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

DFCI Protocol #: 19-817

Statistical Analysis Plan

March 20, 2022

Design: This protocol was designed as an open-label, two cohort, phase I 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 were divided into two cohorts based on their history of prior HSCT for a lymphoproliferative disorder or hematologic malignancy (Cohort 1), or a history of prior renal transplantation (Cohort 2). In the rare event that a patient had 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 would receive cemiplimab at standard dosing (350 mg IV every 21 days) until disease progression or unacceptable toxicity (including graft-versus- host disease [GVHD]), whichever occurred first. Cohort 2 mandated that the patient follow a standard immunosuppressive regimen that included: 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 repeated). Prophylactic antibiotics were permitted at the discretion of the treating physician while the patient was on immunosuppression and for the duration of the study. Treatment continued 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 was 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.

Original Design: The 3+3 design was adapted to determine the safety and toxicity of immunotherapy in Cohort 1 and Cohort 2. To that end, while accrual was expected to be slow, two patients were to enroll into each cohort at a time to monitor toxicity appropriately. For each cohort, the maximum sample size was 12. The actual sample size was dependent upon the observed GVHD rate or acute organ rejection rate. Endpoint assessments would be done when up to 12 patients had been enrolled and observed in each cohort. For Cohort 1, a GVHD rate exceeding 33% was considered unacceptable. The following table shows the stopping 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% was considered unacceptable. This cutoff was selected given that previously published data, including 23 renal transplant recipients who received various checkpoint inhibitors, experienced a 50% rate of acute kidney rejection on variable immunosuppressive regimens. Since enrolled subjects in the current study had incurable, metastatic, and life-threatening cutaneous SCC, the investigators felt 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 stopping rule:

Number of patients treated in **Cohort 2**	3	6	12
Stop recruitment if # of rejections ≥	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 in Cohort 1.** With those updates, the

final sample size was set at a maximum of 12 patients overall (in Cohort 2 only). The analysis plan is presented for Cohort 2 only.

Endpoints

Primary Endpoint: The primary end point was safety and toxicity, specifically the rate of kidney allograft rejection or loss (GVHD). Adverse events to assess the safety and side-effect profile of cemiplimab were recorded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Secondary Endpoints:

a. Objective antitumor response: Best overall response (complete response (CR) or partial response (PR)) per RECIST 1.1.

b. Progression-free survival (PFS): Time from date of enrollment until objective disease progression (per RECIST) or death, whichever occurred first. For patients without progression, follow-up was censored at the date of last adequate restaging.

c. Overall survival (OS): Time from enrollment to death from any cause. For patients lost to follow-up or who had no documentation of death at the time of final analysis, follow-up was censored at the date of last assessment of vital status.

d. Duration of response: Estimated only in patients with objective response. The time between the date when response was originally suspected until documented disease progression. The follow-up of patients who did not progress was censored at the date of last adequate restaging.

Variables and Derived Data

1. Patient Enrollment and Demographics

CRF: q_demo

Variable Name	Values
Casenum	Patient ID
Dt_regdt	Study registration date
Dt_birthdt	Date of birth
D_sex	Sex
D_race	Race
D_ethnicity	Ethnicity

Code for age (years):

```
age = floor((dt_regdt - dt_birthdt)/365.25);
```

2. Disease Characteristics

CRF: q_studyentry

Variable Name	Values
Dt_dtdiag	Date of original diagnosis
Dt_dtmetadiag	Date metastatic diagnosis
D_primarysite	Primary site of initial diagnosis
D_side	Side of disease
D_site	Site of recurrent disease
D_stage	Stage at initial diagnosis
D_diseasestagerec	Stage at local/regional recurrence
D_smokingstatus	Smoking status
D_alcohohistyn	Alcohol history

Years between initial diagnosis and enrollment:

```
yrs_post_pdiag = (dt_regdt - DT_DTDIAG)/365.25;
```

Weeks to local/regional recurrence:

```
wks_met_recur = (DT_DTMETADIAG - dt_dtdiag)/7;
```

3. Prior Therapies

CRF: q_priortx

Variable Name	Values
D_chemoyn	Prior chemotherapy
D_radyn	Prior radiation therapy
D_targyn	Prior targeted therapy
D_priorsurgyn	Prior surgery

4. Response to Therapy

CRF: q_response

Variable Name	Values
D_overall	Best response to therapy
DT_DTOVERALLRESP	Date best overall response

5. Cycles Therapy Attempted

CRF: q_cemiplimimab

if (date of administration) not missing.
proc freq; table casenum; ods output onewayfreqs=owf; run;
proc means data = owf n mean std min median max; run;

6. On-study Toxicities

CRF: q_ae

Variable Name	Values
toxcode	CTCAE toxicity code
C_toxgrd	Toxicity grade
C_attrib	Relatedness to therapy (if 2, 3, 4 then deemed at least possibly related)
toxdesc	Text for toxicity
toxcat	Medra System Organ Class
dltxx	Was event a DLT?
cmnts	Description text for toxicities coded as “other”

Toxicities presented according to worst grade occurring per patient:
Proc sort data=tox; by subject toxcode descending c_toxgrd;

```
data tox_unique;
set tox; by casenum toxcode;
if first.toxcode;
if index(toxdesc,"Other") gt 0 then toxdesc = propcase(cmnts);
run;

proc tabulate data=tox_unique format=6.1;
class toxcode toxdesc toxcat c_toxgrd/style={font_weight=bold};
table toxcat="System-Organ Class"*toxdesc = "Description",(all="Number patients"
c_toxgrd="Grade")*N/misstext="-";
run;
```

To select toxicities that are at least possibly related to therapy:
Subset to those events where c_attrib is 2, 3, or 4.

7. Deaths and Overall Survival

CRF: q_followup

Variable Name	Values
Dt_dtstatus	Month/day/year death or last follow-up
C_ptstatus	Patient status (death = 2)

Code for Overall survival:

```
data os;
*Need date of enrollment: dt_regdt;
if c_ptstatus = 2 then os_cns = 1;
else os_cns = 0;
os_mos = (dt_dtstatus - dt_regdt)/30.4375;
run;
```

8. Time to Progression

CRF: q_response

Variable Name	Values
C_overall	Value = 5 for patients with PD
dt_dtoverallresp	Date of disease progression

Code for PFS

```
proc sort; by casenum DT_DTOVERALLRESP;
run;

data firstpd;
set pd; by casenum;
if first.casenum;
run;

data pfs;
merge os (in=o) firstpd(in=p); by casenum; if o;
if p or os_cns = 1 then pfs_cns = 1; else pfs_cns = 0;
if pfs_cns = 1 then pfs_mos = (min(last_date,dt_dtoverallresp) -
dt_regdt)/30.4375;
else pfs_mos = os_mos;
```

Statistical Analyses

Primary Endpoints

Safety and toxicity

a. Rates of GVHD

Proportion of patients who developed GVHD as a result of therapy.

b. Rates of Grade 3-5 adverse events

Proportion of patients with at least one grade 3, 4, or 5 adverse event.

Both rates will be accompanied by 90% exact binomial confidence intervals.

Secondary Endpoints

a. Overall Survival and Progression-Free Survival

The distributions of progression-free and overall survival will be summarized using the method of Kaplan-Meier. Median times for each therapy arm will be accompanied by 90% confidence intervals based on log(-log(endpoint)) methodology.

b. Response Rate

The proportion of patients who had best RECIST response of CR or PR. The denominator is the number of patients with at least one scan to assess RECIST. One patient died before such a scan, resulting in a denominator of 11 patients. Response rate will be summarized with a 90% exact binomial confidence interval.