoietic stem cell transplant [allo-HSCT] history) or **Cohort 2** (prior renal or kidney transplant history).

#### 5.1.1 Cemiplimab Treatment (same for both **Cohort 1** and **Cohort 2**)

Cemiplimab (350 mg IV) will be administered in the outpatient setting at the beginning of the study (following a prednisone lead-in in **Cohort 2 only**) and will be dosed every 21 days (3 weeks) until disease progression, intolerability, or limiting toxicity.

#### 5.1.2 Dynamic Immunosuppression (**Cohort 2 only**)

Patients in **Cohort 2** with a history of prior renal transplant will need to transition to dynamic immunosuppression with either sirolimus or everolimus (mTOR inhibitors) during a lead-in phase of the study, 7-10 days prior to receiving the first dose of cemiplimab. If the patient is on an existing immunosuppression regimen that includes other agents (azathioprine, tacrolimus, MMF) they will need to be cross-tapered in discussion with the lead transplant nephrologist on the study team, Dr. Naoka Murakami.

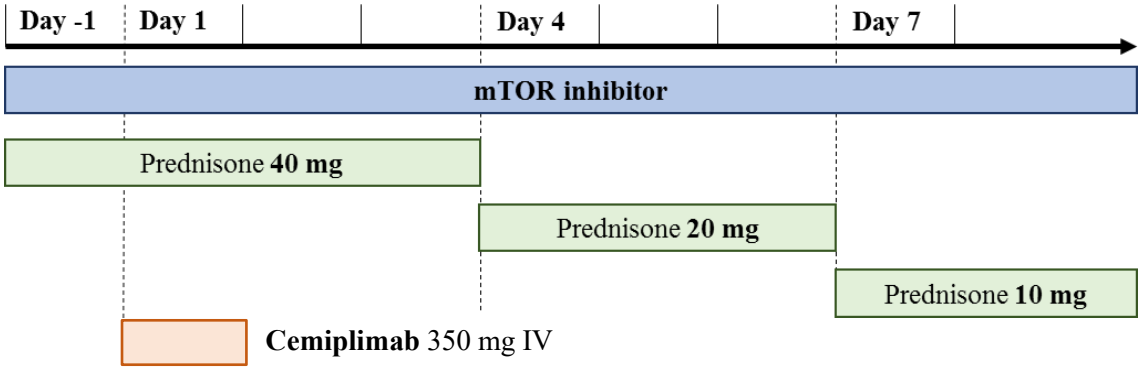
##### 5.1.2.1 mTOR inhibitor and Prednisone Lead-in

Patients in **Cohort 2** will start mTOR inhibition with either sirolimus or everolimus at least 7-10 days prior to receiving the first dose of cemiplimab (Cycle 1, Day 1). The choice of agent, starting dose, and titration of mTOR dosing to optimal blood levels is at the discretion of the treating transplant nephrologist.

Patients in **Cohort 2** will also receive prednisone 40 mg orally the day prior to the start of cemiplimab dosing (Cycle 1, Day 1).

##### 5.1.2.2 mTOR inhibitor and Prednisone dosing Scheme After Lead-in

In **Cohort 2,** after the patient starts mTOR inhibition and receives 40 mg of prednisone as their lead-in to the first dose of cemiplimab, the patient then receives 40 mg of prednisone orally on the day of cemiplimab treatment (Cycle 1, Day 1) and for 2 days after cemiplimab dosing, followed by 20 mg daily for three additional days after anti-PD-1 dosing. Then on Cycle 1, Day 7 the patient tapers to prednisone 10 mg orally daily and remains on this dose continuously until the day prior to the next cycle when the schedule repeats:




5.1.2.3 Antibiotic prophylaxis on immunosuppression

Prophylactic antimicrobial and antiviral use is permitted while patients are receiving mTOR inhibition and prednisone as part of dynamic immunosuppression.

Dose adjustments of mTOR inhibitors based on trough levels throughout the study do not impact the timing or dosing schedule of cemiplimab in the absence of toxicity concerns.

## 5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

Laboratory evaluations need to be repeated (except mTOR monitoring levels) and reviewed to re-meet eligibility criteria on Cycle 1, Day 1. In **Cohort 2,** patients must be on mTOR inhibition and have taken their 40 mg prednisone oral dose prior to cemiplimab on Cycle 1, Day 1.

5.2.2 Subsequent Cycles

Reasonable effort should be made to conduct study visits on the day scheduled (± 3 days). Laboratory evaluations should be reviewed prior to the start of each cycle.

Any changes from screening clinical evaluation findings that meet the definition of an adverse event (AE) will be recorded on the AE page of the eCRF. The drug diary for the prior cycle should be reviewed at each study visit by the clinical staff.

## 5.3 Agent Administration

5.3.1 Cemiplimab

No pre-medications are recommended prior to the administration of cemiplimab. Day -1 prednisone is part of dynamic immunosuppression, not pre-medication.

Cemiplimab (350 mg flat dose IV every 21 days) will be administered in an outpatient setting as an approximately 30-minute infusion (+/- 20 minutes). Post-treatment observation is required for 30-minutes after the first infusion only to monitor for immune-mediated infusion reactions.

### 5.3.2 Dynamic Immunosuppression (**Cohort 2**)

Participants in **Cohort 2** will receive everolimus or sirolimus and prednisone on an outpatient basis. Everolimus or sirolimus pills can be taken with or without food as prescribed based on desired dosing (although ingestion of a high-fat meal should be avoided with sirolimus). As noted below in *Section 5.4.2*, grapefruit juice should be avoided. Dosing of mTOR inhibitors is often once or twice daily (aiming for approximately 10-12 hours between doses) and the patient should try to be consistent with dose administration timing. Prednisone dosing daily should also be timed so as to maintain consistent time intervals between daily doses.

Immunosuppression compliance will be monitored as part of the study. Each participant will be required to maintain a medication diary of each dose of immunosuppressive medication. The medication diary will be returned to the clinic study staff at the end of each 21-day cycle.

If a dose of immunosuppression is missed by ≥ 6 hours from the last oral dose, then the next dose should be retimed for the morning of the following day. Any dose of immunosuppression that was missed less than 6 hours from the last administration should be taken, and the following dose retimed for the morning of the following day. If immunosuppression is not tolerated, or vomiting results in loss of the ingested dose, the dose should be skipped, and the next planned dose attempted when possible. The immunosuppressive drugs may be crushed, chewed, or dissolved if necessary (everolimus is also available in a liquid suspension preparation).

## 5.4 General Concomitant Medication and Supportive Care Guidelines

### 5.4.1 Concomitant Medical Guidelines

Pertinent concomitant medications will be recorded on the case report form (CRF). If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

Topical, intradermal, and intraarticular corticosteroids are permitted.

### 5.4.2 CYP3A4 Interactions among mTOR inhibitors

mTOR inhibitors are a known substrate of **CYP3A4 and P-glycoprotein/ABCB1** and therefore medications which can cause drug-drug interactions are listed in the Table below. Strong inducers of CYP3A4 are identified below with monitoring during concomitant therapy recommended. Category X drugs below should be **avoided**.

| | | | | | | |
|---|---|---|---|---|---|---|
| **Strong CYP3A4 inducers** | Angiotensin-converting enzyme inhibitors (ACEI) | Antidiabetic agents | Aripiprazole | Bosenten | Chloramphenicol | Clofazimine |
| | Clotrimazole (topical)* | Deferasirox | Efavirenz | Erythromycin | Fluconazole* | Micafungin* |
| | Clozapine | CYP3A4 inducers | CYP3A4 inhibitors | Denosumab | Dofetilide | Echinacea |
| | Flibanserin | Fosaprepitant | Nimodipine | P-glycoprotein | Ranolazine | Roflumilast |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Rifampin | Rifabutin | Phenobarbital | inhibitors Carbamezapine | Phenytoin | |
| **Risk X** | Antihepaciviral combination products | Conivaptan | Cyclosporine | Grapefruit juice | St. John's Wort | Voriconazole |

* azole antifungal agents may cause an increase in serum concentration of sirolimus only

### 5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until *any of the following* criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s), *see Section 6.1.3*
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Pregnancy

The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant. When a participant is removed from protocol therapy and/or is off study, participant's status must be updated in OnCore in accordance with REGIST-OP-1.

Following completion of 2 years or 24 months of protocol therapy with cemiplimab, the patient can be moved to commercial product at the discretion of the treating physician.

### 5.6 Duration of Follow-Up

Participants will be followed for best overall response and development and documentation of first disease progression and for survival throughout the course of the trial for 1 years from the time of end of treatment visit Participants who are removed from protocol therapy for an unacceptable adverse event and who have not developed first disease progression at time of discontinuation of protocol therapy will continue to be followed for 1 year from EOT visit. Follow-up after discontinuation of the cemiplimab study treatment should include one 30-day follow up visit, then routine check-ins every 3-4 months up to 12 months (1 year), which can overlap with routine clinic visits or include telephone encounters. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

### 5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when *any of the following* criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant. In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, Glenn J. Hanna, MD, call Partners paging directory at (617) 732-5500 and ask for pager #46231.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated below. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

### 6.1 Cemiplimab

There will be no dose reductions for cemiplimab permitted. Doses of cemiplimab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Cemiplimab dosing visits are not skipped, only delayed. If cemiplimab doses are delayed or skipped, study testing resumes when the next cycle of cemiplimab begins and drug is resumed. However, immunosuppression dosing continues during the delay or skipped periods.

#### 6.1.1 Cemiplimab Dose Delays or Holds

Administration of cemiplimab should be **delayed and the dose held** for the following adverse events:

- Grade II, III, or IV acute GVHD according to the modified Glucksberg scale (*see Section 7.7*) in **Cohort 1**
- Moderate to severe chronic GVHD by the revised NIH consensus scoring system (*see Section 7.8*) in **Cohort 1**
- Grade 2 non-skin, drug-related adverse event (AE), with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or total bilirubin abnormalities unless specifically due to chronic GVHD and not meeting stopping criteria in bullet two above
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions: lymphopenia or asymptomatic amylase or lipase does not require dose delay

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

**Note:** see Cemiplimab investigator brochure and guidelines on managing immune-related toxicities (*Appendix E*)

### 6.1.2 Re-treatment Criteria for Cemiplimab

Participants who require delay of cemiplimab should be re-evaluated weekly or more frequently if clinically indicated and resume dosing when re-treatment criteria (as described below) are met. Participants with a delay in dosing *beyond 12 weeks* should be considered for discontinuation of protocol treatment and discussed with the Overall PI.

Subsequent dosing may be re-started if subjects continue to meet laboratory criteria (eligibility criteria values). The investigator will determine if subsequent dosing is appropriate for subjects who have laboratory or clinical abnormalities that do not meet dose discontinuation criteria.

Immune-mediated adverse events or acute/chronic GVHD episodes or flares managed with oral steroid doses or standard treatment need (1) to resolve to Grade I for acute GVHD within 10 days of starting GVHD treatment, (2) to mild NIH consensus score for chronic GVHD, or (3) to grade 1 AE symptoms or less for immune-related AEs, and the patient needs to be on ≤ 10 mg prednisone daily equivalent dose before resuming cemiplimab on study.

All related grade 3+ toxicities and cases of acute or chronic GVHD should be discussed with the Overall PI, prior to subsequent dosing.

### 6.1.3 Cemiplimab Discontinuation

Administration of cemiplimab should be **discontinued** for the following AEs:

- Unresolved Grade II, III, or IV acute GVHD according to the modified Glucksberg scale despite 14 days (or 2 weeks) of systemic corticosteroids (*see Section 7.6.1*) in **Cohort 1**
- Any degree of *biopsy proven* acute renal allograft rejection (*see Section 7.6.3*) in **Cohort 2**
- A grade 3 pneumonitis and grade 3 uveitis will require permanent discontinuation.
- A *recurrent* grade 3 immune-mediated adverse reactions, grade 2 or 3 immune-mediated adverse reactions persistent for 12 weeks or longer, and any grade 3+ infusion-related immune reaction.
- Any grade 4 treatment-related adverse event will require permanent discontinuation with the following exceptions:
  - Certain grade 4 electrolyte abnormalities (specifically hypo/hypercalcemia, hypo/hyperchloremia, hypo/hypermagnesemia, hypo/hyperphosphatemia) that < 72 hours in duration
  - Grade 4 neutropenia < 5 days in duration
  - Grade 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis
  - Grade 4 lymphopenia < 5 days in duration

The consideration to re-initiate study therapy under these exceptions will be made on a case by case basis after considering the overall benefit/risk profile and in consultation with the Overall PI.

### 6.2 Dynamic Immunosuppression

Dose delays of prednisone and mTOR inhibition are discouraged as to promote immune tolerance of the bone marrow and kidney organ graft while the patient is receiving immune checkpoint blockade with cemiplimab.

Dose modifications for prednisone may be required outside of the planned treatment dosing outlined above if the patient has immune-mediated AEs or graft rejection issues that require a change in dosing. Prednisone adjustments will be made by the treating investigator at their discretion.

Everolimus or sirolumus dosing will be determined by target trough levels obtained or drawn every 7-10 days (± 3 days) in cycles 1-2, then on days 1, 8 for cycles 3-6, and on day 1 only for cycle 7 onward while on the study. There is delay in outside reporting of mTOR drug levels and this must be accounted for with periodic monitoring. The involved transplant nephrologist participating in the patient's care should determine the dose and schedule of mTOR inhibition based on a target trough level of 4-6 ng/mL for everolimus or sirolimus.

## 7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (*Section 7.1*) and the characteristics of an observed AE (*Section 7.2*) will determine whether the event requires expedited reporting **in addition** to routine reporting.

All adverse events experienced by participants will be collected during screening, from the time of the first dose of cemiplimab study treatment, through the study and within 30 days of the last study intervention. Participants continuing to experience toxicity at the last scheduled study visit may be kept on the study until the toxicity has resolved, or until the toxicity is deemed irreversible.

**7.1 Expected toxicities or** adverse events are those that have been previously identified as resulting from administration of cemiplimab. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list in the investigator brochure or is included in the informed consent document as a potential risk. Most common adverse events or expected toxicities are listed below. Management of expected immune-related toxicities is described in *Appendix E*.

Toxicities related to mTOR inhibitors and prednisone will be managed according to their respective package insert.

7.1.1 Adverse Events List

7.1.1.1 Adverse Event List(s) for *cemiplimab*

The most common adverse reactions (> 10%) related to cemiplimab alone are: diarrhea, fatigue, nausea, constipation, rash, cough, decreased appetite, pruritis, and headache [10]. It is important to distinguish common immune-related AEs from cemiplimab with manifestations of acute or chronic GVHD (in **Cohort 1**) and possible acute renal allograft rejection (in **Cohort 2**).

7.1.1.2 Adverse Event List(s) for mTOR inhibitors, Everolimus and Sirolimus

7.1.1.2.1. Everolimus

Stomatitis, infections, rash, fatigue, diarrhea, edema, abdominal pain, nausea, fever asthenia, cough, headache, and decreased appetite.

Please see package insert for a comprehensive list of adverse events.

7.1.1.2.2. Sirolimus

Peripheral edema, hypertriglyceridemia, hypertension, hypercholesterolemia, creatinine increased, abdominal pain, diarrhea, headache, fever, urinary tract infection, anemia, nausea, arthralgia, pain, and thrombocytopenia.

Please see package insert for a comprehensive list of adverse events.

7.1.1.3 Adverse Event List for Prednisone

Fluid retention, alteration in glucose intolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

Please see package insert for a comprehensive list of adverse events.

7.2 Adverse Event Characteristics

An adverse event (AE) is any undesirable sign, symptom or medical condition, or experience that develops or worsens in severity after starting the first dose of study treatment (cemiplimab) specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events *only* if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the

CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

Attribution of the AE:

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

### 7.3 Adverse Event Reporting

7.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI

7.3.2 Investigators **must** report to the Overall PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 90 days of the last dose of cemiplimab treatment on the local institutional SAE form.

7.3.3 DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

#### Serious Adverse Events

Definition of SAEs

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g. medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (e.g. pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g. death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

#### 7.3.4 Protocol-Specific Adverse Event Reporting Exclusions

There are no protocol-specific adverse event reporting exclusions for this protocol.

### 7.4 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA. Submit by fax to 1-800-FDA-0178.

### 7.5 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

### 7.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

### 7.7 Routine Adverse Event Reporting to Regeneron

Routine Adverse Events will not be reported to Regeneron. Regeneron will be collecting SAE

reports only.
All SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 90 days of discontinuation of cemiplimab dosing. All SAEs should be followed to resolution or stabilization.

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (e.g., a follow-up skin biopsy). The sponsor-investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

The sponsor-investigator will reconcile the clinical database SAE cases (case level only) transmitted to Regeneron, but all SAEs must be reported to Regeneron within 24 hours of occurrence, and sent to medical.safety@regeneron.com.

**Serious Adverse Events**

Definition of SAEs

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g. medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (e.g. pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g. death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs following the subject's written consent, during treatment, or within 90 days of the last dose of treatment on the local institutional SAE form.

Investigators will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy, using the local institutional SAE form.

### 7.6.1 Acute GVHD Adverse Event Grading (Cohort 1)

Symptoms of *acute* GVHD among **Cohort 1** require staging at initial and subsequent visits to ensure accuracy of severity. The National Institutes of Health (NIH) consensus criteria use of clinical findings [41], rather than a set of time periods, defines acute vs. chronic GVHD for the purpose of this study.

The modified Glucksberg grade (I-IV) should be utilized for on-study documentation (Table below).

| Organ | Stage | Description |
|---|---|---|
| Skin | 1 | Maculopapular rash over <25% of body area |
| | 2 | Maculopapular rash over 25 to 50% of body area |
| | 3 | Generalized erythroderma |
| | 4 | Generalized erythroderma with bullous formation and often with desquamation |
| Liver | 1 | Bilirubin 2.0 to 3.0 mg/dL; SGOT 150 to 750 international units |
| | 2 | Bilirubin 3.1 to 6.0 mg/dL |
| | 3 | Bilirubin 6.1 to 15.0 mg/dL |
| | 4 | Bilirubin >15.0 mg/dL |
| Gut | 1 | Diarrhea >30 mL/kg or >500 mL/day |
| | 2 | Diarrhea >60 mL/kg or >1000 mL/day |
| | 3 | Diarrhea >90 mL/kg or >1500 mL/day |
| | 4 | Diarrhea >90 mL/kg or >2000 mL/day; or severe abdominal pain with or without ileus |
| **Glucksberg grade** | | |
| I – Stage 1 or 2 skin involvement; no liver or gut involvement; ECOG PS 0 | | |
| II – Stage 1 to 3 skin involvement; Grade 1 liver or gut involvement; ECOG PS 1 | | |
| III – Stage 2 or 3 skin, liver, or gut involvement; ECOG PS 2 | | |
| IV – Stage 1 to 4 skin involvement; Stage 2 to 4 liver or gut involvement; ECOG PS 3 | | |

### 7.6.2 Diagnostic Criteria for Chronic GVHD (Cohort 1)

Symptoms of *chronic* GVHD among **Cohort 1** require staging at initial and subsequent visits to ensure accuracy of severity. The National Institutes of Health (NIH) consensus criteria use of clinical findings as summarized in the Table below [42], rather than a set of time periods, defines acute vs. chronic GVHD for the purposes of this study.

| Organ/Site | Diagnostic (sufficient alone for the diagnosis of chronic GVHD) | Distinctive (see in chronic GVHD, but insufficient alone for the diagnosis) |
|---|---|---|
| **Skin** | Poikiloderma<br>Lichen planus-like features<br>Sclerotic features<br>Morphea-like features<br>Lichen sclerosis-like features | Depigmentation |
| **Nails** | | Dystrophy<br>Longitudinal ridging, splitting, or brittle features<br>Onycholysis<br>Pterygium unguis<br>Nail loss (usually symmetric; affects most nails)* |
| **Scalp and body hair** | | New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy)<br>Scaling, papulosquamous lesions |
| **Mouth** | Lichen-type features<br>Hyperkeratotic plaques<br>Restriction of mouth opening from sclerosis | Xerostomia<br>Mucocele<br>Mucosal atrophy<br>Pseudomembranes*<br>Ulcers* |
| **Eyes** | | New-onset dry, gritty, or painful eyes¶<br>Cicatricial conjunctivitis<br>Keratoconjunctivitis sicca¶<br>Confluent areas of punctate keratopathy |
| **Genitalia** | Lichen planus-like features<br>Vaginal scarring or stenosis | Erosions*<br>Fissures*<br>Ulcers* |
| **GI tract** | Esophageal web<br>Strictures or stenosis in the upper to mid third of the esophagus* | |
| **Lung** | Bronchiolitis obliterans diagnosed with lung biopsy | Bronchiolitis obliterans diagnosed with PFTs and radiology¶ |
| **Muscles, fascia, joints** | Fasciitis<br>Joint stiffness or contractures secondary to sclerosis | Myositis or polymyositis¶ |

* In all cases, infection, drug effects, malignancy, or other causes must be excluded.
¶ Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer test for eyes).
PFTs = pulmonary function tests

The NIH GVHD scoring system includes information on the number of organs or sites involved and the severity within each affected organ (e.g., skin, mouth, eyes, gastrointestinal tract, liver, lungs, joints/fascia, and genital tract) (*see Form in Appendix F*). Organ specific severity is scored from 0 to 3 with higher scores reflecting more severe disease. Based upon this information, the overall severity is scored as mild, moderate, or severe:

- *Mild* – Involves **two or fewer** organs/sites with no clinically significant functional impairment
- *Moderate* – Involves **three or more** organs/sites with no clinically significant functional impairment or at least one organ/site with clinically significant functional impairment, but no major disability
- *Severe* – Major disability caused by chronic GVHD

### 7.6.3 Suspected Acute renal allograft rejection (Cohort 2)

For the purposes of this study, acute renal allograft rejection should be *suspected* in patients with **one or more** of the following:

- New increase in serum creatinine of ≥ 25% from baseline which is persistent for at least 7 days or a serum creatinine that is higher than expected (such as in recently transplanted patients whose serum creatinine stops decreasing earlier than expected after transplantation).
- Worsening hypertension
- Proteinuria >1 g/day
- Plasma donor-derived cell-free DNA (dd-cfDNA) >1%

Any participant in **Cohort 2** with suspected acute renal allograft rejection would **require a renal allograft biopsy at the discretion of the involved transplant nephrologist** to make the diagnosis, accurately grade the severity of rejection, and determine the degree of irreversible kidney damage. Biopsy of the renal allograft can also reveal other causes of renal inflammation and injury, including: cytomegalovirus (CMV) disease, BK (polyomavirus) nephropathy, interstitial nephritis, pyelonephritis, de novo or recurrent glomerular disease, and posttransplant lymphoproliferative disease (PTLD).

## 8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in *Section 7*.

### 8.1 Cemiplimab

#### 8.1.1 Description

Cemiplimab is a covalent heterotetramer consisting of two disulfide-link human heavy chains, each of which is covalently bonded through disulfide linkages to a human kappa light chain. The antibody possesses an approximate molecular weight of 143.6 kilounified atomic mass unit (kDa) based on the primary sequence. There is a sing N-linked glycosylation site on each heavy chain, located within the constant region in the Fc portion of the molecule. The cemiplimab heavy chain possesses an IgG4 isotype constant region. The variable domains of the heavy and light chains combine to form PD-1 binding site within the antibody.

Cemiplimab-rwlc (REGN-8210 or Libtayo®) is a recombinant human IgG4 monoclonal antibody that inhibits programmed death-1 (PD-1) activity by binding to PD-1 and blocking the interactions with the ligands PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of immune response, including anti-tumor response. PD-1 ligand upregulation may occur in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Blocking PD-1 activity has resulted in decreased tumor growth. Distribution: $V_d$: 5.3L, half-life elimination: 19 days, excretion: first dose clearance: 0.32 L/day, steady state: 0.21 L/day.

#### 8.1.2 Form

Solution, Intravenous [preservative free]: Libtayo®: 350 mg/7 mL (7 mL) [contains polysorbate 80]. Clear to opalescent colorless to pale yellow liquid. May contain particles.

#### 8.1.3 Storage and Stability

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of cemiplimab include laboratory coats and gloves.

#### 8.1.4 Compatibility

Do not administer with other medications. Flush with NS or D5W at the end of infusion.

#### 8.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

#### 8.1.6 Preparation

Cemiplimab-rwlc can be prepared per the package insert which can be referenced at:
https://www.regeneron.com/sites/default/files/Libtayo_FPI.pdf

#### 8.1.7 Availability

Free of cost, investigational supply of cemiplimab, will be provided by Regeneron pharmaceuticals.

#### 8.1.8 Ordering

Dana-Farber Research Pharmacy and all pharmacies at all participating sites will request supply of cemiplimab, directly from Regeneron, by submitting an order form, provided by Regeneron.

#### 8.1.9 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).

#### 8.1.10 Destruction and Return

Unused supplies and expired supplies of the investigational agents will be destroyed on site, by the pharmacy, per institutional standard operating procedures.

### 8.2 Other Agents

Everolimus or sirolimus (mTOR inhibitors) and prednisone will be stored and prepared per

standard of care/institutional guidelines. Everolimus or sirolimus (mTOR inhibitors) and prednisone will be obtained per standard of care clinical supply.

## 9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

### 9.1 Laboratory Correlative Studies

Correlative studies are planned as part of this study in order to characterize the peripheral and tumor immune microenvironment and perform tumor immunophenotyping and functional assays. A peripheral blood sample and fresh tissue tumor biopsy (**B1**) is required as part of enrollment to the study and after (30 days or 2 cycles of therapy but before cycle 3, [**B2**]) anti-PD-1 therapy. Blood and tissue will be sent for tumor immune profiling and other studies, which will include genomic and mutational analysis. Fine needle aspiration cytology samples alone are discouraged, but acceptable if no core material is available.

An additional required tissue biopsy (**B3R**) is required at the time of organ rejection or the development of GVHD to assess the off-target immunologic effects of treatment.

#### 9.1.1 Specimen Collection and Handling

The study aims for 2-3 cores per mandatory *tumor biopsy* obtained throughout the study. The tumor biopsy may be core, a fine needle aspiration (FNA), or skin biopsy. If doing a skin core, any size up to 6mm is acceptable.

- 1 core is fresh tissue placed in RPMI containing 10% fetal bovine serum (FBS) 5 mL microcentrifuge tube for multiparametric flow cytometry or CyTOF, or other genomic or molecular studies. The tissue will and delivered to the Belfer Center for Applied Cancer Science, 360 Longwood Avenue, Boston, MA 02215, phone: 207-423-0958 or 631-487-6573 (contact: Patrick Lizotte, Ph.D.). The specimen must arrive in a timely fashion to facilitate processing for evaluation of immune cells.
- 1 or 2 cores are fixed or placed a standard specimen cup containing 10% neutral buffered formalin for IHC/MIF, genomic, and functional assay work. Once prepared, aliquoted core material for will be delivered immediately to the laboratory of Dr. Ravindra Uppaluri at the DFCI [Dana Building, 8$^{th}$ floor, room 819, 450 Brookline Avenue, Boston, MA 02215, phone: 617-632-3091].

The study aims to collect mandatory *peripheral blood* samples throughout the study.

- 4 tubes drawn in phlebotomy or clinic and captured in 8 mL whole blood, purple top tubes are collected at each time point for peripheral immunophenotyping. The volume of blood to be collected per blood draw for study purposes will not exceed 40 mL. After collection, two blood tube samples should be delivered immediately to the Belfer Center for Applied Cancer Science, 360 Longwood Avenue, Boston, MA 02215, phone: 207-423-0958 or 631-487-6573 (contact: Patrick Lizotte, Ph.D.). The other two samples should be delivered immediately to the Transplant Research Center, 221 Longwood Avenue, Boston, MA 02215, phone: 617-732-5252 (contact: Naoka Murakami, MD

PhD). The specimens must arrive in a timely fashion (ideally within 4 hours of colelction) to facilitate processing for evaluation of immune cells.

The study aims to collect mandatory *urine samples* throughout the study for the detection of potential biomarkers of kidney rejection.

- 1 urine cup (at least 10 mL) should be collected in clinic and after collection, the urine sample should be delivered immediately to the Transplant Research Center, 221 Longwood Avenue, Boston, MA 02215, phone: 617-732-5252 (contact: Naoka Murakami, MD PhD). The specimen must arrive within 4 hours of collection to facilitate processing for evaluation of immune cells.

All specimens will be de-identified and labeled with the participant's study ID number, the date of acquisition, and timepoint on study [**B1, B2, B3R** as above]. Leftover specimens may be banked for future use and would be accessible to Dr. Glenn Hanna, the overall PI.

### 9.1.2 Planned Correlative Studies

Peripheral blood and tumor biopsy samples will be treated with monoclonal antibodies specific for different immune cell markers (CD3, CD8, PD-1/L1, TIM-3, LAG-3, CTLA-4, FOXp3, CD56, etc.) to identify immune cell subsets (or phenotypes) and tumor cells. After incubation of cells with monoclonal antibodies, individual subsets are then enumerated by flow cytometry. These studies will allow us to measure quantitative changes of individual cell populations that occur as a result of anti-PD-1 treatment. Mass cytometry (CyTOF) will permit high throughput analysis of single cells for a large number of parameters, to deeply immunophenotype and track the inhibitory and activating receptor diversity of immune cells among samples.

IHC/MIF is additionally planned on tumor biopsy specimens to identify immune cell population geographic and spatial interactions not depicted by flow cytometry or CyTOF. Antibody staining for immune cell markers noted above will be employed for slide overlay comparison among matched pre- and post-immunotherapy tumor biopsies (when available).

Paired tumor biopsy material is also partitioned to perform whole-exome sequencing analyses on DNA, bulk RNA, or both (as tissue and resources permit). Additional T cell receptor (TCR) sequencing may also be explored. Mutational burden and individual alterations will be correlated with response.

Peripheral blood and urine samples will be used for immune cell characterization with above flow cytometry, and matched to tumor samples to compare immune subsets in circulation with those in the tumor microenvironment. In addition, plasma and urine cytokine profiling will be employed to measure key inflammatory cytokines (IL-2, IFN-γ) to correlate with response.

## 10. STUDY CALENDAR

Baseline or screening evaluations are to be conducted within 2 weeks (14 days, ± 3 days) of the start of protocol therapy (either cemiplimab in **Cohort 1**, or the lead-in phase for **Cohort 2**).

Baseline imaging must be done ≤ 3 weeks (21 days, ± 5 days) prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

| | Screening[Q] | Lead-in Phase | C1-2 [3] | | | C3-6 [3] | | C7+ [3] | End of Treatment Visit +/- 3 days | Follow-up[R] 30 day f/u visit then Q 3-4 months up to 1 year +/- 7 days | EDC Timepoints |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | D1 +/- 3 days (window for cycle 2 only) | D8 +/- 3 days | D15 +/- 3 days | D1 +/- 3 days | D8 +/- 3 days | D1 +/- 3 days | | | |
| mTOR inhibitor (Everolimus or Sirolimus)[A,2] | | X[2] | X[2] ——► | | | | | | | | N/A |
| Prednisone[B,2] | | X[2] | X[2] ——► | | | | | | | | N/A |
| Cemiplimab | | | X | | | X | | X | | | Day 1 of every Cycle |
| Informed consent | X | | | | | | | | | | N/A |
| Demographics | X | | | | | | | | | | Screening |
| Medical history | X | | X | | | X | | X | X | X | Screening |
| Concurrent meds[C] | X | | X | | | X | | X | X | | N/A |
| Physical exam | X | | X | | | X | | X | X | | Screening |
| Vital signs | X | | X | | | X | | X | X | | Screening |
| Height | X | | | | | | | | | | Screening |
| Weight | X | | X | | | X | | X | X | | Screening |
| Performance status[D] | X | | X | | | X | | X | X | | Screening, D1 of every Cycle, EOT |
| Hematology labs[E] | X | | X | | | X | | X | X | | Screening, D1 of every Cycle, EOT |
| BUN/creatinine | X | | X | X[2] | X[2] | X | X[2] | X | X | | Screening, Days 1, 8 and 15 for Cycles 1&2, Day 1 for Cycles 7+, EOT |
| Urinalysis[F, 2] | X[2] | | X[2] | X[2] | X[2] | X[2] | | X[2] | X[2] | | Screening, Day 1 of Cycles 1-7+, EOT |
| Spot urine protein/creatinine ratio[G,2] | X[2] | | X[2] | X[2] | X[2] | X[2] | | X[2] | X[2] | | Screening, Day 1 of Cycles 1-7+, EOT |
| Other Chemistries[H] | X | | X | X[2] | X[2] | X | | X | X | | Screening, Day 1 of Cycles 1-7+, EOT |
| Urine or serum HCG[I] | X | | X[I] | | | | | | | | N/A |
| HIV, CMV, hepatitis panel[J,1,2] | X | | | | | | | | | | Screening |
| HTLV[1] | X[1] | | | | | | | | | | Screening |
| BK virus[1] | X[1] | | | | | | | | | | Screening |
| mTOR blood levels[K,2] | X[2] | X[2] ——► | | | | | | | | | N/A |
| ECG | X | | | | | | | | | | Screening |
| Tumor assessments[L] | X[L] | | X[L] ——► | | | | | | | | Screening, Day 1 of Cycles 1-7+, EOT |
| Mandatory Tumor or tissue biopsy[M] | X | | | | X[M] | | | | X[M] | | Screening, Cycle 2 Day 15 |
| Mandatory Research blood[N] | X | X | X | | | X | | X | X | | Screening, lead in phase, Day 1 of Cycles 1-7+, EOT |
| Mandatory Research | X | | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | | Screening, Every visit of Cycles 1-7+, |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| urine[S,2] | | | | | | | | | | | EOT |
| AE evaluation[O] | | | X | | | X | | X | X | X | Screening, lead in phase, Day 1 of Cycles 1-7+, EOT |
| Acute/Chronic GVHD scoring[P,1] | X[1] | | X[1] | | | X[1] | | X[1] | X[1] | | Day 1 of all cycles, EOT, Follow up |

[1] items marked with a #1 are only required for **Cohort 1** (post-allo-HSCT patients)
[2] items marked with a #2 are only required for **Cohort 2** (post-renal transplant patients)
[3] Cycles are 21 days in length.
[A] either everolimus or sirolimus at the discretion of the treating transplant nephrologist
[B] dynamic dosing scheme based on timing of PD-1 blockade: 40 mg the day before D1 of each cycle, 40 mg on D1 of each cycle through D3, then 20 mg D4 through D6 followed by 10 mg on D7-20 of each cycle until the day prior to the next cycle when the schedule of dosing repeats back to 40 mg, and so on
[C] see prohibited concurrent medications and CYP3A4 interaction table in *Section 5.4.2*.
[D] using ECOG performance status scale in *Appendix B*
[E] hematology panel should include: CBC with differential, hemoglobin, hematocrit, platelets, absolute neutrophil count
[F] urinalysis without a reflex culture required in **Cohort 2** only
[G] spot protein-creatinine ratio calculation required in **Cohort 2** only
[H] Chemistry panel should include: comprehensive metabolic panel, magnesium, phosphorus, LDH, and thyroid function testing (TSH, free T4). Only a BMP is required on D8 and D15 of cycles 1 and 2 in **Cohort 2**
[I] Urine HCG testing: women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of cemiplimab
[J] HIV-1/2 antibody, CMV serologies (IgG/IgM), and hepatitis panel should include: HAV antibody, HbsAg, HbcAb, HbsAb, HCV antibody
[K] everolimus or sirolimus trough levels should be drawn in the morning before the patient's AM dose and the goal range is 4-6 ng/mL (reporting is delayed due to send out testing). Testing intervals are every 7-10 days (± 3 days) in cycles 1-2, then on days 1, 8 for cycles 3-6, and on day 1 only for cycle 7 onward. The treating transplant nephrologist will determine any dose changes based on trough levels while on study.
[L] radiographic imaging with CT scans of the chest, abdomen and pelvis are required at screening (baseline imaging must be done ≤ 3 weeks [21 days, ± 5 days] prior to the start of therapy), and every 8 weeks [± 5 days] on study through cycle 10 at which point restaging scans can occur every 12 weeks [± 5 days]. CT neck with contrast should be included at each scan time point if clinical evidence of or concern for involved cervical neck disease. A PET-CT from scalp to toe can be used in lieu of CT imaging for some patients if clinically indicated
[M] fresh tissue tumor biopsy is required; an on-treatment biopsy is required after 30 days or 2 cycles of treatment but before start of cycle 3. The end of visit biopsy is only required if this was obtained for acute organ rejection or GVHD in which case the involved organ (kidney, skin, GI tract) should be biopsied and not the tumor
[N] research peripheral blood samples required (see *Section 9.1* for details about collection)
[O] Adverse event evaluations should be recorded using CTCAE version 5.0
[P] only in **Cohort 1**, patients require both acute GVHD score (*Section 7.6*) and chronic NIH GVHD scoring (*Section 7.7*) if there is clinical concern for the development of GVHD
[Q] baseline screening evaluations (except for informed consent and imaging, see *Footnote L*) are to be conducted within 2 weeks [14 days, ± 5 days] of the start of protocol therapy (either cemiplimab in Cohort 1, or the lead-in phase for Cohort 2)
[R] follow-up beyond the study should include routine check-ins every 3-4 months up to 12 months or 1 year from EOT visit, which can overlap with routine clinic visits or include telephone encounters
[S] research urine samples collected as at least 100 mL aliquots in a standard sample cup will be obtained at screening and each cycle visit; if local labs are collected then day 8, 15 urine samples for research can be skipped

## 11. MEASUREMENT OF EFFECT

### 11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 8 weeks through cycle 10 at which point restaging scans can occur every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [43] and by WHO response criteria [44]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. Changes in the sum of the products of the two longest diameters in perpendicular directions (bidimensional measurements) are used in the WHO criteria.

#### 11.1.1 Definitions

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

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

#### 11.1.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area may be considered measurable.

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

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

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

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

Target lesions (per RECIST v1.1). All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. For the purpose of this study, when using WHO criteria, up to 5 lesions are measured, or are deemed target lesions.

Non-target lesions (per RECIST v1.1). All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

### 11.1.3 Methods for Evaluation of Disease

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

The same method of assessment and the same technique should be used to characterize

each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

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

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

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

### 11.1.4 Response Criteria

#### 11.1.4.1 Evaluation of Target Lesions

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

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters per RECIST v1.1. At least a

50% reduction in the sum of the products of the two longest diameters among all lesions per WHO criteria.

Progressive Disease (PD): Per RECIST v1.1, at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Per WHO criteria, at least a 25% increase in the sum of the product of the two longest diameters among all lesions, or at least 25% increase in any 1 lesion.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study per both RECIST v1.1 and WHO criteria.

#### 11.1.4.2 Evaluation of Non-Target Lesions for RECIST v1.1

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

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

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

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

#### 11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

#### 11.1.4.4 Second Primary Cutaneous and Other Malignancies

Given this study involves high-risk and immunosuppressed transplant survivors, the finding of a new, spatially or regionally distinct (not in-transit) non-melanomatous skin cancer (squamous cell carcinoma) thought to be a second primary is **not** considered a new lesion for the definition of PD. In addition, the development of a second primary malignancy with squamous histology (in the lungs, head and neck) is also **not** considered a new lesion for the definition of PD.

#### 11.1.4.5 Treatment Beyond Disease Progression

The decision to treat any study participant beyond progression of disease is at the discretion of the treating investigator and can be discussed with the Overall PI. Patients who are assigned a best response of PD at any time point can continue on-study treatment if the patient is receiving some reasonable clinical benefit and is tolerating the study drug.

Patients treated beyond disease progression should be re-consented at the time of initial imaging showing possible progression to ensure they are aware of alternative therapies and investigational options that may be available in lieu of continued study treatment.

In this scenario, it is recommended that repeat restaging imaging be performed 4-6 weeks after the documentation of PD to re-evaluate for ongoing clinical benefit.

#### 11.1.4.6 Evaluation of Best Overall Response

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

**For Participants with Measurable Disease (*i.e.*, Target Disease) per RECIST v1.1**

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Overall Response when Confirmation is Required* |
|---|---|---|---|---|
| CR | CR | No | CR | > 4 wks Confirmation** |
| CR | Non-CR/Non-PD | No | PR | ≥ 4 wks Confirmation** |
| CR | Not evaluated | No | PR | |
| PR | Non-CR/Non-PD/not evaluated | No | PR | |
| SD | Non-CR/Non-PD/not evaluated | No | SD | Documented at least once ≥ 4 wks from baseline** |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD*** | Yes or No | PD | |
| Any | Any | Yes | PD | |

* See *Section 11.4.1.3* for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.

| | |
|---|---|
| *** | In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. |
| Note: | Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment. |

**For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease) per RECIST v1.1**

| Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD* |
| Not all evaluated | No | not evaluated |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |
| * 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised | | |

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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

11.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from registration to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from registration to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Duration of Response: Time from documentation of PR or CR at first reporting (later confirmed with 4-week imaging) to time of progression or censored at date of last disease evaluation.

## 12. DATA REPORTING / REGULATORY REQUIREMENTS

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

### 12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Study team is responsible for entering data in the eDC system (InForm), within the timeframe, in accordance with DF/HCC SOPs.

Tumor genomic and molecular profiling results that are available or become available during the study will be recorded during study participation.

### 12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

## 13. STATISTICAL CONSIDERATIONS

This study is not designed for statistical hypothesis testing.

Original biostatistical design:

The 3+3 design is adapted to determine the safety and toxicity of immunotherapy in Cohort 1 and Cohort 2. To that end, while accrual is expected to be slow, we will approve **two** patients to enroll into to each cohort at a time to monitor toxicity appropriately. For each cohort, the **maximum sample size is 12.** The actual sample size is dependent upon observed GVHD rate or acute organ rejection rate. The assessments will be done when up to 12 patients have been enrolled and observed in each cohort. For **Cohort 1**, a GVHD rate exceeding 33% is considered unacceptable. The following table shows the stop rule:

| Number of patients treated in **Cohort 1** | 3 | 6 | 12 |
|---|---|---|---|
| Stop recruitment if # of GVHD ≥ | 2 | 3 | 6 |

For **Cohort 2**, a renal transplant rejection rate exceeding 60% is considered unacceptable. This cutoff was selected given that recently published data including 23 renal transplant recipients who received various checkpoint inhibitors experienced a 50% rate of acute kidney rejection [19] on variable immunosuppressive regimens. Since enrolled subjects in the current study have incurable, metastatic, and life-threatening cutaneous SCC, the investigators feel that an acute renal graft rejection rate above 60% would mitigate the exposure risk to PD-1 blockade in the present study. Therefore, the following table shows the stop rule:

| Number of patients treated in **Cohort 2** | 3 | 6 | 12 |
|---|---|---|---|
| Stop recruitment if # of rejection ≥ | 2 | 4 | 6 |

Modified biostatistical design: Due to slower than expected accrual in Cohort 1 and the observation of safety and efficacy in Cohort 2, the Sponsor-Investigator and study team discussed closure of Cohort 1 with a focus on Cohort 2 in November 2021. No patients enrolled to Cohort 1. With those updates, the final sample size was set at a maximum of 12 patients overall (in Cohort 2 only).

### 13.1 Study Design/Endpoints

**Primary Endpoints:** To determine the safety and toxicity of immunotherapy in advanced cutaneous squamous cell carcinoma (cSCC) patients having undergone prior hematopoietic stem cell or renal transplant.

**Secondary Endpoints:** To evaluate the anti-tumor activity and survival benefit in advanced cSCC patients receiving immunotherapy despite a history of transplant:

- To estimate progression-free survival (PFS) and overall survival (OS)
- To estimate duration of therapeutic response
- To estimate the propensity for secondary infection on treatment

Follow-up visits will occur every 3-4 months up to 1 year. Accrual is expected to be slower than other therapeutic protocols given the rarity of the condition, but we expect 1 patient to enroll

every 3 months among each cohort (1 renal transplant patient, and 1 stem cell transplant patient) which would result in an estimated 18 months or 1.5 years to accrue the study.

### 13.2 Stratification Factors

There are no planned stratification factors.

### 13.3 Analysis of Primary Endpoints

Patient safety will be assured by monitoring the proportions of patients who have observed GVHD in **Cohort 1** or renal transplant rejection in **Cohort 2** when 3 to 12 patients have been enrolled into each cohort.

Participants will be evaluable for toxicity from the time of their first treatment. The toxicity will be presented in frequency tables (overall and by cohort). In tables showing the overall incidence of adverse events, patients who experienced the same event on more than one occasion will be counted only once in the calculation of the event frequency. The worst grade of an event will be reported for any patient.

### 13.4 Analysis of Secondary Endpoints

Time-to-event endpoints will be summarized using the method of Kaplan-Meier. Point estimates for each endpoint will be presented with 90% confidence intervals derived using log(-log(survival)) methodology. The other secondary endpoints including anti-tumor activity will be summarized descriptively.

## 14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in *Section 13* on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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**APPENDIX A CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION**

## CKD-EPI Equation

$$GFR = 141 \times [\min(Scr/\kappa),1)^{\alpha} \times \max(Scr/\kappa),1)^{-1.209}] \times Age^{-0.993} \times 1.018 \text{ [if female]} \times [1.157 \text{ if Black}]$$

*$\alpha$ is 0.329 for females and 0.411 for males; min indicates minimum of Scr/$\kappa$ or 1, and max indicates maximum of Scr/$\kappa$ or 1*

| | | | | |
|---|---|---|---|---|
| Female | ≤0.7 → | $GFR = 144 \times (Scr/0.7)^{-0.329}$ | $\times Age^{-0.993}$ | $\times 1.157$ [if black] |
| | >0.7 → | $GFR = 144 \times (Scr/0.7)^{-1.209}$ | | |
| Male | ≤ 0.9 → | $GFR = 141 \times (Scr/0.9)^{-0.411}$ | | |
| | >0.9 → | $GFR = 141 \times (Scr/0.9)^{-1.209}$ | | |

## APPENDIX B PERFORMANCE STATUS CRITERIA

| **ECOG Performance Status Scale** | | **Karnofsky Performance Scale** | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

## APPENDIX C GUIDANCE ON CONTRACEPTION

**Highly Effective Methods of Contraception:**
Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner.

At a minimum, subjects must agree to use one highly effective method of contraception as listed below:

**For WOCBP** highly effective methods of birth control include the following:
- Progestogen only hormonal contraception associated with inhibition of ovulation
- Hormonal methods of contraception including oral contraceptive pills (combination of estrogen and progesterone), vaginal ring, injectables, or implants
- Intrauterine devices (IUDs) (hormonal or non-hormonal)
- Intrauterine Hormone-releasing System (IUS)
- Bilateral tubal ligation
- Vasectomy
- Complete abstinence (complete avoidance of heterosexual intercourse)

**For male subjects with partners that are WOCBP:**
- Condom

All male subjects who have partners who are WOCBP must use condoms as their second method of contraception.

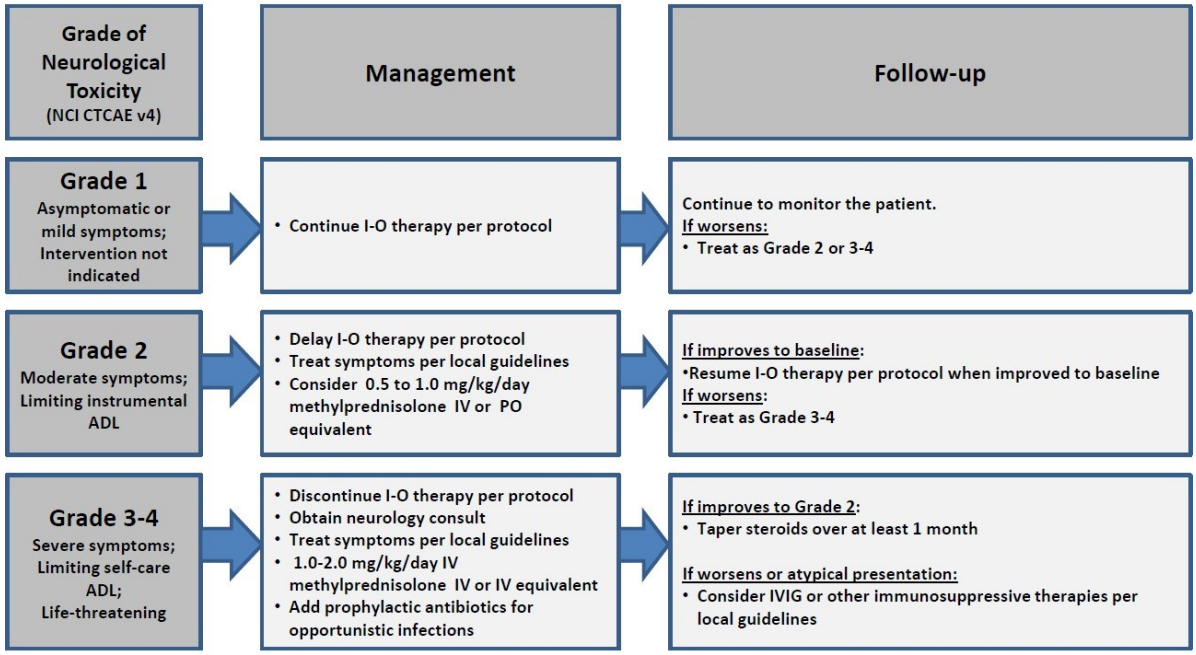
Women of childbearing potential (WOCBP) receiving cemiplimab will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational product. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational product. These durations have been calculated using the upper limit of the half-life for cemiplimab (25 days) and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days after the last dose of cemiplimab.

## APPENDIX D IMMUNE-MEDIATED TOXICITY MANAGEMENT ALGORITHMS

- These general guidelines constitute guidance to the Investigator. The guidance applies to all immuno-oncology (I-O) agents and regimens.
- A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.
- Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
- Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.
- The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

# Neurological Adverse Event Management Algorithm

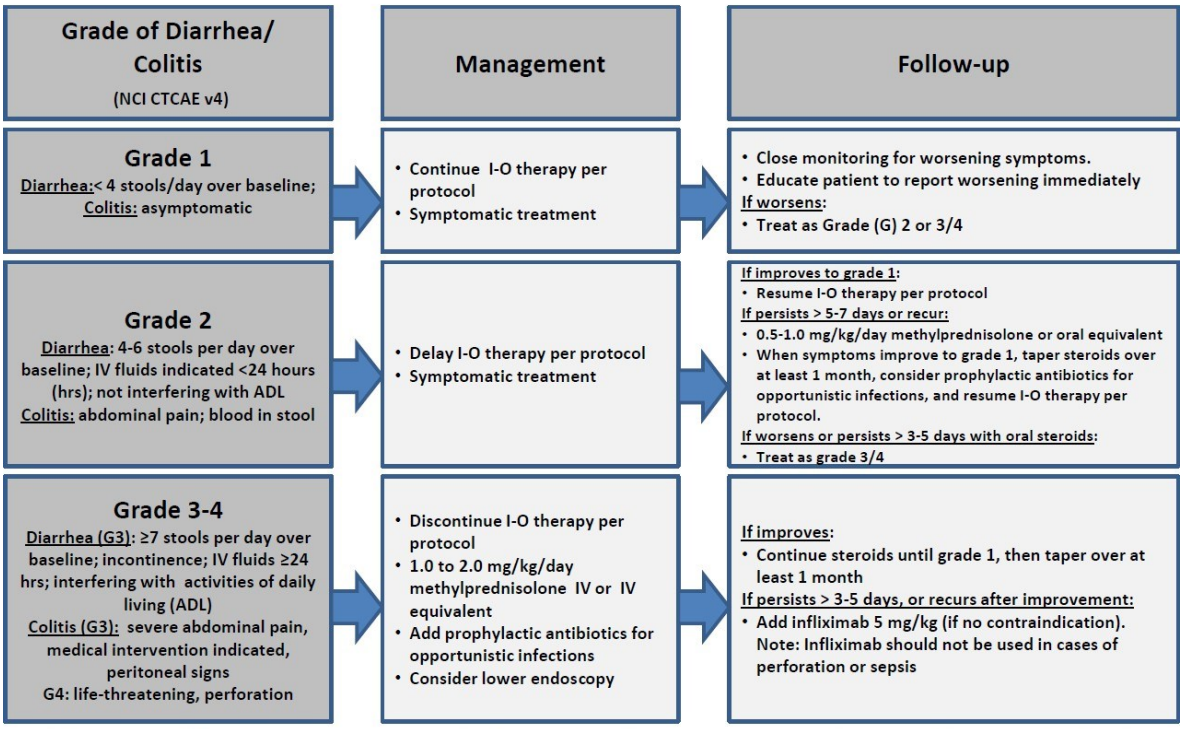
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.




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

# GI Adverse Event Management Algorithm

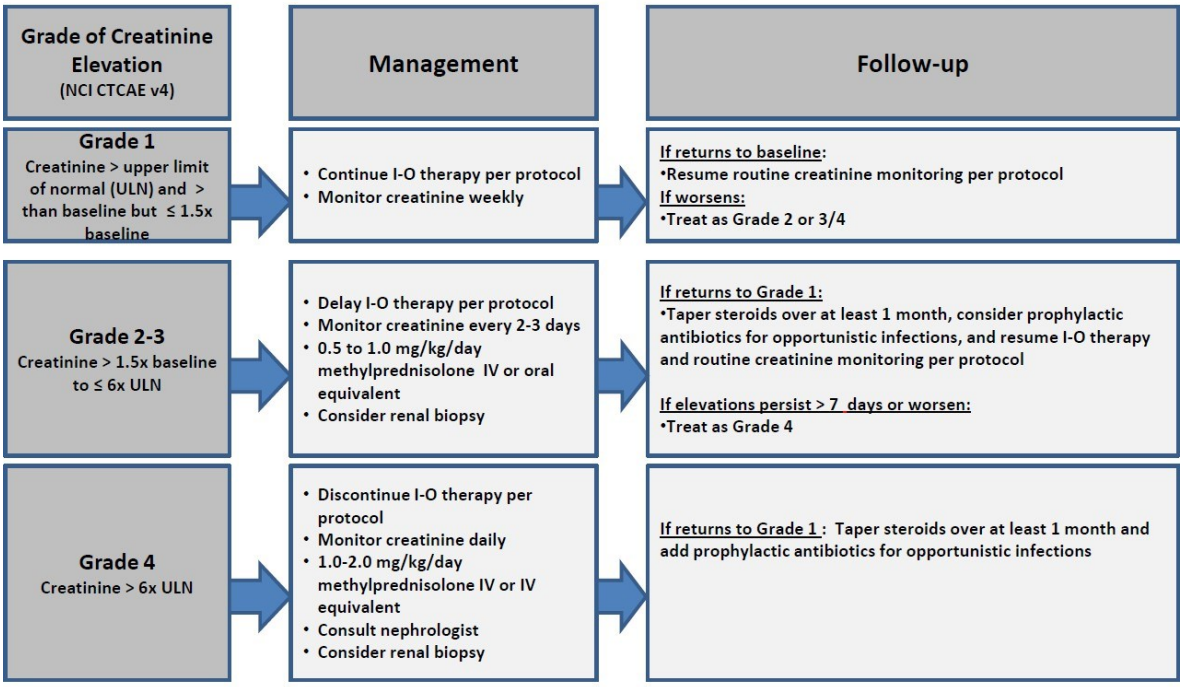
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.




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

## Renal Adverse Event Management Algorithm

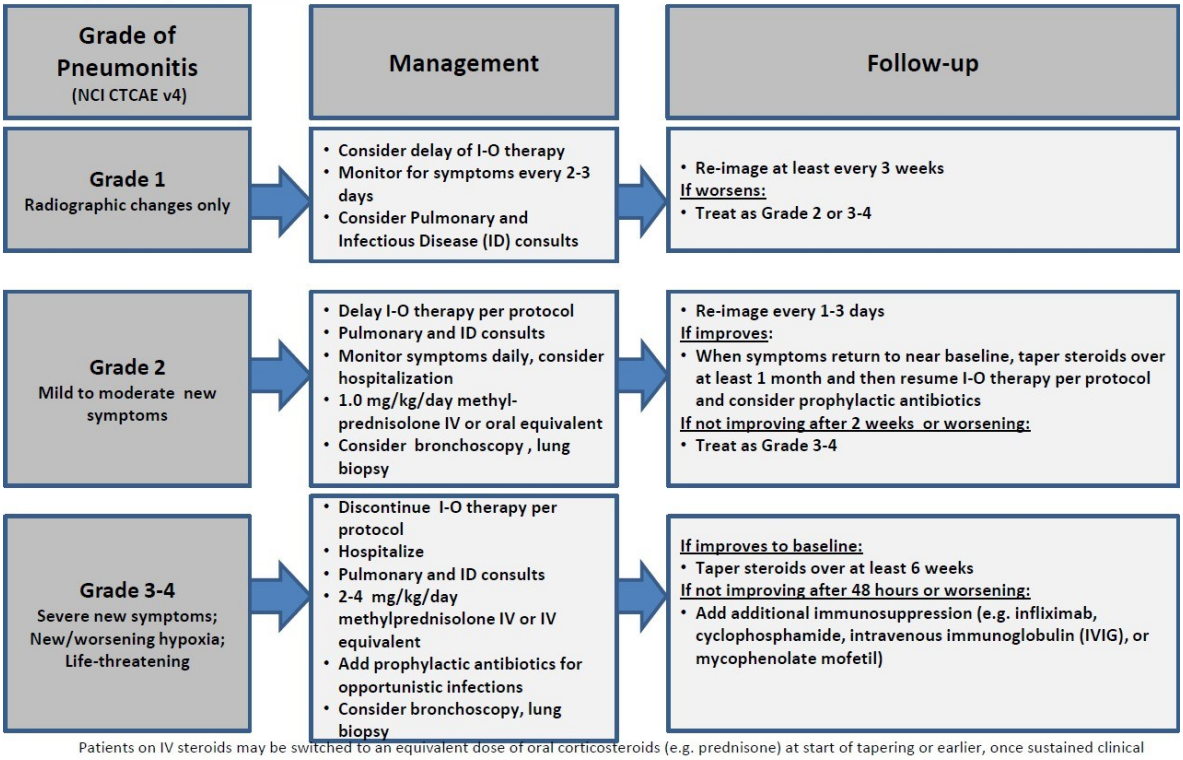
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy




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

# Pulmonary Adverse Event Management Algorithm

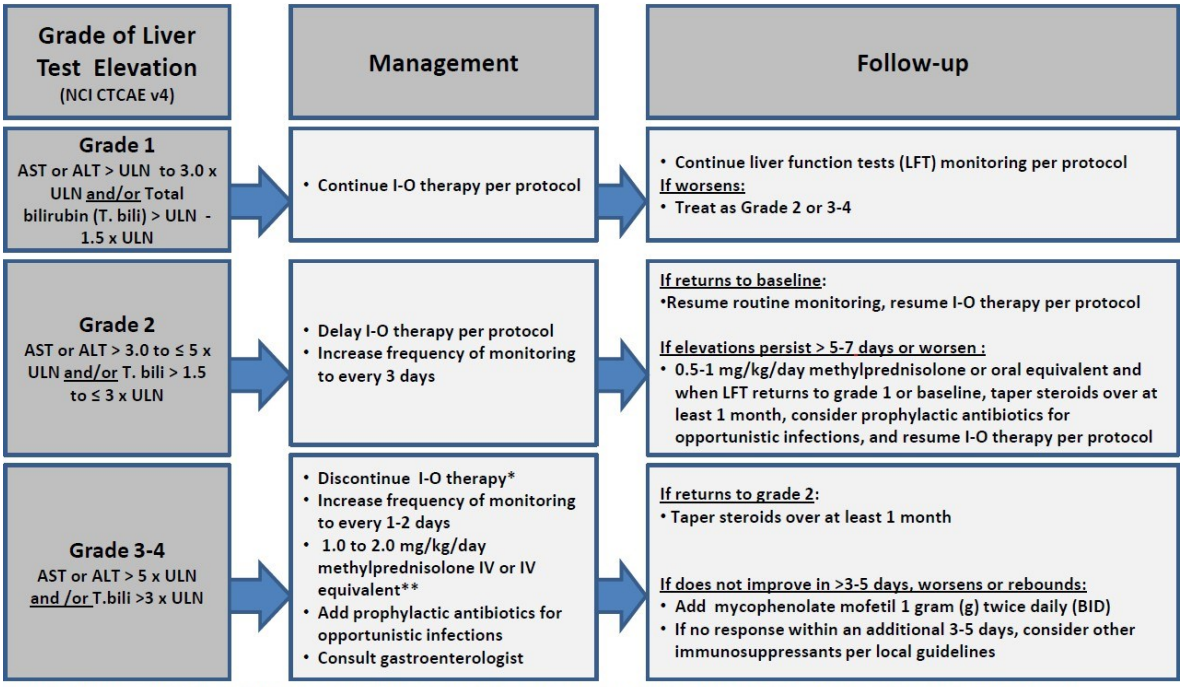
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.




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

# Hepatic Adverse Event Management Algorithm

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



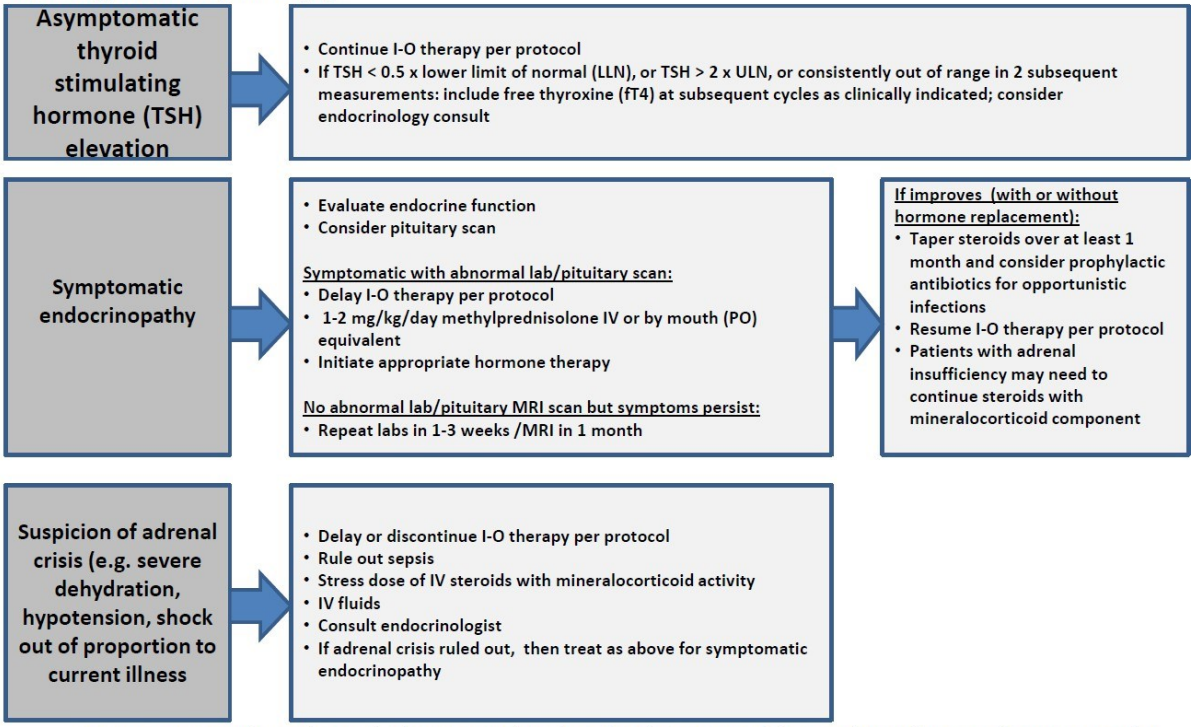

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

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

# Endocrinopathy Management Algorithm

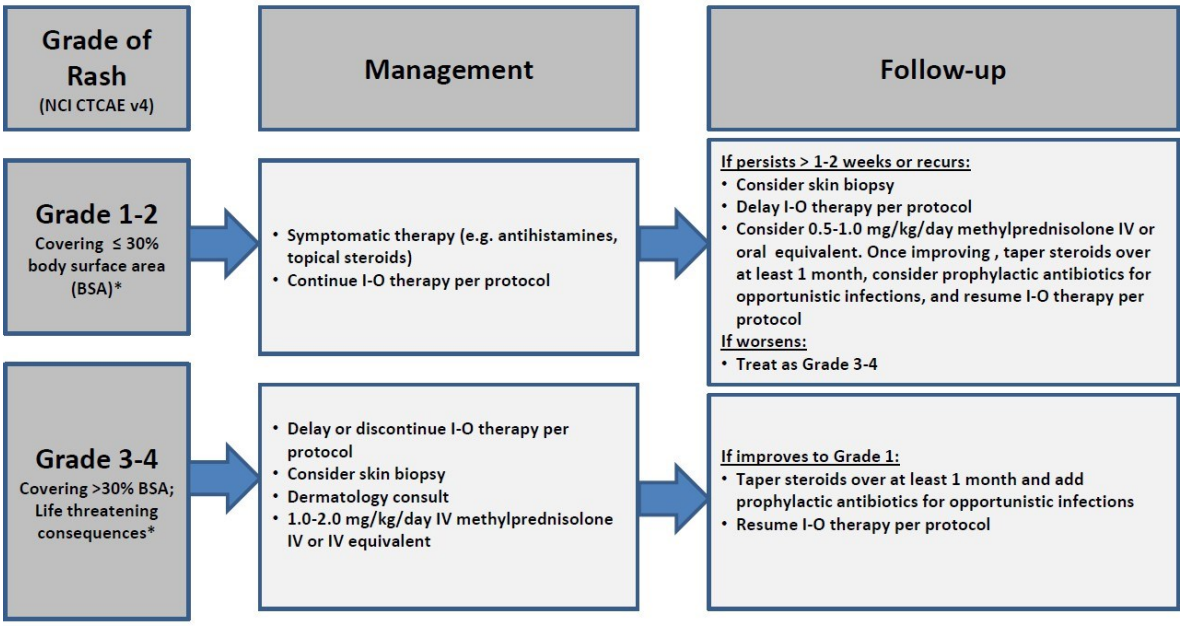
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.




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

## Skin Adverse Event Management Algorithm

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




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

## APPENDIX E NIH CONENSUS FORM FOR SCORING CHRONIC GVHD

| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| **PERFORMANCE SCORE:** ☐ **KPS ECOG LPS** | Asymptomatic and fully active (ECOG 0; KPS or LPS 100%) | Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%) | Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%) | Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%) |
| **SKIN†** ☐ **SCORE % BSA** *GVHD features to be scored by BSA:* **Check all that apply:** Maculopapular rash/erythema; Lichen planus-like features; Sclerotic features; Papulosquamous lesions or ichthyosis; Keratosis pilaris-like GVHD | No BSA involved | 1-18% BSA | 19-50% BSA | >50% BSA |
| **SKIN FEATURES SCORE:** | No sclerotic features | | **S**uperficial sclerotic features "not hidebound" (able to pinch) | **Check all that apply:** Deep sclerotic features; "Hidebound" (unable to pinch); Impaired mobility; Ulceration |
| *Other skin GVHD features (NOT scored by BSA)* **Check all that apply:** Hyperpigmentation; Hypopigmentation; Poikiloderma; Severe or generalized pruritus; Hair involvement; Nail involvement; *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____ | | | | |
| **MOUTH** *Lichen planus-like features present:* **Yes** **No** | No symptoms | Mild symptoms **with** disease signs but not limiting oral intake significantly | Moderate symptoms with disease signs **with** partial limitation of oral intake | Severe symptoms with disease signs on examination **with** major limitation of oral intake |
| *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____ | | | | |

| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| **EYES**<br><br>*Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:*<br>**Yes**<br>**No**<br>**Not examined** | No symptoms | Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day) | Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS | Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS |
| *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____ | | | | |
| **GI Tract**<br>***Check all that apply:***<br>Esophageal web/ proximal stricture or ring<br>Dysphagia<br>Anorexia<br>Nausea<br>Vomiting<br>Diarrhea<br>Weight loss ≥5%*<br>Failure to thrive | No symptoms | Symptoms without significant weight loss* (<5%) | Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living | Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living |
| *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____ | | | | |
| **LIVER** | Normal total bilirubin and ALT or AP < 3 x ULN | Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN | Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN | Elevated total bilirubin > 3 mg/dL |
| *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____ | | | | |
| **LUNGS****<br>**Symptom score**: | No symptoms | Mild symptoms (shortness of breath after climbing one flight of steps) | Moderate symptoms (shortness of breath after walking on flat ground) | Severe symptoms (shortness of breath at rest; requiring $0_2$) |
| **Lung score:**<br>**%** FEV1 ☐<br><br>*Pulmonary function tests*<br>Not performed | FEV1≥80% | FEV1 60-79% | FEV1 40-59% | FEV1 ≤39% |
| *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____ | | | | |

| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| **JOINTS AND FASCIA**<br>P-ROM score<br>*(see below)*<br>Shoulder (1-7):___<br>Elbow (1-7): ____<br>Wrist/finger (1-7):___<br>Ankle (1-4):___ | No symptoms | Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL | Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL | Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.) |
| *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____ | | | | |
| **GENITAL TRACT**<br>(*See Supplemental figure*‡)<br>Not examined<br>*Currently sexually active*<br>Yes<br>No | No signs | Mild signs‡ and females with or without discomfort on exam | Moderate signs‡ and may have symptoms with discomfort on exam | Severe signs‡ with or without symptoms |
| *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____ | | | | |

**Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)**

| | | |
|---|---|---|
| Ascites (serositis)___ | Myasthenia Gravis___ | |
| Pericardial Effusion___ | Peripheral Neuropathy___ | Eosinophilia > 500/µl___ |
| Pleural Effusion(s)___ | Polymyositis___ | Platelets <100,000/µl ___ |
| Nephrotic syndrome___ | Weight loss>5%* without GI symptoms ___ | Others (specify):_____ |

**Overall GVHD Severity** *(Opinion of the evaluator)* ❑ **No GVHD** ❑ **Mild** ❑ **Moderate** ❑ **Severe**

**Photographic Range of Motion (P-ROM)**


† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

* Weight loss within 3 months.

**Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

Abbreviations: ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphatase); ALT (alanine aminotransferase); ULN (normal upper limit).

‡ To be completed by specialist or trained medical providers (see Supplemental Figure).

Table 2

NIH Global Severity of Chronic GVHD

**Mild chronic GVHD**

1 or 2 organs involved with no more than score 1 *plus*
Lung score 0

**Moderate chronic GVHD**

3 or more organs involved with no more than score 1

OR

At least 1 organ (not lung) with a score of 2

OR

Lung score 1

**Severe chronic GVHD**

At least 1 organ with a score of 3

**OR**

Lung score of 2 or 3

**Key points:**

1. In skin: higher of the two scores to be used for calculating global severity.
2. In lung: FEV1 is used instead of clinical score for calculating global severity.
3. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
4. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).