Statistical Analysis Plan (SAP) – Clinical Endpoints

A SU2C CATALYST® RANDOMIZED PHASE II TRIAL OF THE PD1 INHIBITOR PEMBROLIZUMAB (KEYTRUDA®) WITH OR WITHOUT A VITAMIN D RECEPTOR AGONIST PARICALCITOL (ZEMPLAR®) IN PATIENTS WITH STAGE IV PANCREATIC CANCER WHO HAVE BEEN PLACED IN BEST POSSIBLE RESPONSE (WITH NO FURTHER IMPROVEMENT IN THEIR TUMOR)

Clinicaltrials.gov: NCT03331562

July 10, 2020

1 INTRODUCTION

The 5-year survival rate for pancreatic ductal adenocarcinoma (PDA) is only 8%, as detection is usually very late in the disease, most patients are not eligible for potentially curable resection, and those with resection usually experience fatal reoccurrence within 2 years. There are some new treatments that improve survival for patients with stage IV PDA, but keeping patients in partial or complete remission is a major challenge. A maintenance regimen based on a vitamin D receptor (VDR) agonist, paricalcitol, could improve the activity of an immune checkpoint inhibitor, pembrolizumab. The combination regimen of paricalcitol + pembrolizumab is hypothesized to give benefit for maintenance of remission for patients with advanced pancreatic cancer (over pembrolizumab alone).

2 DATA SOURCE

Datasets will come from the phase II clinical trial titled: A SU2C Catalyst® Randomized Phase II Trial of the PD1 Inhibitor Pembrolizumab (Keytruda®) with vitamin D receptor agonist Paricalcitol (Zemplar®) in Patients with Stage IV Pancreatic Cancer Who Have Been Placed in Best Possible Response (with no further improvement in their tumor).

3 ANALYSIS OBJECTIVES

The primary objective is to determine whether combined paricalcitol + pembrolizumab reduces disease progression compared to pembrolizumab alone among patients with stage IV pancreatic cancer who have been put in best response.

The primary endpoint is the percent of patients with radiographic disease progression according to RECIST 1.1 at 6 months.

Secondary objectives include:

(1) Evaluate the toxicity of the combination of paricalcitol + pembrolizumab versus pembrolizumab alone.
(2) Evaluate the difference in overall survival in patients administered the combination of paricalcitol + pembrolizumab versus pembrolizumab alone.

Exploratory objectives include:
(1) Evaluate the difference in disease progression according to iRECIST vs. RECIST 1.1 criteria.

4 ANALYSIS SETS/ POPULATIONS/ SUBGROUPS

This trial will have 24 patients randomized to paricalcitol + pembrolizumab (n=12) or pembrolizumab alone (n=12). No stratification will be performed.

5 ENDPOINTS AND COVARIATES

Primary endpoint: Percent of patients with radiographic disease progression according to RECIST 1.1 at 6 months, defined as 180 days from initial treatment (C1/D1).

Secondary endpoints:
(1) Incidence of toxicities
From initial treatment to end-of-treatment
(2) Overall survival
Time from initial treatment to death

Exploratory endpoints:
(1) Disease progression according to RECIST 1.1 versus iRECIST criteria
Percent of patients with radiographic disease progression at 6 months

6 HANDLING OF MISSING VALUES AND OTHER DATA CONVENTIONS

Patients with missing values at a particular time point will be unevaluable at that time point. Missing data will not be imputed.

7 STATISTICAL METHODOLOGY
7.1 STATISTICAL PROCEDURES

Primary outcome: Progression-free survival

The proportion of patients in each arm who are progression-free at 6-months will be compared using a one-sided test of binomial proportions (equivalent to a Pearson's chi-squared test). If the assumptions of the Pearson's chi-squared test are not met, Barnard's exact unconditional test of equality will be used, as implemented in StatXact.

Patients unevaluable for progression at 6-months due to a non-progression related event will be excluded from analysis.

Statistical comparison of progression-free survival between the two treatment arms will be performed using a log-rank test, with estimation of the hazards ratio using a Cox proportional hazards model. A sensitivity analysis will include patients with an outcome of death due to another cause (other than progressive disease), which will be considered a competing event for progression. Analysis will be performed using the Fine and Gray (1999) approach.

Secondary outcome 1: Toxicity

All adverse events (AE) occurring on or after C1/D1 will be summarized by body systems and per grade according to NCI-CTCAE Version 4. Additionally, all serious adverse events (SAE) and events of clinical interest (ECI) will be listed separately and tabulated. ECIs for this trial include an overdose of pembrolizumab and an elevated AST or ALT lab value, as defined in section 6.2.3.2 of the protocol. All patients who receive any amount of trial treatment will be included in the analysis. The proportion of patients in each arm with toxicity will be compared using a chi-squared test or Barnard's exact unconditional test of equality as outlined above.

Secondary outcome 2: Overall survival

Overall survival will be calculated for each arm using a Kaplan-Meier estimate. Statistical comparison of overall survival between the two treatment arms will be performed using a log-rank test, with estimation of the hazards ratio using a Cox proportional hazards model. Patients with an outcome of death due to another cause (other than progressive disease) will be considered a competing event for death. Analysis will be performed using the Fine and Gray (1999) approach.

Exploratory outcome 1: RECIST 1.1 versus iRECIST

Comparison of the proportion of patients who are progression-free at 6 months using iRECIST will be performed using the same method as for the primary endpoint of RECIST 1.1. McNemar's test will be used to estimate the concordance between RECIST 1.1 and iRECIST.

7.2 MEASURES TO ADJUST FOR MULTIPLICITY, CONFOUNDERS, HETEROGENEITY, ETC.

Since all primary and secondary endpoints are pre-specified, there will be no adjustment for multiple comparisons. In the context of a randomized clinical trial, the two treatment arms are expected to be balanced with regard to potential confounders, therefore, adjustment is generally not necessary.

References:

Fine, J. P., and R. J. Gray. 1999. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association 94: 496–509.

Proposed Tables

Table 1. Characteristics of patients at baseline

Characteristic	**Pembrolizumab** *n* **= x**	**Pembrolizumab + Paricalcitol** *n* **= x**	**Total** *n* **= x**
Age, y			
Median			
Range			
Sex, *n* (%)			
Female			
Male			
Race/ethnicity, *n* (%)			
Asian			
Black			
White			
Hispanic			
Other			
Study site, *n* (%)			
HonorHealth Research Institute			
City of Hope			
Atlantic Health System			
Baylor Scott and White Research Institute			
University of Kansas Medical Center			
Medical College of Wisconsin			
Pancreatic tumor location, *n* (%)			
Head			
Body			
Tail			
Unknown			
Site of metastatic disease, *n* (%)			
Liver			
Lung			
Peritoneum			
No. of metastatic sites, *n* (%)			
1			
2			
3			
>3			

Carbohydrate antigen (CA) 19-9			
Median, U/mL			
Range, U/mL			
Normal (0-35 U/mL), *n* (%)			
ULN to <59x ULN, *n* (%)			
≥59x ULN, *n* (%)			
Previous therapy, *n* (%)			
Radiation therapy			
Chemotherapy			
Whipple procedure			
Biliary stent			

Figure 1. (A) Progression-free survival by investigator-assessment, (B) Progression-free survival by independent assessment, (C) Overall survival

Table 2. Progression-free survival and overall survival in the intention-to-treat population

Efficacy variable	**Pembrolizumab** *n* **= x**	**Pembrolizumab + Paricalcitol** *n* **= x**	**Hazard ratio or Response-rate ratio (95% CI)**	***P* value**
Progression-free survival by investigator-assessment				
RECIST 1.1				
Rate of progression-free survival, % (95% CI)				
6 mo				
12 mo				
Median progression-free survival, mo (95% CI)				
Progression-free survival by independent assessment				
Rate of progression-free survival, % (95% CI)				
6 mo				
12 mo				
Median progression-free survival, mo (95% CI)				
Overall survival				
Median overall survival, mo (95% CI)				
Survival rate, % (95% CI)				
6 mo				
12 mo				

Table 3. Common adverse events of grade 3 or higher

Event	**Pembrolizumab** ***n* = x**	**Pembrolizumab + Paricalcitol** ***n* = x**	***P* value**
Adverse event leading to death, no. (%)			
Serious Adverse Events			
Anemia			
Cataract			
Nausea			
Abdominal pain			
Diarrhea			
Vomiting			
Bloating			
Constipation			
Fatigue			
Gait disturbance			
Urinary tract infection			
AST increased			
ALT increased			
Alkaline phosphatase increased			
Arthralgia			
Pain in extremity			
Back pain			
Hypertension			

Note: these were the most common events on the Nov 2019 DSMB report (> 10% of patients)