Protocol #TGen 17-001
MISP# 56240
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)

Short Title: A SU2C Catalyst® Trial of a PD1 Inhibitor With or Without a Vitamin D Analog for the Maintenance of Pancreatic Cancer

Original Version: 1.0 September 25, 2017
First Revision: Version 2.0 October 13, 2017
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Eighth Revision: Version 9.0 12 Jun 2019
Ninth Revision: Version 10.0 29 Aug 2019

IND EXEMPT
March 22, 2017

Clinicaltrials.gov: NCT03331562

Sponsor
Translational Genomics Research Institute (TGen) An Affiliate of City of Hope
445 N. Fifth Street. Phoenix, AZ 85004
Funding provided by a Stand Up To Cancer (SU2C) Catalyst® Merck Grant

Consulting Investigator:
[redacted]

Patient Advocates:
[redacted]

Lead Scientific Investigator:	Principal Scientific Investigator:
[redacted]	[redacted]

Contract Research Organization (CRO)
[redacted]

CO-PRINCIPAL INVESTIGATORS	
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[redacted]	[redacted]
[redacted]	

SUB-INVESTIGATORS	
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[redacted]	[redacted]
Biostatistician: [redacted]	
Independent Medical Monitor [redacted]	

INVESTIGATOR PROTOCOL AGREEMENT

Protocol #TGen 17-001 MISP # 56240

Title: 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)

Version 10.0 Aug 29, 2019

I confirm that my staff and I have carefully read and understand this protocol. I/we agree to comply with the procedures and terms of the clinical trial specified herein. In particular, I/we have agreed to:

- Abide by all obligations stated on the Form FDA 1572 and on other document(s) required by local regulatory authority.
- Comply with Good Clinical Practice (GCP) and all applicable regulatory requirements.
- Maintain confidentiality and assure security of TGen and SU2C confidential documents.
- Obtain Institutional Review Board (IRB) approval of the protocol, any amendment to the protocol, and periodic re-approval as required, and to keep the IRB informed of any adverse events and periodically report the status of the trial to the IRB.
- Not implement any deviations from or changes to the protocol without agreement from the Sponsor and prior review and written approval from the IRB, except where necessary to eliminate an immediate hazard to the patients or for administrative aspects of the trial (where permitted by all applicable regulatory requirements).
- Assure that each patient enrolled into the trial has read, understands, and has signed the informed consent.
- Ensure that I and all persons assisting me with the trial are adequately informed and trained about the trial treatment and of their trial-related duties and functions as described in the protocol.
- Make prompt reports of serious adverse events (SAEs) and deaths (within 1 business day of learning) to the Sponsor.
- Assure access by the Sponsor, the assigned CRO [redacted]), and/or FDA to original source documents.
- Prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation.
- Arrange for the transfer of appropriate data from case histories to case report forms for the collection and transmission of data to the Sponsor.
- Retain records and documents related to this trial for at least 3 years after the completion of the trial as confirmed by the sponsor.
- Cooperate fully with any trial-related GCP audit as performed by the assurance group specified by the Sponsor, SU2C, or [redacted].
  Abide by the stipulations in the Confidentiality and Financial Disclosure sections and the manuscript preparation/authorship guidelines established at the outset of the trial.

Investigator's Printed Name: _____

Investigator' Signature: _____ Date: _____

Protocol Amendment Summary

Protocol Title: 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)		
Date of Revision: Version 10.0 Aug 29, 2019		
Section(s) of Change	**Description of Change**	**Rationale for Change**
Protocol Face Page CO-PRINCIPAL INVESTIGATORS	**Added the following Sub-Investigator:** [redacted] **Reformatted, and reordered Sub-Investigators, Medical Monitor, biostatistician on page in order to include the additional author.**	Revision to include the additional Sub-Investigator working on this trial.
Glossary of Abbreviations	**Added the following abbreviations:** *ALK* *CPS* *DSMP* *ECI* *FDA* *GEJ* *GvHD* *HCC* *HIV* *HNSCC* *HRT* *irAEs* *mAb* *MCC* *MDSC* *MSI-H* *NCSLC* *OTC* *PMBCL* *RCC* *SJS* *TAM* *TEN* *TPS* *Tregs* *UC*	Revision to include the update to section 1.4 Pembrolizumab (Keytruda®) per the updated Investigator Brochure V 17.0 dated 26 Jul 2019 and Risk Language dated 29 Jul 2019 provided by Merck. Revision to include other abbreviations previously included within the protocol.
TRIAL SCHEMATIC	**Added the following additional text:** *(or at time of progression)*	Revision to include that the optional biopsy is to be collected at 9 weeks or at the time of disease progression.

Section 1.4 Pembrolizumab (Keytruda®)	**Deleted the following bullets:** • *Metastatic NSCLC whose tumors have high PD-L1 expression [(Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.* • *Patients with metastatic NSCLC in combination with chemotherapy.* • *Metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy.* **Added the additional bullets:** • *As adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection* • *In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or anaplastic lymphoma kinase (ALK) genomic tumor aberrations* • *In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC* • *As a single agent for the first-line treatment of patients with Stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.* • *As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease*	Revision to include the update to the approved indications for Pembrolizumab in the US as per the updated Investigator Brochure Version 17 dated 26 Jul 2019 and Risk Language dated 29 Jul 2019 provided by Merck.

	progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA®. • *Adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy* • *Patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.* • *Patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.* • *Patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.* • *Adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).* • *In combination with axitinib, for the first-line treatment of patients with advanced renal cell carcinoma (RCC).* **Revised the following bullets (additions <u>underlined:</u>** • *Patients with locally advanced or metastatic urothelial carcinoma <u>(UC)</u> who are not eligible for cisplatin-containing chemotherapy <u>and whose tumors express PD-L1 (combined positive score (CPS) ≥10) as determined by an FDA-approved test, or in patients who are not eligible for any platinum containing chemotherapy regardless of PD-L1 status.</u>* • *<u>Patients with locally advanced or metastatic UC</u> who have disease*	

	progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.	
Table 7. Screen – Treatment Period Schedule	**Added the following text:** *Optional* **Added the following row to the table:** *Tumor Tissue Collection [Tumor tissue collection for those that consent to this optional collection and undergo a routine care biopsy of their tumor during their participation in the study]* [q] **Added Footnotes:** *p. All patients are required to provide archival tumor specimen from either a primary or metastatic site. (Refer to 4.1.1 and 6.1.2.8)* *q. For only those patients that consent to the optional tissue collection. (Refer to 6.1.2.8).* *r. For only those patients consenting to the optional tumor biopsy, a baseline tumor biopsy will be collected and used for profiling. If possible (patient condition permitting) this will be repeated after 9 ± 1 weeks on trial treatment, or at the time of disease progression. (Refer to 6.1.2.8).*	Revision to distinguish the Optional tumor biopsy. Revision to include the additional optional tissue collection as part of a routine care biopsy if performed during the patient's participation in the study. Revision to provide clarification for the required archival tissue and the optional tissue collection. Revision to include that the optional biopsy is to be collected at 9 weeks or at the time of disease progression.
Table 8. Post Treatment Period (EOT- Follow-Up) Schedule	**Added the following row to the table:** *Optional -Tumor Tissue Collection [Tumor tissue collection for those that consent to this optional collection and undergo a routine care biopsy of their tumor during their participation in the study]* [j] **Added Footnotes:** *j. For only those patients that consent to the optional tissue collection. (Refer to 6.1.2.8).*	Revision to include the additional optional tissue collection as part of a routine care biopsy if performed during the patient's participation in the study.
Section 6.1.2.7 Blood Collection	**Replaced the previous text:** *flow cytometry based immune profiling* **With the following text:** *existing technologies, such as flow cytometry, CyTOF, single-cell RNA-Seq, and single cell ATAC-Seq, as well as various new technologies as they become available.*	Revised to specify the types of technologies to be used for analysis and allow for the use of additional technologies as they become available.

Section 6.1.2.8 Tumor Tissue Collection	**Replaced the previous text:** *block* **with** *specimen* **Added the following text:** *Archival tissue will be analyzed in a similar manner as described below for formalin fixed paraffin embedded (FFPE) biopsy samples. Specific details for archival tissue processing and distribution will be provided to the investigative sites in the Trial Laboratory Manual. Sites will be asked to indicate whether blocks will be available for additional sectioning at a later point in time if additional tissue is needed.* *Patients will be provided with the following two additional options to provide fresh tumor tissue for the analysis as described below.* **Revised the following text (additions <u>underlined).</u>** *Patients will be provided the option <u>to consent</u> to provide fresh tissue samples from a newly obtained core or excisional biopsy of a tumor lesion <u>if performed recently (within 30 days prior to Cycle 1/Day 1) and during their participation in the study should they be scheduled for a biopsy as part of their routine care during their participation in the study through the follow-up period.</u>* *<u>Additionally, patients will also be provided with the option to consent to undergo a biopsy of a tumor lesion</u> at baseline, <u>at the completion of 3 cycles of treatment (9 weeks after starting trial treatment), or at the time of disease progression if prior to week 9</u>, unless tumor is considered inaccessible or biopsy is otherwise considered not in the patients best interest. Participation in this trial is therefore not contingent on the patient consenting to optional tumor biopsies for fresh tissue.* *For patients consenting to the optional tumor biopsy, a baseline tumor biopsy will be collected and used for profiling. If possible (patient condition permitting) this will be repeated after 9 ± 1 weeks on trial treatment, <u>or at the time of disease progression</u>.* *Two passes will be split evenly and processed for formalin-fixed paraffin (FFP) and optimal cutting temperature (OCT) embedding and samples will be centrally analyzed <u>using existing technologies, such as</u> immunohistochemistry, <u>immunofluorescence, and RNA-in situ</u>*	Revision to specify archival specimen will be collected, as these may be submitted by the site either as a block or slides per the sites policy. Revision to specify the planned analysis for the archival specimen. Revision to include the additional optional tissue collection as part of a routine care biopsy if performed during the patient's participation in the study. Revision to include that the optional biopsy is to be collected at 9 weeks or at the time of disease progression. Revisions to include specifications on the planned analysis based on existing technologies as well as other various new technologies as

	hybridization, as well as various new technologies as they become available to evaluate the following: • *Stromal/extracellular matrix content (e.g. collagen and hyaluronic acid)* • *Quantity and quality of vascularization (e.g. CD31)* • *Expression of pembrolizumab related targets (e.g. PD-1 and PD-L1)* • *Presence/ distribution, and activation of key immune cell populations (e.g. cytotoxic T Cells, TAMs, MDSCs, and Tregs)* • *Presence, distribution, and activation of other stromal cell populations, including fibroblasts (e.g. αSMA).* *Two passes will be immediately frozen in Bambanker™ freezing media for the following central analysis:* • *Genomic analysis of T-cell receptor clonality by sequencing (a measure of intratumoral T cell response)* *Bulk and single-cell analysis of mutational profiles, transcriptional profiles, and epigenetic states within tumors, including analysis of sorted tumor cell nuclei.* *In the event that biopsy tissue becomes limiting for certain analyses, snap frozen and Bambanker™ frozen tissue may be used interchangeably where technically feasible.*	they become available.
Section 6.1.4 Patient Personalized Clinical Benefit (PPCB)	**Revised the following text (additions underlined):** *In the event that a patient does not have the type of mobile device required to access the APP, or the patient chooses not to complete the PPCB via the APP, the patient will be provided a paper questionnaire to complete. The site will record the reason the patient is not utilizing the APP in the source documents. Refer to Appendix 6 for more details on the PPCB App.*	Revisions to account for the various scenarios that a patient may not use the PPCB APP and the reason for not using the APP to be collected.

Section 6.1.7.1 Screening Period	**Added the following:** *17. For those patients consenting to the optional fresh tissue collection: Obtain fresh tissue from a newly obtained core or excisional biopsy if performed within the last 30 days prior to first dose of trial medication (C1/D1). Refer to Section 6.1.2.8.* **Revised the previous text to include the following additions <u>underlined:</u>** *18. <u>For those patients consenting</u> to the optional baseline biopsy:* Fresh tissue *is to be obtained up to 3 weeks (21 days) prior to first dose of trial medication (C1/D1). Refer to Section 6.1.2.8.* **Added the following:** *19.Obtain archival tumor specimen for all patients - as required for eligibility. Refer to Section 6.1.2.8.* *Refer to Section 6.1.2.7.* *Refer to Section 6.1.6.*	Revision to include the additional optional tissue collection as part of a routine care biopsy if performed during the patient's participation in the study. Revision to include the steps pertaining to the required archival tissue specimen. Revision to include reference to other sections of the protocol pertaining to Blood and Tumor Tissue Collection.

EXPEDITED REPORTING REQUIREMENTS

For this trial, the following events require expedited reporting to the sponsor and must be reported within 1 business day (24 hours) of the site becoming aware of the event. Refer to protocol section 6.2.1 Assessing and Recording AEs.

- All Serious Adverse Events (SAE), whether or not related to the trial treatment, as defined in section 6.2.3.1
- Events of Clinical Interest (ECI) as defined in section 6.2.3.2
- Pregnancy as defined in section 6.2.2
- Lactation as defined in section 6.2.2
- Overdose of pembrolizumab as defined in section 6.2.1

The site must report these specified events to [redacted] by one of the following methods:

1. Completing the AE eCRF form in the trial EDC and providing a narrative summary via fax to: [redacted] or email to: [redacted].

2. Completing a hard copy of the AE eCRF form (or an approved form) and providing along with a narrative summary via fax to: [redacted] or email to: [redacted].

[redacted] will then report the event within 1 business day (24 hours) to Merck Global Safety.

For any additional questions, or any issue regarding expedited reporting requirements, please contact [redacted] by email: [redacted] or by Telephone at: [redacted].

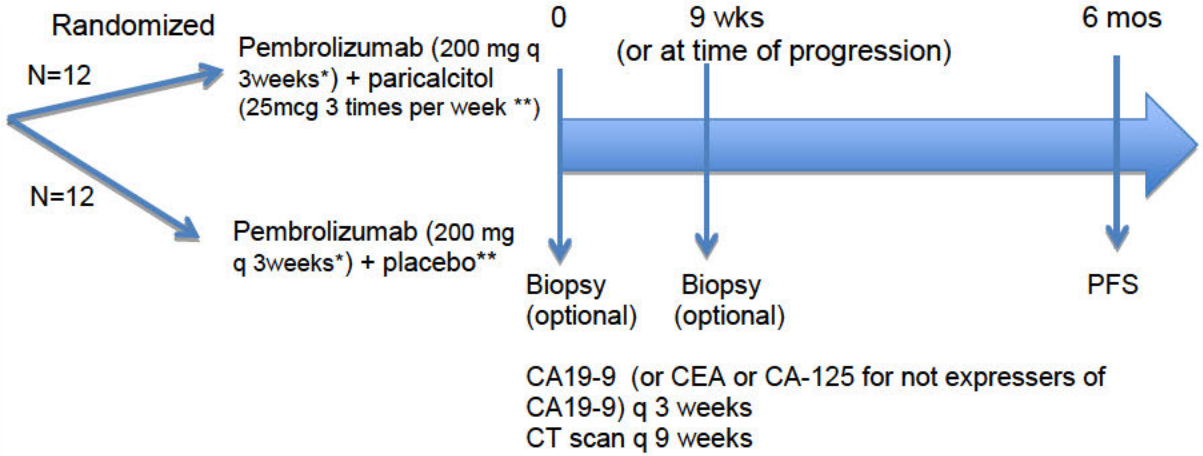
Glossary of Abbreviations	
AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CA-125	Cancer antigen 125
CA19-9	Carbohydrate antigen 19-9
CBC	Complete Blood Count
CEA	Carcinoembryonic Antigen
cHL	Classical Hodgkin's Lymphoma
CMH	Cochran-Mantel-Hanzel
CNS	Central Nervous System
CPS	Combined Positive Score
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
ECI	Event of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
ERC	Ethical Review Committee
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FU	Follow-Up
GCP	Good Clinical Practice
GEJ	Gastroesophageal Junction
GvHD	Graft versus Host Disease
HBsAg	Hepatitis B Surface Antigen
HCC	Hepatocellular Carcinoma
HCV RNA	Hepatitis C Virus RNA
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HRT	Hormonal Replacement Therapy
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
INR	International Normalized Ratio

irAEs	Immune-Related Adverse Events
iRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IRB	Institutional Review Board
IV	Intravenous
mAb	Monoclonal Antibody
MCC	Merkel Cell Carcinoma
MDSC	Myeloid-Derived Suppressor Cells
MRI	Magnetic Resonance Imaging
MSI-H	Microsatellite Instability-High
Nab	Nanoparticle albumin bound
NCI	National Cancer Institute
NIH	National Institutes for Health
NSCLC	Non-Small Cell Lung Cancer
OCT	Optimal Cutting Temperature
OS	Overall Survival
OTC	Over-the-Counter
PBMC	Peripheral Blood Mononuclear Cells
PBPK	Physiologically-based Pharmacokinetic
PDA	Pancreatic Ductal Adenocarcinoma
PHI	Protected Health Information
PK	Pharmacokinetic
PMBCL	Primary mediastinal large B-cell lymphoma
PPCB	Patient Personalized Clinical Benefit
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QTA	Quantitative Textural Analysis
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SJS	Stevens-Johnson Syndrome
SU2C	Stand Up to Cancer
T3	Triiodothyronine
T4	Thyroxine
TAM	Tumor Associated Macrophages
TB	Mycobacterium tuberculosis
TEN	Toxic Epidermal Necrolysis
TGen	Translation Genomic Research Institute
TKI	Tyrosine Kinase Inhibitor
TMDD	Target-Mediated Drug Disposition
TPS	Tumor Proportion Score
Tregs	Tregulatory Cells
TSH	Thyroid-Stimulating Hormone
UC	Urothelial Carcinoma
ULN	Upper Limit of Normal
VDR	Vitamin D Receptor
WOCBP	Women of Childbearing Potential

TRIAL SCHEMATIC

Patients with stage IV pancreatic cancer who have been placed in best possible response with first line chemotherapy for their advanced disease defined as:

Must have obtained a best response of at least stable disease (SD) or partial response (PR) for a period of 2 months with no further shrinkage of ≥ 30% on scan.



* Pembrolizumab: 200 mg infused q 3 weeks, on day 1 of each 21- day cycle

**Paricalcitol: 25 mcg IV (or for placebo, equivalent volume) 3 times per week (given on day 1 prior to Pembrolizumab) and days 3, 5, 8, 10, 12, 15, 17, and 19 (±1 day allowed for dosing of each 21- day cycle)

Refer to Section 5 for the detailed Trial Schedule

TRIAL SYNOPSIS

Title and No: 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). Protocol #TGen 17-001, MISP # 56240
IND Exempt March 22, 2017
Version 10.0 dated Aug 29, 2019

An Investigator Initiated Trial Funded by a SU2C Catalyst ®and Merck Grant

Sponsor: Translational Genomics Research Institute (TGen) an Affiliate of City of Hope
445 N. Fifth Street. Phoenix, AZ 85004

Consulting Investigator:
[redacted]

Principal Investigator Sites:
1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]

Clinical Phase: Double-Blind Randomized Phase II

Objectives:

Primary: To estimate the percentage of patients progressing at 6 months by RECIST1.1 when maintained on a combination regimen of paricalcitol plus pembrolizumab versus pembrolizumab alone.

Secondary:

1. Evaluate the toxicity of the combination of paricalcitol plus pembrolizumab versus pembrolizumab alone.

2. Evaluate the difference in overall survival (OS) in patients administered the combination of paricalcitol plus pembrolizumab versus pembrolizumab alone.

3. Define the impact of the combination of paricalcitol and pembrolizumab on tumor mutational landscape and transcriptional programs.

4. Identify cellular VDR targets in the immune microenvironment with PD1 blockade.

Exploratory:

1. Evaluate the difference in disease progression according to iRECIST vs. RECIST 1.1 criteria (Appendix 5)

2. Assess the utility of a Patient Personalized Clinical Benefit (PPCB) phone-based

application

3. Assess the association between improvement in symptoms as recorded by the Patient Personalized Clinical Benefit (PPCB) with progression at 6 months by RECIST 1.1

4. Assess any changes in tumor and/or tissue texture on imaging in both arms of the trial

5. To monitor and compare the gut microbial communities in both arms of the trial.

Trial Design: Randomized Double Blind, Placebo Controlled

No. Patients: Total of 24, 12 randomized to each treatment arm

Name, dose of drugs:

- Pembrolizumab (Keytruda®) 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.

- Paricalcitol (Zemplar®) 25 mcg administered intravenously 3 times per week (given on days 1, 3, 5, 8, 10, 12, 15, 17, 19 ± 1 day of each 21 day cycle) and prior to each pembrolizumab infusion.

- Placebo- equivalent volume administered intravenously, 3 times per week and prior to each pembrolizumab infusion.

Treatment Arms:
Arm1: pembrolizumab + paricalcitol
Arm 2: pembrolizumab + placebo (saline solution)

Patient Population: Patients with stage IV pancreatic cancer who have been put in best response, defined as: Must have obtained a best response of at least stable disease (SD) or partial response (PR) for a period of 2 months with no further shrinkage of ≥ 30% on scan.

Endpoints:
Primary: The percent of patients with radiographic disease progression according to RECIST 1.1 at 6 months.

Secondary:

- Incidence of toxicities

- Overall survival

- Mutational landscape

- Transcriptional programs

- Cellular (immunity) VDR targets in the immune microenvironment

Exploratory:

- Difference in disease progression according to RECIST 1.1 and iRECIST (Appendix 5) criteria

- Compliance rate responding to a phone - based application for the assessment of patient

defined symptoms

- Improvement in symptoms as recorded by the Patient Personalized Clinical Benefit (PPCB)
- Differences in tumor and/or tissue texture on CT scans between the two treatment arms
- Differences in gut microbial communities within and between fecal samples using alpha and beta diversity metrics based on 16S rRNA sequencing

Inclusion criteria:

1. Be willing and able to provide written informed consent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Histologically or cytologically confirmed pancreatic adenocarcinoma with metastasis, who had obtained a best response of at least stable disease (SD) or a partial response (PR) for a period of 2 months with no further shrinkage of ≥ 30% on scan on their first line of chemotherapy for their advanced metastatic disease. ***Note:*** *Patients that have had prior chemotherapy as adjuvant or neoadjuvant therapy are permitted.*
4. Have a performance status of 0 or 1 on the ECOG performance scale.
5. Able to submit an archival tumor specimen (primary or metastatic site) and a discussion is documented with trial investigator at screening that patient will consider providing tissue from a newly obtained core or excisional biopsy of a tumor lesion at baseline and a second biopsy 9 weeks after starting trial treatment, unless tumor is considered inaccessible or biopsy is otherwise considered not in the patients' best interest. *Participation in this trial is not contingent on patient consenting to optional tumor biopsies.*
6. Demonstrate adequate organ function as defined in Table 2, AND serum corrected calcium value must be ≤ Institutional ULN and ≥ 8.0 mg/dL, and phosphorus levels must be ≤ Institutional ULN and ≥ 2.5 mg/dL.
7. Female participants of childbearing potential should have a negative serum pregnancy test within 24 hours prior to receiving first dose of trial medication.
8. A female participant is eligible to participate if she is not pregnant (see Section 4.7.2), not breastfeeding, and at least one of the following conditions applies:

    a.) Not a woman of childbearing potential (WOCBP) as defined in Section 4.7.2.

    OR

    b.) A WOCBP who agrees to follow the contraceptive guidance in Section 4.7.2 during the treatment period and for at least 180 days after the last dose of trial treatment.

9. Male participants must agree to use contraception as detailed in Section 4.7.2 of this protocol during the treatment period and for at least 120 days after the last dose of trial treatment and refrain from donating sperm during this period.

Exclusion criteria:

1. Is currently participating and receiving trial therapy or has participated in a trial of an investigational agent and received trial therapy or used an investigational device within 4 weeks of the first dose of trial treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

3. Has a known history of active TB (*Mycobacterium tuberculosis*).

4. Hypersensitivity to pembrolizumab or paricalcitol or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to Cycle 1/Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Cycle1/ Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent(s).

   Note: Patients with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the trial.

   Note: If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10. Has history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

11. Has an active infection requiring systemic therapy.

12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion

of the treating investigator.

13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

14. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

15. Has a serum vitamin D level of ≥ 50 ng/mL.

16. Currently taking a strong CYP3A inhibitors that cannot be discontinued prior to trial enrollment and for the duration of trial. This includes but is not is limited to: boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir.

17. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

18. Has a known history of or is positive for Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

    Note: Without known history testing needs to be performed to determine eligibility.

19. Current, serious, clinically significant cardiac arrhythmias as determined by the investigator, or patient receiving a digitalis derivative.

20. Has received a live vaccine within 30 days of planned start of trial therapy.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

Statistical Methods: The primary endpoint for this clinical trial is the percent of patients with radiographic disease progression according to RECIST 1.1 at 6 months. Without maintenance therapy, 92% of patients are expected to progress by 6 months. Therefore, we assume 1/12 (0.083) pembrolizumab + placebo arm show no progression versus 7/12 pembrolizumab + paricalcitol. This gives 90% statistical power with one side alpha = (0.05).

Statistical analysis will compare the proportion progression free at 6 months using a one-sided test comparing binomial proportions (equivalent to a Pearson's chi-square test). The incidence of toxicities will be tabulated. Overall survival will be estimated for each arm using a Kaplan-Meier estimate. Statistical comparison of overall survival will be performed using a log-rank test with estimation of the hazards ratio using a Cox proportional hazards model.

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1.0 BACKGROUND AND RATIONALE

1.1 Overview

Pancreatic cancer continues to be a very lethal disease. It was estimated that in 2016, 53,070 Americans would be diagnosed with pancreatic ductal adenocarcinoma (PDA), and 41,780 would die from the disease. This makes pancreatic cancer the third leading cause of death from cancer in the US.[1]

Furthermore it is projected that by 2030, PDA will be the second leading cause of death from cancer in the US. Worldwide, PDA is the twelfth most common cancer, accounting for an estimate of > 300,000 deaths a year. [2]

Detection of pancreatic cancer has been notoriously very late in the disease and therefore the 5-year survival rate is only 8%. Right now, the only potential cure for pancreatic cancer is surgical resection (if the disease is caught early). However only about 20% of PDA patients are eligible for potentially curable resection and unfortunately most (> 80%) have reoccurrence of their cancer within 2 years of resection, and those reoccurrences are almost universally fatal. [3,4]

But there is some hope. Recently there are regimens that actually improve survival for patients with advanced stage IV PDA. Conroy and colleagues have developed the Folfirinox regimen, which in a large randomized trial improved survival over gemcitabine as a single agent.[5] Von Hoff and colleagues developed the nanoparticle albumin (nab) associated paclitaxel plus gemcitabine regimen which improved survival over single agent gemcitabine again in a single randomized trial.[6] Even more recently Jameson and colleagues have presented a combined regimen of nab-paclitaxel + gemcitabine + cisplatin in a small 24 patient phase Ib/II trial that gave a response rate of 71% with 2 patients having complete response and a median survival of 16+ months.[7]

1.2 A major developing problem in the care of patients with advanced pancreatic cancer

With the greater chance of getting patients with advanced pancreatic cancer into remission, there is a new challenge - keeping the patient in partial or complete remission. The rough parts of trying to keep patients in remission include:

- Cumulative toxicities of the treatment regimens keeping one from continuing the chemotherapeutic regimen.
- Patients get to a maximum amount of tumor shrinkage but that shrinkage often stops after a partial response is reached, e.g. we can see it is likely the patient is no longer benefitting from that regimen or we can see resistance developing.
- Patients get tired of the treatment regimen and want a rest

1.3 Rationale - The reasoning behind a maintenance regimen

It would be wonderful to have an option for patients for when they have achieved the most benefit from the induction regimen they are on if that option:

a) had a real chance of helping them continue to benefit from treatment

b) was non-cross resistant and helped improve the patient's chance of non- progression and of improving their survival

c) caused minimal toxicities

d) was a very well tolerated regimen and convenient for the patient to take

e) has a very solid rationale and is worth trying

A real foundation for this rationale for patients who are in best response from their induction chemotherapy is provided by the trial conducted by Reni and colleagues.[8] In this first phase II randomized maintenance trial, 56 patients who previously had positive optimal response to chemotherapeutic regimens (no progression after 6 months of chemotherapy) were randomized to either observation or treatment with the tyrosine kinase inhibitor (TKI) sunitinib. The results were impressive: 96% of patients had progression after 6 months in the observation arm, while only 78% progressed on sunitinib (p = 0.04), 2-year survival was 23% in sunitinib arm versus 7% in the observation arm (p=0.18). This important trial demonstrates that a maintenance approach is promising and should be further explored in patients with advanced pancreatic cancer. [redacted]

However this Reni study did demonstrate that this type of maintenance trial could finally be done in patients with advanced pancreatic cancer put in best response with currently available regimens (and importantly, it could be done in a single institution)!

While immune checkpoint inhibitors have been transformative against multiple types of cancer, patients with advanced pancreatic cancer have been refractory to an immune-oncology approach. The table below details all of the published results from the use of immune checkpoint inhibitors against pancreatic cancer.

Table 1. Immune Checkpoint Inhibitors in PDA

Target	Agent	n	Responses CR	PR	Reference
CTLA	Ipilumumab	27	0	1-late	Royal et al. 2010[9]
PD-L1	MDX-1105	14	0	0	Brahmer et al.2012 [10]
PD-L1	Atezolizumab	1	0	0	Herbst et al. 2014[11]
PD-1	Nivolumab		-		- -
PD-1	Pembrolizumab (MK-3475)	1	0	0	Patnaik et al. 2015 [12]
Note: Possible efficacy in selected patients with MMR deficient tumors. Le et al. NEJM 2016					

There are multiple possible reasons postulated for the real inactivity of the immune-oncology agents (besides the fact that the patients had very advanced pancreatic cancer). These include:

a) The PDA microenvironment could limit efficacy because it is a very desmoplastic tumor (a physical barrier to therapeutics, driven by tissue resident stellate cells) which reduce intratumor vasculature and delivery of drugs and immune-oncology blockade agents. This desmoplastic reaction has been documented in both the primary pancreatic lesions and in metastatic sites.[13]

b) The PDA microenvironment is an immunosuppressive cancer cell friendly environment with abundant tumor associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs) and Tregulatory cells (Tregs). This microenvironment excludes T effector cells which inhibits the patient's antitumor immune response. Therefore the tumor microenvironment is a site of immune privilege for pancreatic cancer cells.

A recent very remarkable finding is that vitamin D receptor (VDR) agonists will sensitize both primary and metastatic pancreatic cancer lesions to PD-1 blockade (in addition to, on its own) making the tumor microenvironment more hostile to the pancreatic cancer cell and more vulnerable to the patient's own immune system. Sherman and colleagues [redacted] noted that VDR agonists, particularly those that are synthetic and which cannot be degraded by up-regulated CYP24A1 in the cancer, can reduce tumor fibrosis, can permit drug delivery and can reduce an immunosuppressive environment.[14] Very important is a pilot pre-op SU2C supported clinical trial of nab-paclitaxel plus gemcitabine with the addition of paricalcitol where there were remarkable decreases in extracellular matrix collagen, incredible increases in tumor vascularity, and an enhanced infiltration of CD3 cells. This really set up the question as to whether or not the VDR agonist paricalcitol could improve the activity of an immune checkpoint inhibitor - pembrolizumab.

However we need to have a clinical situation which gives the optimal opportunity for an immune checkpoint inhibitor with or without paricalcitol to work for patients and we think examining the agent in a randomized fashion in a maintenance design is the way to do just that.

1.4 Pembrolizumab (Keytruda®)

Refer to the Pembrolizumab Investigator Brochure for complete information on preclinical and clinical data and Appendix 1 – Package Insert for Pembrolizumab for complete safety and dosing information.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda® (pembrolizumab) has been approved in the United Stated for the treatment of patients with:

- Unresectable or metastatic melanoma

- As adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection

- In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or anaplastic lymphoma kinase (ALK) genomic tumor aberrations

- In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC

- As a single agent for the first-line treatment of patients with Stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

- As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA®.

- Recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

- Adult and pediatric patients with refractory classical Hodgkin's Lymphoma (cHL) or who have relapsed after 3 or more prior lines of therapy.

- Adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy

- Adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient

    - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or

    - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

- Patients with locally advanced or metastatic urothelial carcinoma (UC) who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (combined positive score (CPS) ≥10) as determined by an FDA-approved test, or in patients who are not eligible for any platinum containing chemotherapy regardless of PD-L1 status.

- Patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

- Patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.

- Patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

- Patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

- Adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

- In combination with axitinib, for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

The most common side effects of treatment with pembrolizumab include decreased appetite, fatigue, pruritis, rash, diarrhea, nausea, vomiting, constipation, dyspnea, cough, pyrexia, arthralgia, asthenia, headache, back pain, anemia, and peripheral edema.

Most frequently reported serious adverse events related to pembrolizumab include immune-mediated pneumonitis, colitis, diarrhea, pyrexia, autoimmune hepatitis, pneumonia, adrenal insufficiency, hyponatremia, dyspnea, hyperthyroidism, and nausea.

Less common risks associated with treatment with pembrolizumab are as follows:

- Symptoms of pneumonitis e.g. shortness of breath, chest pain, new or worsened cough.

- Symptoms of colitis e.g. diarrhea, abnormal stool, severe abdominal pain.

- Symptoms of hepatitis e.g. jaundice, nausea, vomiting, appetite loss, right abdominal pain, more frequent bleeding or bruising, dark urine.

- Symptoms of endocrinopathies, including hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorders (hypo or hyperthyroidism and thyroiditis), Type 1 diabetes mellitus, rapid heart rate, change in weight, increased sweating, hunger and/or thirst, frequent urination, hair loss, feeling cold, constipation, deeper voice, muscle aches, unusual and persistent headache, dizziness or fainting.

- Symptoms of nephritis or kidney failure e.g. change in amount or color or urine.

- Symptoms of Guillain-Barre syndrome, pancreatitis, myasthenic syndrome, encephalitis, uveitis, sarcoidosis, and myocarditis (some fatal).

- Symptoms of solid organ transplant rejection, and graft versus host disease (GvHD) in patients who had an allogeneic stem cell transplant after treatment with pembrolizumab.

- Symptoms of other organ issues e.g. rash, changes in eyesight, severe or persistent muscle or joint pain, severe muscle weakness, myositis, severe skin reactions, and anemia. Rarely, severe skin reactions have included cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) some with fatal outcome.

- Symptoms of infusion reactions which may be life-threatening e.g. chills, shaking, shortness of breath, wheezing, itching, rash, flushing, dizziness, fever or feelings of passing out.

Patients with the following may be at particular risk:

- Immune system disorders e.g. Crohn's, ulcerative colitis, lupus.

- Organ transplant – solid organ transplant rejection in donor recipients has been reported. Consider the benefit of treatment with pembrolizumab versus the risk of possible organ rejection in the patients.

- Lung or breathing conditions e.g. interstitial lung disease.

- Liver problems e.g. hepatitis.

The effects of pembrolizumab on unborn fetus and possible transmission through breast milk have not been established. Patients on pembrolizumab should not become pregnant or breast-feed. It is recommended that patients should use adequate birth control and abstain from breast-feeding until at least 4 months after dosing with this product.

1.5 Paricalcitol (Zemplar®)

Refer to Appendix 2- Package Insert for Paricalcitol for complete information.

Paricalcitol is a vitamin D analog used for the prevention and treatment of secondary hyperparathyroidism. Excessive amounts of vitamin D compounds including paricalcitol can cause over suppression of the parathyroid hormone, hypercalcemia, hypercalciuria, hyperphosphatemia and adynamic bone disease.

Paricalcitol should not be given to patients with evidence of vitamin D toxicity, hypercalcemia, or hypersensitivity to any ingredient in this product.

The most common side effects of treatment with paricalcitol are diarrhea, nasopharyngitis, dizziness, vomiting, hypertension, hypersensitivity, nausea and edema.

Taste perversion, such as metallic taste, and allergic reactions, such as rash, urticaria and pruritus rarely have been reported.

Risks associated with treatment with paricalcitol include: Symptoms of elevated calcium levels e.g. feeling tired, difficulty in thinking clearly, loss of appetite, nausea, vomiting, constipation, increased thirst, increased urination and weight loss. Prescription based doses of vitamin D should be withheld during treatment with paricalcitol.

The effects of paricalcitol on unborn fetus and possible transmission through breast milk have not been fully established. Patients on paricalcitol should avoid pregnancy and should not breast feed.

1.6 Trial Dose Rationale and Sequence

1.6.1 Pembrolizumab Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda® development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg

Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

1.6.2 Paricalcitol Dose

The dose for paricalcitol is 25 mcg IV (or equivalent volume for placebo) three times per week given on days 1, 3, 5, 8, 10, 12, 15, 17, 19 (+/-1 day allowed for dosing per 21 day cycle) and prior to pembrolizumab. This dosing schedule has been evaluated in a pilot SU2C protocol (in 24 patients) in which patients were administered 25 mcg of paricalcitol intravenously weekly X 3 (with nab-paclitaxel + gemcitabine) the paricalcitol was well tolerated, with only report of a renal calculus in one elderly patient .[17]

2.0 HYPOTHESIS

The combination regimen of paricalcitol plus pembrolizumab can give benefit for maintenance of remission for patients with advanced pancreatic cancer (over pembrolizumab alone).

3.0 OBJECTIVES

3.1 Primary Objective

To estimate the percentage of patients with radiographic disease progression according to RECIST1.1 at 6 months when maintained on a combination regimen of paricalcitol plus pembrolizumab versus pembrolizumab alone.

3.2 Secondary Objectives

1. Evaluate the toxicity of the combination of paricalcitol plus pembrolizumab versus pembrolizumab alone.

2. Evaluate the difference in overall survival (OS) in patients administered the combination of paricalcitol plus pembrolizumab versus pembrolizumab alone.

3. Define the impact of the combination of paricalcitol and pembrolizumab on tumor mutational landscape and transcriptional programs.

4. Identify cellular VDR targets in the immune microenvironment with PD1 blockade.

3.3 Exploratory Objectives

1. Evaluate the difference in disease progression according to RECIST 1.1 vs iRECIST (Appendix 5) criteria.

2. Assess the utility of a Patient Personalized Clinical Benefit (PPCB) phone based application.

3. Assess the association between improvement in symptoms as recorded by the Patient Personalized Clinical Benefit (PPCB) with progression at 6 months by RECIST 1.1.

4. To assess any changes in tumor and/or tissue texture on imaging in both arms of the trial.

5. To monitor and compare the gut microbial communities in both arms of the trial.

3.4 Primary Endpoints

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

3.5 Secondary Endpoints

- Incidence of toxicities
- Overall survival
- Mutational landscapes
- Transcriptional programs
- Cellular (immunity) VDR targets in the immune microenvironment

3.6 Exploratory Endpoints

- Difference in disease progression according to RECIST 1.1 and iRECIST (Appendix 5) criteria
- Compliance rate responding to a phone - based application for the assessment of patient defined symptoms
- Improvement in symptoms as recorded by the Patient Personalized Clinical Benefit (PPCB)
- Differences in tumor and/or tissue texture on CT scan between the two treatment arms
- Differences in gut microbial communities within and between fecal samples using alpha and beta diversity metrics based on 16S rRNA sequencing

4.0 METHODS

4.1 Eligibility

Twenty-four eligible patients will be recruited from up to 7 centers. Patients with stage IV pancreatic cancer who had been placed in best possible response with first line chemotherapy for their advanced metastatic disease as defined by at least stable disease (SD) or a partial response (PR) for a period of 2 months with no further shrinkage of ≥ 30%

on scan. The best response on prior therapy will need to be evaluated and documented by treating investigator at time of determining eligibility for this trial.

4.1.1 Inclusion Criteria

Patients must meet the following criteria in order to be eligible for participation in the trial:

1. Be willing and able to provide written informed consent for the trial.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Histologically or cytologically confirmed pancreatic adenocarcinoma with metastasis, who had obtained a best response of at least stable disease (SD) or a partial response (PR) for a period of 2 months with no further shrinkage of ≥ 30% on scan on their first line of chemotherapy for their advanced metastatic disease.
   Note: *Patients that have had prior chemotherapy as adjuvant or neoadjuvant therapy are permitted.*

4. Have a performance status of 0 or 1 on the ECOG performance scale.

5. Able to submit an archival tumor specimen (primary or metastatic site) and a discussion is documented with trial investigator at screening that patient will consider providing tissue from a newly obtained core or excisional biopsy of a tumor lesion at baseline and a second biopsy 9 weeks after starting trial treatment, unless tumor is considered inaccessible or biopsy is otherwise considered not in the patients best interest. *Participation in this trial is not contingent on patient consenting to optional tumor biopsies.*

6. Demonstrate adequate organ function as defined below in Table 2. AND serum corrected calcium value must be ≤ Institutional ULN and ≥ 8.0mg/dL, and phosphorus levels must be ≤ Institutional ULN and ≥ 2.5 mg/dL.

Table 2. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN

AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal. [a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks. [b] Creatinine clearance (CrCl) should be calculated per institutional standard. Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.	

7. Female participants of childbearing potential should have a negative serum pregnancy test within 24 hours prior to receiving first dose of trial medication.

8. A female participant is eligible to participate if she is not pregnant (see Section 4.7.2 not breastfeeding, and at least one of the following conditions applies:

    a.) Not a woman of childbearing potential (WOCBP) as defined in Section 4.7.2.

    OR

    b.) A WOCBP who agrees to follow the contraceptive guidance in Section 4.7.2 during the treatment period and for at least 180 days after the last dose of trial treatment.

9. Male participants must agree to use contraception as detailed in Section 4.7.2 of this protocol during the treatment period and for at least 120 days after the last dose of trial treatment and refrain from donating sperm during this period.

4.1.2 Exclusion Criteria

Patients meeting the following criteria will NOT be eligible to participate in this trial:

1. Is currently participating and receiving trial therapy or has participated in a trial of an investigational agent and received trial therapy or used an investigational device within 4 weeks of the first dose of trial treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

3. Has a known history of active TB (*Mycobacterium tuberculosis*).

4. Hypersensitivity to pembrolizumab or paricalcitol or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to Cycle 1/ Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Cycle 1/ Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   Note: Patients with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the trial.

   Note: If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10. Has history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

11. Has an active infection requiring systemic therapy.

12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

14. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

15. Has a serum vitamin D level of ≥ 50 ng/mL

16. Currently taking a strong CYP3A inhibitor that cannot be discontinued prior to trial enrollment and for the duration of trial. This includes but is not is limited to: boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir.

17. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

18. Has a known history of or is positive for Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

    Note: Without known history testing needs to be performed to determine eligibility.

19. Current, serious, clinically significant cardiac arrhythmias as determined by the investigator, or patient receiving a digitalis derivative.

20. Has received a live vaccine within 30 days of planned start of trial therapy (Cycle 1 /Day 1).

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

4.2 Trial Treatments

The treatments to be used in this trial are outlined below in Table 3.

Table 3. Trial Treatments

Drug	Dose/ Potency	Dose Frequency	Route	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Paricalcitol (or placebo)	25 mcg	3 X Week	IV	3 times per week (Day 1*,3 ,5, 8 10, 12, 15, 17 and 19 (+/-1 day) per 21 day cycle	Experimental
* paricalcitol will be injected ≥30 mins prior to the pembrolizumab infusion					

4.2.1 Dose Selection/Modification

The rationale for selection of doses to be used in this trial is provided in Section 1.

On Day 1 of each three - week cycle, patients will receive 25 mcg of paricalcitol or placebo intravenously followed ≥ 30 minutes later by 200 mg of pembrolizumab infused over 30

minutes. Patients will then receive 25 mcg of paricalcitol or placebo intravenously on days 3, 5, 8, 10, 12, 15, 17, 19 (± 1 day) of each 21 day cycle.

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

4.2.2 Paricalcitol (Zemplar®) and Placebo

Dosage Form: Paricalcitol is available as a sterile, clear, colorless aqueous solution for injection, in concentrations of 2mcg/mL and 5mcg/mL. Each site will be using their local pharmacy supply of paricalcitol and will use the necessary volume for the given concentration and per the product labeling instructions (Appendix 2) to administer a total dose of 25mcg. Patients will receive either paricalcitol or the equivalent volume of placebo (saline solution) intravenously at each dosing point.

The doses will be prepared in an aseptic manner and documented by the unblinded Pharmacist just prior to dosing. Documentation relating to this preparation will be available for independent monitoring and verification.

Further details of preparation are provided in the Pharmacy manual.

There must be ≥ 30 minutes in between the completion of the paricalcitol injection and the start of the pembrolizumab infusion.

Note: The same IV line may be used to administer both the paricalcitol and the pembrolizumab. However there must be at least 30 minutes in between the completion of the paricalcitol injection and the start of the pembrolizumab infusion. Sites should use normal saline to keep line open for this period in between paricalcitol injection and subsequent pembrolizumab infusion.

4.2.3 Pembrolizumab (Keytruda®)

Dosage Form: Pembrolizumab Solution for Infusion, 100 mg/ 4 mL vial to be stored under refrigerated conditions (2 – 8 °C (36 °F to 46 °F)) and protected from light in the original container and outer box.

Pembrolizumab Solution for Infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab. The product is preservative-free solution which is essentially free of extraneous particulates.

Preparation and Storage for Intravenous Infusion:

Specific instructions on the aseptic technique used to prepare the intravenous solution will be provided in a Pharmacy manual.

In summary the process will involve:

- Two vials of pembrolizumab solution will be used for each infusion. Each vial is 100mg/4 mL.

- Infusion solutions will be prepared in 0.9% Sodium Chloride Injection, USP (normal saline). Pembrolizumab SHOULD NOT BE MIXED WITH OTHER DILUENTS.

- The diluted solution will be mixed by gentle inversion, should not contain visible particulate matter or discoloration and should not be frozen.

- When removed from refrigeration the vials of solution and/or the prepared infusion may be stored at room temperature for a cumulative total of 6 hours only. This time includes the time of the infusion.

- The prepared infusion IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) for up to 24 hours. If refrigerated, allow the IV bags to come to room temperature prior to use and the infusion should be completed within 6 hours.

- Specific materials for infusion bags and infusion sets are approved for administration of pembrolizumab. A list of approved materials is provided in the Pharmacy manual.

- **There must be 30 minutes in between the completion of the paricalcitol injection and the start of the pembrolizumab infusion**.

- The solution is slowly infused over a period of 30 minutes through an approved IV line with no other drugs co-administered through the same line.

The infusions will be prepared and documented by the unblinded pharmacist just prior to dosing. Documentation relating to this preparation will be available for independent monitoring and verification.

4.2.4 Dose Modification (Escalation/Titration/Other) of Pembrolizumab (Keytruda®) in cases of Toxicity

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

Table 4. Dose Modification and Management Guidelines for Drug-Related Adverse Events

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

irAEs	Toxicity grade or conditions (NCI CTCAE v4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

AST / ALT elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function.
	Grade 3 or 4	Permanently discontinue		

Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3 or 4	Permanently discontinue		
All Other irAEs	Intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barré Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1.Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

Dose modification and toxicity management of infusion-reactions related to pembrolizumab
Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.

Table 5. Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

4.2.4.1 Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

4.2.5 Dose Interruption of Paricalcitol in Cases of Toxicity

In the event there is an AE that is attributable to paricalcitol, the paricalcitol would be held until the AE resolves. The management of patients with clinically significant hypercalcemia should follow guidelines as detailed in Section 4.6.2

4.2.6 Timing of Dose Administration

Trial treatment with paricalcitol followed by pembrolizumab should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Schedule (Section 5). Following the initial dose (cycle1 day1), pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Paricalcitol 25mcg IV (or equivalent volume for placebo) will be administered intravenously three times per week given on day 1 prior to pembrolizumab, and on days 3, 5, 8, 10, 12, 15, 17, and 19 (+/-1 day allowed for dosing per 21 day cycle). Site should make every effort to standardize the time and day of administration of paricalcitol.

There must be at least 30 minutes in between the completion of the paricalcitol injection and the start of the pembrolizumab infusion.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks on C1/Day1 of each 21 week cycle. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Note: The same IV line may be used to administer both the paricalcitol and the pembrolizumab. However there must be at least 30 minutes in between the completion of the paricalcitol injection and the start of the pembrolizumab infusion.

The Pharmacy Manual contains specific instructions for the preparation and administration of the pembrolizumab infusion fluid and paricalcitol IV doses.

4.2.7 Trial Blinding/Masking

This is a double-blind, randomized, placebo-controlled phase II trial with the identity of the treatment unknown to the patients, investigators, and the Sponsor. Only the site pharmacist and unblinded monitor will be aware of the assigned treatment arm.

4.3 Randomization or Treatment Allocation

Randomization will be in a 1:1 ratio to pembrolizumab + paricalcitol or pembrolizumab + placebo. Randomization will be performed by the trial biostatistician or designee using a computer-generated algorithm with a block size of 4. The RAND function in MySQL is used to generate a random number, with a value based on the computer clock used as seed. The program randomly assigns participants to one of the two treatments with the pre-selected block size. After study initiation, the randomization sequence will be provided to the unblinded central monitor. After consent and confirmation of eligibility, the site study coordinator will notify the site pharmacist and the unblinded monitor. The unblinded monitor will provide the next randomized treatment from the sequence to the site pharmacist. The unblinded monitor also will notify the trial biostatistician. The trial biostatistician or designee will be available to assist with identifying the next randomized treatment if the unblinded central monitor is not available.

4.4 Stratification

No stratification will be performed.

4.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial treatment or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician.

4.5.1 Acceptable Concomitant Medications

All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), multivitamins, nutritional and/or herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be reported for SAEs and ECIs as defined in Section 6.2.

4.5.2 Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial. For specific therapies there is a washout window prior to cycle1/day1, indicated below and per eligibility criteria in Section 4.1.

- Antineoplastic systemic chemotherapy or biological therapy. Prior anti-cancer monoclonal antibody (mAb) must be > 4 weeks prior to Cycle 1/Day 1.

- Immunotherapy

- Chemotherapy targeted small molecule therapy, or radiation therapy within 2 weeks prior to Cycle 1/Day 1.

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

- Investigational agents within 4 weeks prior to Cycle 1/Day 1

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

- Systemic glucocorticoids in doses of ≥ 10 mg/day prednisone or equivalent for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

- Strong inhibitors of CYP3A, digitalis or its compounds, aluminum containing preparations should not be used during the trial due to their potential to interact with paricalcitol.

- Phosphate or vitamin-D related compounds should not be taken concomitantly with paricalcitol. Patients will be asked to report vitamin and nutritional supplement use at baseline and throughout the trial.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Patients may receive other medications (not listed here as prohibited) that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Survival Follow-up Phase of the trial.

4.6 Rescue Medications & Supportive Care

4.6.1 Rescue Medication and Supportive Care Guidelines

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 4.2.4, Table 4. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 4 in Section 4.2.4 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

4.6.2 Treatment of Patients with Hypercalcemia

Treatment of patients with clinically significant hypercalcemia consists of immediate dose interruption of paricalcitol therapy and includes a low calcium diet, withdrawal of calcium supplements, patient mobilization, attention to fluid and electrolyte imbalances, assessment of electrocardiographic abnormalities (critical in patients receiving digitalis), and hemodialysis or peritoneal dialysis against a calcium-free dialysate, as warranted. Serum calcium levels should be monitored frequently until normal calcemia ensues.

4.7 Diet/Activity/Other Considerations

4.7.1 Diet

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

4.7.2 Contraception

Pembrolizumab or paricalcitol may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:
Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol - defined timeframe in section 5.0:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 6 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

    - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:
Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 6 during the protocol-defined time frame in Section 5.0.

Table 6. Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency Failure rate of <1% per year when used consistently and correctly.
• Progestogen- only contraceptive implant [a, b] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion
• **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.

b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 6 months after the last dose of study treatment.

Pregnancy Testing
WOCBP should only be included after a negative serum pregnancy test and in accordance with local requirements. When applicable this test should be repeated a maximum of 24-hours before the first dose of trial treatment.

Following initiation of treatment additional pregnancy testing will be performed prior to day 1 of each cycle during the treatment period and at 30 days after the last dose of study treatment and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

4.7.3 Use in Pregnancy

If a patient inadvertently becomes pregnant while on trial treatment, the patient will immediately be removed from the trial. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours. The Sponsor will report to Merck within 24 hours (working days) if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The trial investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male patient impregnates his female partner, the trial personnel at the site must be informed immediately and the pregnancy reported to the Sponsor. The Sponsor will report to Merck and follow the pregnancy as described above and in Section 6.2.2.

4.7.4 Use in Nursing Women

It is unknown whether pembrolizumab or paricalcitol is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

4.8 Patient Withdrawal/Discontinuation Criteria

Patients may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a patient may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding assessments to be done at an End of Treatment (EOT) visit at time of discontinuation or withdrawal are provided in Section 6.1.7.3.

A patient must be discontinued from the trial for any of the following reasons:

- The patient or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed disease progression
- Unacceptable adverse experiences as described in Section 4.2.4
- Inter-current illness that prevents further administration of treatment
- Investigator's decision to withdraw the patient
- The patient has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The patient is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 cycles of trial treatment whichever is later. 24 months of trial medication is calculated from the date of first dose.
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 5 (Trial Schedule) and Section 6.1.7 (Visit Requirements). After the end of treatment, each patient will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 6.2.3.1). Patients who discontinue for reasons other than progressive disease will have post-treatment follow-up every 90 days for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up, or the end of the trial, whichever occurs first.

4.9 Patient Replacement Strategy

Patients who are randomized to the trial but who then do not go on to initiate trial treatment, for any reason, will be replaced. The reason for not initiating treatment will be documented by the investigator. Patients who initiate trial treatment and discontinue from the trial for any reason will not be replaced. Patients who discontinue treatment without progression will be followed to determine their disease status every 90 days by phone until the trial ends.

4.10 Clinical Criteria for Early Trial Termination by the Sponsor

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to patients

4. Plans to modify or discontinue the development of the trial treatment

In the event of Merck's decision to no longer supply pembrolizumab, ample notification will be provided so that appropriate adjustments to patient treatment can be made.

5.0 Trial Schedule

The trial will consist of the following three periods:

Screening (SCN) Period: The screening period will take place only after informed consent is obtained and within the 21 days prior to C1/D1. The screening visit may be counted as the baseline visit if completed within 7 days of initial dosing on C1/D1.

Treatment Period: Patients will be treated at 21 ± 3 day intervals. Patient must begin cycle 1 within 21 days of signing the IRB approved informed consent document and after the screening assessments have been performed and reports have been reviewed to confirm eligibility. The patient will continue on maintenance therapy until there is evidence of clear-cut tumor progression, has treatment ending toxicities, or withdraws from treatment (refer to section 4.8). Table 7 below summarizes the Screen-Treatment Period Schedule.

Post Treatment Period: Patients will return to the investigative site for an End of Treatment (EOT) visit within 5 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first (refer to Section 6.1.7.3). An additional mandatory Safety Follow- up visit should be conducted approximately 30 days after the last dose of trial treatment and before initiation of a new anti-cancer treatment, whichever comes first (6.1.7.4). WOCBP will be required to have a pregnancy test at this visit.

After the 30 day-FU visit, patients will then move into the Survival Phase and be contacted by telephone every 90 days thereafter until death, withdrawal of consent, or the end of the trial, whichever occurs first. The protocol approved contraceptive guidance (Section 4.7.2) must be followed for at least 120 days (for males) and 180 days (for WOCBP) after the last dose of trial treatment. Table 8 below summarizes the Post Treatment Period Schedule.

Table 7. Screen – Treatment Period Schedule

	SCN	Treatment CYCLE 1									Treatment CYCLE 2									Treatment CYCLE 3 and beyond								
Trial week		1			2			3			4			5			6			7			8			9		
Cycle day	-	1	3	5	8	10	12	15	17	19	1	3	5	8	10	12	15	17	19	1	3	5	8	10	12	15	17	19
Window (Days):	-21 to -1	- 7[o]									± 3									± 3								
Informed Consent	X [a, c]																											
Inclusion/ Exclusion Criteria	x																											
Medical History	X [b]																											
Prior and Concomitant Medication Review	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Assess & Report Adverse Events [c]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Examination [d]	x	x			x			x			x			x			x			x			x			x		
Patient Personalized Clinical Benefit App	x	x			x			x			x			x			x			x			x			x		
Vital Signs [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x																											
ECOG [f](see appendix 4)	x	x			x			x			x			x			x			x			x			x		
Serum β HCG Pregnancy Test (if applicable) [g]	x	x [g]									x									x								
PT/INR and aPTT	x																											
CBC with Differential	x	x			x			x			x			x			x			x			x			x		
Comprehensive Serum Chemistry Panel [h]	x	x			x			x			x			x			x			x			x			x		
Urinalysis	x	x									x									x								
T3, FT4, TSH, & PTH	x	x[i]																		x								
HBsAg HCV RNA (qualitative)	x[n]																											
Serum vitamin D	x																											
Tumor Imaging & Response Assessment	x [j]																						[----------X[i]----------]					
CA19-9 (CA 125, or CEA if not expressers of CA19-9) [k]		x									x									x								
Optional-Tumor Biopsy (refer to 6.1.2.8)	x																									x[r]		
Central Lab Blood Sample	x																									x		
Central Lab Fecal Swab	x[l]	x[m]	x[m]							x[l]	x[m]	x[m]							x[l]	x[m]	x[m]							
Tumor Tissue Collection	X[p]	[Tumor tissue collection for those that consent to this optional collection and undergo a routine care biopsy of their tumor during their participation in the study] [q]																										
Pembrolizumab infusion		x									x									x								
Paricalcitol iv		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Footnotes for Table 7. Screen – Trial Treatment Period Schedule

a. Written IRB-approved informed consent must be obtained prior to any screening assessments being performed.

b. Documented medical history to include, demographics, concurrent baseline conditions (using NCI-CTCAE V4. Appendix 3), prior cancer treatment and surgeries.

c. For the time that the consent form is signed until treatment allocation/randomization, any events of clinical interest (ECI, refer to 6.2.3.2), serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 6.2.3.3 for additional details) that occurs to any patient must be reported within 24 hours to the Sponsor. AEs will continue to be assessed and reported throughout the trial treatment period, for 30 days following the EOT and again at 90 days for serious adverse events (refer to Section 6.2 for complete details).

d. Complete physical exam at screening including height and weight, directed physical exam with weight for day 1, 8, 15 of each cycle and at the EOT.

e. Vital signs to include: Blood pressure, pulse, respiratory rate, and temperature.

f. ECOG Performance Status must be 0 or 1 to be eligible for entry to the trial.

g. Negative serum pregnancy test is required for women of child-bearing potential (WOCBP) within 24 hours of start of trial medication. Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected. Participants must agree to use a contraception as detailed in Section 4.7.2

h. Refer to Table 9 for details of required labs to be included. Adequate organ function must be demonstrated in accordance with protocol criteria within 10 days of start of trial medication as defined in Table 2.

i. TSH, T3, Free T4, and PTH (not required at C1/Day 1 if completed at SCN within 21 days). Results must be reviewed prior to treatment initiation. Repeated every other cycle throughout treatment period (i.e. prior to Cycle 3, 5, 7, etc.).

j. CT/MRI scan to document disease status at baseline to include chest abdomen and pelvis and other regions as clinically indicated. Brain scan is required to rule out brain metastases if clinically indicated. The same radiographic procedures used to document disease status at baseline must be used throughout the trial. If a CT scan was taken within 28 days prior to first dose, a new scan is not necessary. However, if a new scan is to be done, it should be performed within 10 ± 2 days prior to starting trial medication. Tumor assessments will be conducted using CT or MRI, approximately every 9 ± 1 weeks until trial discontinuation or disease progression, whichever is later. All sites of disease must be followed using the same baseline assessment method. The investigator will complete tumor measurements and response evaluation per RECIST 1,1 and iRECIST. The central radiologist will also perform an independent read of each scan. (Refer to section 6.1.2.6)

k. CA19-9 (or CEA or CA-125 if not expressers of CA19-9) assessments will be taken at baseline and approximately every 21 days during the trial treatment period. All CA19-9 assessments must be assayed by the same laboratory for each patient. The Investigator is encouraged to obtain radiological assessments and CA19-9 values earlier if there is a strong clinical suspicion of disease progression, in order to confirm or refute the clinical impression.

l. Site will provide to patient the Fecal Swab sample collection kits and instructions to collect two samples at home per each treatment cycle as follows: Pre-Dose Sample 1. within 72 hours **prior** to scheduled Day 1 of each treatment cycle and Post Dose Sample 2. between 24 - 72 hours **after** Day 1 study treatment. Refer to Section 6.1.6 for complete details.

m. Patient will return Fecal samples to clinic during scheduled apt, must be within 72 hours of fecal sample collection.

n. Required only if not performed within the 3 months prior to informed consent.

o. Screening clinical evaluations and laboratory assessments may be used as the Cycle 1/ Day 1 evaluations if they are completed within 7 days prior to trial treatment administration.

p. All patients are required to provide archival tumor specimen from either a primary or metastatic site . (Refer to 4.1.1 and 6.1.2.8)

q. For only those patients that consent to the optional tissue collection. (Refer to 6.1.2.8).

r. For only those patients consenting to the optional tumor biopsy, a baseline tumor biopsy will be collected and used for profiling. If possible (patient condition permitting) this will be repeated after 9 ± 1 weeks on trial treatment, or at the time of disease progression. (Refer to 6.1.2.8).

Table 8. Post-Treatment Period (EOT– Follow-Up) Schedule

Post-Treatment Period	EOT	30 days from EOT	Every 90 days post EOT
Scheduling Window (Days)	At time of discontinuation (within 5 days of last dose)	30 ± 5 days from EOT	90 ± 5 days from EOT then every 90 ± 15 days [i]
Post-trial anticancer treatment status	X	X	X
Disease/Survival Status [a]	X	X	X
Concomitant Medication Review	X	X	X
Assess & Report Adverse Events [b]	X	X	X
Directed Physical Examination	X		
Patient Personalized Clinical Benefit App	X		
Vital Signs and Weight [c]	X		
ECG	X		
ECOG (see appendix 4)	X		
Serum β HCG Pregnancy Test for WOCBP	X	X	
CBC with Differential	X		
Comprehensive Serum Chemistry Panel	X		
Urinalysis	X		
T3, FT4 and TSH	X		
Tumor Imaging [d]	X		
CA19-9 [e]	X		
Central Lab Samples (Blood and Fecal Swab[f])	X	X[f]	
Review contraception use as required by protocol Section 4.7.2 (where applicable) [g]	X	X	X
Optional -Tumor Tissue Collection	[Tumor tissue collection for those that consent to this optional collection and undergo a routine care biopsy of their tumor during their participation in the study] [j]		
Contact Information Review [h]	X	X	X

Footnotes for Table 8. Post –Treatment Period

a. Post-treatment follow-up for disease status until documented disease progression, initiating a non-trial cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each pt will be followed by telephone for survival status.

b. Assess and record any new or ongoing AEs at time of EOT. Following the EOT, each patient will be followed for 30 days, for adverse event monitoring. Serious adverse events and Events of Clinical Interest (ECI) will be collected for 90 days after the end of treatment as described in Section 6.2.3.1.

c. Vital signs to include: Blood pressure, pulse, respiratory rate, and temperature.

d. Tumor assessments will be conducted using CT or MRI at trial discontinuation or disease progression, whichever is later. All sites of disease must be followed using the same baseline assessment method.

e. CA19-9 assessments will be taken at baseline and approximately every 3 weeks during the trial treatment period and at the end of treatment visit. All CA19-9 assessments are to be assayed by the same laboratory for each patient. The Investigator is encouraged to obtain radiological assessments and CA19-9 values earlier if there is a strong clinical suspicion of disease progression, in order to confirm or refute the clinical impression.

f. Site to provide patient with Fecal Swab sample collection kit and instructions to collect sample at home within the 72 hours prior to the scheduled 30-day follow-up visit. Patient will return fecal sample to clinic during the scheduled visit, or make

arrangements to drop sample off within 72 hours of collection.
g. Adequate contraception as defined by the protocol should be used throughout the trial and for at least 120 days for males w/WOCBP sexual partner and 180 days for WOCBP from the last dose of trial treatment. Refer to Section 4.7.2. for complete details.
h. Site to confirm contact information for patient and a designated family member and remind patient of FU telephone contact that will be conducted every 90 days for survival status
i. During the Survival Follow-up Phase the patient should be contacted by telephone 90 ± 5 days from EOT and every 90 ± 15 days after that until death, withdrawal of consent, or the end of the trial, whichever occurs first.
j. For only those patients that consent to the optional tissue collection. (Refer to 6.1.2.8).

6.0 TRIAL PROCEDURES

6.1 Trial Procedures

Individual trial procedures (Administrative, Clinical, and Laboratory) are described in detail below. The specific visit requirements are detailed in Section 6.1.7. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/ testing may be deemed necessary by the Sponsor for reasons related to patient safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the patient. In these cases, such evaluations/testing will be performed in accordance with those regulations.

6.1.1 Administrative Procedures

6.1.1.1 Informed Consent

The Investigator or qualified designee must obtain documented consent from each potential patient prior to participating in a clinical trial.

6.1.1.1.1 General Informed Consent

Consent must be documented by the patient's dated signature. A copy of the signed and dated consent form should be given to the patient before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the patient must receive the IRB/ERC's approval/favorable opinion in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the patient's dated signature or by the patient's legally acceptable representative's dated signature.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

6.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed and documented by the investigator or qualified designee to ensure that the patient qualifies for the trial.

6.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the patient has enrolled in this trial will be recorded separately and not listed as medical history.

6.1.1.4 Prior and Concomitant Medications Review

6.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the patient within the 30 days before starting the trial. Treatment for the disease for which the patient has enrolled in this trial will be recorded separately and not listed as a prior medication.

6.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medications including prescription, over-the-counter (OTC), multivitamins, nutritional and/or herbal supplements, IV medications and fluids, if any, taken by the patient during the trial. All medications related to reportable SAEs and Events of Clinical Interest (ECIs) should be recorded as defined in Section 6.2.

6.1.1.5 Disease Details and Treatments

6.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

6.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries. The investigator will assess and provide as part of the baseline eCRF data, the Best Response on the last treatment prior to enrollment in this trial.

6.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a patient initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the EOT visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the patient will move into survival follow-up.

6.1.1.6 Assignment of Screening Number

A patient will be assigned a screening number once they provide written informed consented for the trial. This screening number will be site specific and maintained on a Screening log in the Investigator Site File.

6.1.1.7 Assignment of Randomization Number

Eligible patients will be assigned a randomization number that will serve as the patient's number throughout the trial. This randomization number will be maintained on a Randomization log in the Investigator Site File.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each patient to evaluate for potential new or worsening AEs as specified in the Trial Schedule Section 5.0 (during the trial treatment period, for 30 days following end of treatment and again at 90 days for serious adverse events and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the trial and during the follow-up period according to NCI CTCAE Version 4.0 Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 6.2 for detailed information regarding the assessment and recording of AEs.

6.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history.

6.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration on days 1, 8, and 15 of each cycle, and at treatment discontinuation.

6.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Schedule (Section 5.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

6.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (Appendix 4) at screening, prior to the administration of trial treatment, on days 1, 8, and 15 of each cycle, and at discontinuation of trial treatment as specified in the Trial Schedule.

6.1.2.6 Tumor Imaging and Assessment of Disease

The patient's pancreatic cancer will be evaluated by the investigator based on tumor assessments using RECIST 1.1 and iRECIST criteria (Appendix 5).

Tumor assessments for evaluation of response will be conducted using CT or MRI, approximately every 9 ± 1 weeks until trial discontinuation or disease progression, whichever is later. All sites of disease must be followed using the same baseline assessment method.

CT is the preferred imaging modality for this study. I.V. contrast should be administered, unless medically contraindicated.

If CT with I.V. contrast is contraindicated, the alternative is to acquire a CT of the chest without contrast and MRI of the abdomen and pelvis with gadolinium contrast.

Other protocols, such as non-contrast CT of chest abdomen pelvis, should not be performed. For CT scans oral contrast should be administered in addition to IV contrast. Radiolucent agents (e.g., water) are generally preferred over radiopaque agents (e.g., iodine and barium-based agents).

All target lesions will be measured by consistent imaging techniques for each patient throughout the trial. Suitable imaging techniques include CT-scan, or MRI. The same technique should be used for each evaluation in an individual patient. Copies of the scans must be available for review.

In addition, a central radiologist, blinded to the treatment assignment, will perform an independent read of each scan, assessing tumor response using RECIST 1.1 and iRECIST criteria (Appendix 5).

In the event that PD by RECIST 1.1 or iUPD is determined, a repeat scan must be performed within 4 - 6 weeks to confirm PD. Trial treatment may be continued during this time (past the initial PD assessment) but only if patient is clinically stable as defined by:

- No worsening of performance status

- No clinically relevant increase in disease related symptoms

- No requirement for intensified management of disease related symptoms (analgesics, radiation, palliative care)

If the investigator assesses a patient to have PD (defined by RECIST 1.1), the central radiologist will review the scan to confirm the PD, prior to the discontinuation of trial treatment.

CA19-9 assessments (or CEA or CA-125 for not expressers of CA19-9) will be taken at baseline and approximately every 21 days during the trial treatment period. All CA19-9 assessments must be assayed by the same laboratory for each patient. Disease progression will not be determined by CA19-9, however increases in CA19-9 may warrant the investigator to obtain radiographic assessments.

Note: In order to more precisely determine time to progression, the investigator is encouraged to obtain radiological assessments and CA19-9 values earlier if there is a strong clinical suspicion of disease progression. In order to either confirm or refute the clinical impression.

6.1.2.7 Blood Collection

Each patient will have two - 10 mL vials of blood collected at the following timepoints: baseline, 9 ± 1 weeks on trial treatment, at time of confirmed response (if applicable) and at the EOT. Blood samples will be processed for serum and for peripheral blood mononuclear cells (PBMCs). Viable PBMCs will be stored in Bambanker™ freezing media for later analysis of circulating immune cells by existing technologies, such as flow cytometry, CyTOF, single-cell RNA-Seq, and single cell ATAC-Seq, as well as various new technologies as they become available. Serum will be snap frozen and used to evaluate the impact of therapies on circulating cytokine levels (e.g. IL6) by ELISA and multiplex cytokine assays.

Blood samples will be sent and centrally analyzed by [redacted] and the [redacted].

Specific details for blood sample collection and handling will be provided to the investigative sites in the Trial Laboratory Manual.

6.1.2.8 Tumor Tissue Collection

All patients will be required to provide an archival tissue specimen. Archival tissue will be analyzed in a similar manner as described below for formalin fixed paraffin embedded (FFPE) biopsy samples. Specific details for archival tissue processing and distribution will be provided to the investigative sites in the Trial Laboratory Manual. Sites will be asked to indicate whether blocks will be available for additional sectioning at a later point in time if additional tissue is needed.

Patients will be provided with the following two additional options to provide fresh tumor tissue for the analysis as described below.

Patients will be provided the option to consent to provide fresh tissue samples from a newly obtained core or excisional biopsy of a tumor lesion if performed recently (within 30 days prior to Cycle 1/Day 1) and during their participation in the study should they be scheduled for a biopsy as part of their routine care during their participation in the study through the follow-up period.

Additionally, patients will also be provided with the option to consent to undergo a biopsy of a tumor lesion at baseline, at the completion of 3 cycles of treatment (9 weeks after starting trial treatment), or at the time of disease progression if prior to week 9, unless tumor is considered inaccessible or biopsy is otherwise considered not in the patients best interest. *Participation in this trial is therefore not contingent on the patient consenting to optional tumor biopsies for fresh tissue.*

For patients consenting to the optional tumor biopsy, a baseline tumor biopsy will be collected and used for profiling. If possible (patient condition permitting) this will be repeated after 9 ± 1 weeks on trial treatment, or at the time of disease progression. Each tumor biopsy will consist of approximately 5 passes, refer to Trial Laboratory Manual for more details. The site is asked to provide an image (CT image) of needle orientation. Alternatively, if the biopsy is performed under ultrasound guidance, the site is asked to provide details on which lesion and where that lesion is located on a diagnostic CT or MRI (i.e. CT series and slice number). This de-identified image will be sent to [redacted] (refer to protocol section 6.1.5).

Tissue samples will be sent and centrally analyzed by [redacted] and the [redacted].

Two passes will be split evenly and processed for formalin-fixed paraffin (FFP) and optimal cutting temperature (OCT) embedding and samples will be centrally analyzed using existing technologies, such as immunohistochemistry, immunofluorescence, and RNA-in situ hybridization, as well as various new technologies as they become available to evaluate the following:

- Stromal/extracellular matrix content (e.g. collagen and hyaluronic acid)
- Quantity and quality of vascularization (e.g. CD31)
- Expression of pembrolizumab related targets (e.g. PD-1 and PD-L1)
- Presence/ distribution, and activation of key immune cell populations (e.g. cytotoxic T Cells, TAMs, MDSCs, and Tregs)
- Presence, distribution, and activation of other stromal cell populations, including fibroblasts (e.g. αSMA)

One pass will be immediately snap frozen for the following central analysis

- Analysis of bulk tumor RNA for VDR expression and VDR targets (e.g. CYP24A1)
- Analysis of bulk tumor RNA for Expression of VDR regulated inflammatory gene (e.g. IL6, CXCL1, CSF2, CXCLR)

Two passes will be immediately frozen in Bambanker™ freezing media for the following central analysis:

- Genomic analysis of T-cell receptor clonality by sequencing (a measure of intratumoral T cell response)

  Bulk and single-cell analysis of mutational profiles, transcriptional profiles, and epigenetic states within tumors, including analysis of sorted tumor cell nuclei.

  In the event that biopsy tissue becomes limiting for certain analyses, snap frozen and Bambanker™ frozen tissue may be used interchangeably where technically feasible.

  Specific details for tumor tissue collection and handling will be provided to the investigative sites in the Trial Laboratory Manual.

6.1.3 Laboratory Procedures/Assessments

Safety laboratory tests for hematology, chemistry, and urinalysis (as detailed in Table 9) will be performed by the local laboratory for each investigational site at screening, baseline and throughout the trial treatment period. Serum vitamin D levels will be performed at screening. HBsAg and HCV RNA (qualitative) will be performed at screening if not performed within the last 3 months. Thyroid and Parathyroid function (T3, FT4 TSH, and PTH) will be performed as part of screening and every other cycle during the trial treatment period.

Table 9. Laboratory Tests – performed locally

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Thyroid stimulating hormone (TSH)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal results are noted)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡		Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*		PTH (parathyroid hormone)
	Uric Acid		Serum vitamin D (25-

Hematology	Chemistry	Urinalysis	Other
			hyroxy vitamin D)
	Calcium		HBsAG
	Chloride		HCV RNA qualitative
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		
† Perform on women of childbearing potential (WOCBP) only. ‡ If considered standard of care in your region.			

6.1.4 Patient Personalized Clinical Benefit (PPCB)

The exploratory objective to assess Patient Personalized Clinical Benefit (PPCB) will be evaluated based on the improvement in disease-related symptoms. The specific disease-related symptoms that are most bothersome for the individual patient will be identified at baseline and followed throughout the trial. Patients will use a trial-specific phone-based application to record the status of their three most bothersome disease-related symptoms at baseline, weekly during the treatment period, and at the EOT visit. The patient will be provided instructions and download and complete the app during the baseline C1/Day 1 visit. The patient will enter their responses directly into the APP via their mobile device using an assigned patient ID and therefore no protected health information (PHI) will be recorded. In the event that a patient does not have the type of mobile device required to access the APP, or the patient chooses not to complete the PPCB via the APP, the patient will be provided a paper questionnaire to complete. The site will record the reason the patient is not utilizing the APP in the source documents. Refer to Appendix 6 for more details on the PPCB App.

6.1.5 Quantitative Textural Analysis (QTA)

Quantitative Textural Analysis (QTA) will be used to explore differences in tumor and tissue texture between the two treatment arms of this trial using baseline, on treatment, and post treatment CT scans. Such information may provide a basis for establishing a complementary diagnostic biomarker that could 1) predict disease stability in the maintenance environment 2) provide an imaging signature that is associated with immune infiltrative activity, 3) allow a non-invasive method for detecting tumor and tissue texture changes related to vitamin D (paricalcitol) exposure and 4) identify other correlations of imaging to tumor biology, response to treatment, and laboratory assessments.

CT scans will be performed at each investigative site as per protocol schedule.

Sites will be provided instructions for sending de-identified CT scans [redacted] for analysis. Images will be reviewed to ensure appropriate series, images and anatomic coverage is available and that all PHI has been removed. Only query-free studies will be forwarded for analysis. Query-free scans will be loaded onto [redacted] QTA analysis platform for textural analysis. Refer to Appendix 7 for specific information on the planned QTA analysis to be performed.

6.1.6 16S Gut Microbiome rRNA Analysis

The exploratory objective to monitor and compare the gut microbial communities will be evaluated using patient collected fecal samples. The differences in gut microbial communities within and between fecal samples will be compared using alpha and beta diversity metrics based on 16S rRNA sequencing. The DNA extraction and sequencing analysis will be performed at [redacted]. Refer to Appendix 8 for more specific information on the planned analysis to be performed. Specific details for sample handling and shipping will be provided to the investigative sites in the Trial Laboratory Manual.

Fecal samples are relatively easy to collect and non-invasive. They provide an indication of the gut microbiome which may be an indicator of general health, impact drug availability, and indicate the presence of communities associated with inflammation, digestive inefficiencies, and pathogens. Monitoring the gut microbiome may allow us to predict the risk of possible side effects of pembrolizumab (colitis and decreased appetite) and paricalcitol (decreased appetite).

Fecal samples will be collected by the patient at home during trial participation. Patients will be asked to collect two samples per treatment cycle. One fecal swab sample is to be collected within the 72 hours prior to Day 1 of each treatment cycle, and a second fecal swab sample within 24-72 hours after treatment on Day 1. The patient will also be asked to collect one final sample approximately 30 days following treatment discontinuation. Patients will be provided with collection instructions (refer to Appendix 9), collection container, sterile CultureSwabs in individual pre-labeled containers, and a biospecimen bag. Patients will collect fecal material in a collection container, and then transfer a pea size amount of fecal matter using the provided CultureSwabs, into the original pre-labeled fecal swab collection container, and place in the provided biospecimen bag. The patient will be asked to store the fecal samples in the freezer and deliver to the research site within 72 hours of collection (this will correspond with the patients' return to clinic - so it is not anticipated that additional clinic visits should be required).

6.1.6.1 Withdrawal/Discontinuation

When a patient discontinues/withdraws prior to trial completion, all applicable activities scheduled for the EOT visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 6.2 - Assessing and Recording Adverse Events.

6.1.6.2 Blinding/Unblinding

This is a double-blind, randomized, placebo-controlled phase II trial with the identity of the treatment unknown to the patients, investigators and the Sponsor. Only the site pharmacist and unblinded trial monitor will be aware of the assigned treatment arm.

Investigators will be able to unblind in emergency situations when the identity of the treatment must be known in order to provide appropriate treatment. The sponsor must be contacted (if possible) prior to the treating investigator unblinding a patient.

Additionally, at the time of disease progression the treating investigator may request the unblinded treatment assignment for the patient. This will be provided by the unblinded trial monitor to the treating Investigator for the purposes of considering future treatment options. The remainder of the trial team will not have access to this unblinded treatment assignment.

Once a patient is unblinded he/she will not be allowed to continue on trial medication and will be considered an early withdrawal and will need to complete the required EOT procedures and necessary follow-up per section 6.1.5.3.

6.1.7 Visit Requirements

Visit requirements are outlined in Section 5.0 - Trial Schedule. Specific procedure-related details are provided above in Section 6.1 - Trial Procedures.

6.1.7.1 Screening Period

Screening of potential patients will be performed only after informed consent is obtained and within 21 days prior to first dose of trial medication (unless otherwise noted below). All necessary laboratory values and assessment reports must be available and reviewed prior to cycle1/ day 1.

The following will be completed as part of the screening visit:

1. Written informed consent

2. Medical history including concurrent baseline conditions (using NCI CTCAE version 4.0; Appendix 3), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy)

3. Complete physical examination including height (cm) and weight (kg)

4. ECOG Performance Status (see Appendix 4)

5. Vital signs (blood pressure, pulse, respiratory rate, and temperature)

6. Computed tomography (CT) / magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated. In addition, brain scan is required to exclude brain metastases if clinically

indicated only). If a CT scan was taken within 28 days prior to first dose, a new scan is not necessary. However, if a new scan is to be done, it should be performed within 10 ± 2 days prior to starting trial medication. Obtain De-identified Dicomm encoded CT scan for central lab (Appendix 7).

7. Electrocardiogram (ECG)

8. PT/INR and aPTT

9. Complete blood count (CBC) with differential and platelet count

10. Comprehensive serum chemistries (refer to Table 9)

11. TSH, T3, Free T4, and PTH

12. Serum vitamin D level

13. HBsAg and HCV RNA (qualitative) if not performed in the last 3 months

14. Urinalysis (refer to Table 9)

15. Serum β-HCG pregnancy test for women of child-bearing potential (refer to Section 4.7.2 for more details)

16. Concomitant medication notation (to include all medications taken within 30 days prior to enrollment)

17. For those patients consenting to the optional fresh tissue collection: Obtain fresh tissue from a newly obtained core or excisional biopsy if performed within the last 30 days prior to first dose of trial medication (C1/D1). Refer to Section 6.1.2.8.

18. For those patients consenting to the optional baseline biopsy: Fresh tissue is to be obtained up to 3 weeks (21 days) prior to first dose of trial medication (C1/D1). Refer to Section 6.1.2.8.

19. Obtain archival tumor specimen for all patients - as required for eligibility. Refer to Section 6.1.2.8.

20. Central Lab Blood Sample 2 X 10 mL vials . Refer to Section 6.1.2.7.

21. Provide Fecal Swab collection kit and review instructions with patient for return of sample on Cycle 1/Day 1. Refer to Section 6.1.6.

22. Investigator or qualified designee to review and record the patient's three most bothersome disease-related symptoms (as determined by the patient) to be followed during treatment period, via the Patient Personalized Clinical Benefit (PPCB) App – Refer to Appendix 6.

6.1.7.2 Treatment Period

Patients will be treated at 21 ± 3 day intervals. Patient must begin cycle 1 within 21 days of signing the IRB approved informed consent document and after the screening assessments have been performed and reports have been reviewed to confirm eligibility. Screening clinical evaluations and laboratory assessments may be used as the Cycle 1/ Day 1 evaluations if they are completed within 7 days prior to trial treatment administration.

Treatment will be administered by qualified and trained site personnel in a hospital, clinic, or other outpatient setting appropriate for chemotherapeutic infusions.

For subsequent cycles, all assessments must be conducted prior to treatment administration and within 72 hours (except those noted), or if medical or scheduling conditions require a delay.

Day 1 of each cycle

- Inclusion/exclusion review (Cycle 1 only)
- Directed physical exam
- Vital signs
- Measurement of weight (kg) and BSA calculation prior to dosing (After Cycle 1, the BSA only needs to be changed if there has been a change > 10% in body weight from Cycle 1 /Day 1
- ECOG Performance Status (Appendix 4)
- Hematology: CBC with differential and platelet count. Results must be reviewed prior to treatment initiation to ensure patient still meets inclusion criteria.
- Serum chemistries (refer to Table 9). Results must be reviewed prior to treatment initiation to ensure patient still meets inclusion criteria.
- CA19-9 (C1/D1)

  Every other cycle only: TSH, T3, Free T4, and PTH (not required at C1/Day 1 if completed within 21 days). Results must be reviewed prior to treatment initiation. To be repeated every other cycle, i.e. prior to cycle 3, 5, 7, 9, etc.
- Urinalysis
- Serum β-HCG pregnancy test. Results must be reviewed prior to treatment initiation confirming a negative serum β-HCG for women of child-bearing potential and documentation of the patients confirmation of preferred acceptable method of contraception per Section 4.7.2 starting from the day of trial treatment initiation (refer to Section 4.7.2 for more details).

- AEs using the NCI CTCAE V4.0 (Appendix 3)
- Concomitant medication notation of all medications taken within the 30 days prior to C1/D1
- Provide Fecal Swab collection kit and review instructions (Appendix 9) with patient for return of sample on Day 3
- Patient to complete the Patient Personalized Clinical Benefit (PPCB) App (Appendix 6)
- Paricalcitol administration
- Pembrolizumab administration

Day 3, 5 , 8 ,10 ,12, 15, 17, and 19 (± 1 day) of each cycle

- Vital signs
- AEs using the NCI CTCAE (Appendix 3)
- Concomitant medication notation
- **Day 8 and 15 of each cycle only:** Directed physical exam, including weight
- **Day 8 and 15 of each cycle only**: ECOG Performance Status
- **Day 8 and 15 of each cycle only:** Hematology: CBC with differential and platelet count - results must be reviewed prior to paricalcitol administration
- **Day 8 and 15 of each cycle only:** Serum chemistries (refer to Table 9) - results must be reviewed prior to paricalcitol administration
- **Day 8 and 15 of each cycle only:** Patient to complete the Patient Personalized Clinical Benefit (PPCB) App (Appendix 6)
- **Day 19 Only:** Provide Fecal Swab collection kit and review instructions with patient for return of sample on Day 1 on next treatment cycle
- Paricalcitol administration

Week 9 (+/- 1 week)

- Optional repeat biopsy refer to Section 6.1.2.8
- Central Lab Blood Sample, 2 X 10 mL vials refer to Section 6.1.2.7

End of 3 treatment cycles (every 9 ± 1 weeks) until disease progression or end of trial, whichever comes first

- CT/MRI scan to evaluate disease status (using same imaging method as Baseline). Obtain De-identified dicomm encoded CT scan for central lab (Appendix 7).

Note: In order to more precisely determine time to progression, the investigator is encouraged to obtain radiological assessments and CA19-9 values earlier if there is a strong clinical suspicion of disease progression. In order to either confirm or refute the clinical impression.

6.1.7.3 End of Treatment (EOT)

The patient will continue on maintenance therapy until there is evidence of clear-cut tumor progression, has treatment ending toxicities, or withdraws from treatment (refer to section 4.8). The following assessments will be performed within 5 days after completing the last dose of trial medication or before the initiation of a new anti-cancer treatment, whichever comes first:

- Directed physical exam
- ECOG Performance Status (see Appendix 4)
- Vital signs
- ECG
- Hematology: CBC with differential and platelet count
- Serum chemistries
- TSH, T3, T4
- CA19-9 (or CEA or CA-125 if not expressers of CA19-9)
- Urinalysis
- Serum β-HCG pregnancy test (for WOCBP)
- Central lab blood sample, 2 X10 mL vials
- Concomitant medication
- Patient to complete the PPCB App (Appendix 6)

- Provide Fecal Swab collection kit and review instructions(Appendix 9) with patient for return of sample within 72 hours of collection (coordinate with 30 day Safety Follow-Up visit)

- CT/MRI scan to evaluate disease status (using same imaging method as Baseline). Obtain De-identified dicomm encoded CT scan for central lab (Appendix 7).

- AEs using the NCI CTCAE Version 4.0 (see Appendix 3)

- Review contraception use as required by protocol Section 4.7.2 (where applicable)

- Confirm contact information for patient and a designated family member and remind patient of FU telephone contact that will be conducted every 90 days for survival status following the 30 - day follow-up visit.

6.1.7.4 Follow-up Period

30-day Follow-up Visit

The mandatory Safety Follow- up visit should be conducted approximately 30 (± 5 days) after the last dose of trial treatment and before initiation of a new anti-cancer treatment, whichever comes first.

The following assessments will be performed:

- Serum β-HCG pregnancy test (for WOCBP)

- AEs using the NCI CTCAE Version 4.0 (see Appendix 3)

- Review contraception use as required by protocol Section 4.7.2 (where applicable)

- Confirm contact information for patient and a designated family member and remind patient of FU telephone contact that will be conducted every 90 days for survival status.

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Patients with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first.

SAEs that occur within 90 days of the end of trial treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

Survival Follow-up Phase
Once a patient experiences confirmed disease progression or starts a new anti-cancer therapy, the patient moves into the Survival Follow-up Phase and should be contacted by telephone 90 (± 5 days) from EOT and every 90 ± 15 days after that until death, withdrawal of consent, or the end of the trial, whichever occurs first.

6.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the pembrolizumab and /or paricalcitol, is also an adverse event.

Adverse events may occur during the course of the use of pembrolizumab and/or paricalcitol in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study (pancreatic cancer) is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the patient to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 6.2.3.1. The investigator will make every attempt to follow all patients with non-serious adverse events for outcome.

6.2.1 Definition of an Overdose for This Protocol and Reporting to the Sponsor

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥ 5 times the indicated dose).

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

In the event that an inadvertent overdose of pembrolizumab occurs during the trial this should be immediately reported to the Sponsor. Any untoward events occurring as a result of the overdose should be reported within 24 hours to the Sponsor as SAE or ECI per the guidance under section 6.2.3.1

6.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Female patients that are pregnant or breastfeeding, or expecting to conceive within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment are excluded from participating in the trial. However in the unlikely event that pregnancy or lactation occurs during the course of the patient's participation in the trial the following section describes the required reporting of these events.

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the patient to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of trial medication or 30 days following cessation of trial treatment if the patient initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor. The Sponsor will report within 24 hours (working days) to Merck Global Safety.

6.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

6.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of pembrolizumab and/or paricalcitol that results in any of the following:

- Death;
- A life threatening adverse drug experience;
- Persistent or significant disability/incapacity;
- Inpatient hospitalization or prolongation of an existing hospitalization;
- Congenital anomaly/birth defect;

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious drug adverse experience when, based upon

appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor and Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

- Is a new cancer (that is not a condition of the trial);
- Is associated with an overdose.

Refer to Section 6.2.4 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 6.2.3.3 for additional details) that occurs to any patient must be reported within 24 hours to the Sponsor. The Sponsor will report within 24 hours (working days) to Merck Global Safety if it causes the patient to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 6.2.3.3 for additional details), whether or not related to the trial treatment, must be reported within 24 hours to the Sponsor. The Sponsor will report within 24 hours (working days) to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to pembrolizumab that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor. The Sponsor will then report to Merck Global Safety.

All patients with serious adverse events must be followed up for outcome.

6.2.3.2 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and the Sponsor will report within 24 hours (working days) to Merck Global Safety.

Events of clinical interest for this trial include:

1. An overdose of pembrolizumab, as defined in Pharmacy manual and Section 6.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing. *

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any patient must be reported within 24 hours to the Sponsor and the Sponsor will report within 24 hours (working days) to Merck Global Safety if it causes the patient to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to pembrolizumab, must be reported within 24 hours to the Sponsor and the Sponsor will report within 24 hours (working days) to Merck Global Safety.

6.2.4 Evaluating Adverse Events

AE Grade

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP website at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

When specific adverse events are not listed in the CTCAE they will be graded by the investigator according to the following grades and definitions, consistent with the CTCAE Version 4.0.

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to

preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

- Grade 4: Life-threatening consequences; urgent intervention indicated.

- Grade 5: Death related to AE.

Duration

The investigator will record the start and stop dates of the adverse event. If less than1 day, this will be indicated in the appropriate length of time in units.

Action Taken

Did the adverse event cause the trial treatment to be discontinued?

Relationship

All adverse events regardless of CTCAE grade must also be evaluated for relationship (in regards to trial treatment/ trial interventions).

The determination of the likelihood that trial treatment caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame.

The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the trial treatment and the adverse event based upon the available information.

The following components are to be used to assess the relationship between trial treatment and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the trial treatment caused the adverse event (AE):

Exposure: Is there evidence that the patient was actually exposed to trial treatment such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

Time Course: Did the AE follow in a reasonable temporal sequence from administration of trial treatment? Is the time of onset of the AE compatible with a drug-induced effect?

Likely Cause: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?

Dechallenge: Was trial treatment discontinued or dose/exposure/frequency reduced?

If yes, did the AE resolve or improve? **If yes,** this is a positive dechallenge.

If no, this is a negative dechallenge.

Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the trial treatment; or (3) the trial is a single-dose drug trial); or (4) trial treatment is/are only used one time.

Rechallenge: Was the patient re-exposed to trial treatment in this trial?

If yes, did the AE recur or worsen?

If yes, this is a positive rechallenge.

If no, this is a negative rechallenge.

Note: If a rechallenge is planned for an adverse event which was serious and which may have been caused by either of the trial treatments, or if re-exposure to trial treatment poses additional potential significant risk to the patient, then the rechallenge must be approved in advance by the Sponsor as per dose modification guidelines in the protocol.

Consistency with Trial Treatment Profile: **Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding trial treatment or drug class pharmacology or toxicology?**

Relationship	Attribution	Description
Unrelated to the trial treatment/intervention	Unrelated	The AE is clearly NOT related to the trial treatment/intervention
	Unlikely	The AE is *doubtfully related* to the trial treatment/intervention
Related to the trial treatment/intervention	Possible	The AE *may be related* to trial treatment/intervention
	Definite	The AE *is clearly related* to trial treatment/intervention

6.2.5 Investigator Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

7.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

For the purposes of this trial the investigational products refer to both paricalcitol (or placebo) and pembrolizumab.

Paricalcitol will not be provided directly to the site as part of this trial but will be obtained directly from the treating investigator's designated pharmacy supply. Therefore the labeling, storage and, handling, of paricalcitol will follow the dispensing pharmacy's own standard operating procedures.

Pembrolizumab will be provided by Merck in temperature-controlled shipments directly to the site Pharmacy as summarized in Table 10 below. The details for the labeling, storage, handling, and disposal of pembrolizumab provided for use in this trial are therefore detailed below.

Table 10. Pembrolizumab Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100mg/4 mL	Solution for Injection
Pembrolizumab 50 mg	Lyophilized Powder for Injection

7.1 Packaging and Labeling Information

Pembrolizumab will be provided by Merck and will not be distinguished from the commercial product. Therefore, Investigator sites will be required to confirm prior to site initiation and pembrolizumab shipment, their specific plans for maintaining the trial supplied pembrolizumab separate from the pharmacy supply and how this will be distinguished for other pharmacy staff on site.

7.2 Storage and Handling Requirements

Pembrolizumab must be stored in a secure, limited-access location under the storage conditions specified on the label.

The investigator or authorized person at the trial site must maintain records of receipt and ongoing inventory of clinical trial supply of pembrolizumab at the site including the dispensing and administration of the pembrolizumab vials used for each patient.

Clinical trial supplies of pembrolizumab may not be used for any purpose other than that stated in the protocol.

7.3 Returns and Reconciliation

Upon completion or termination of the trial, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

8.0 STATISTICAL CONSIDERATIONS

8.1 Trial Design

This is a randomized, double blind, placebo-controlled clinical trial. Eligible patients will be randomized in a 1:1 ratio to one of two treatment arms: pembrolizumab + paricalcitol or pembrolizumab + placebo.

Trial treatment will be administered every three weeks per the schedule as described in 4.2. The percent of patients with disease progression at six months will be the primary endpoint. Secondary endpoints will include: incidence of toxicities, overall survival, mutational landscape, transcriptional programs and cellular (immunity) VDR targets in the immune microenvironment.

8.2 Sample Size Considerations

The primary endpoint is the percentage of patients progressing at 6 months. Based on a contemporary control of no maintenance after best response to prior chemotherapy[8], the control arm with pembrolizumab alone is expected to have only 8% of patients with no progression at 6 months. To be of clinical interest, at least 58% of patients must be progression-free at 6 months on the pembrolizumab plus paricalcitol arm. A sample size of 12 patients per arm will provide 90% statistical power to detect this difference assuming a one-sided alpha level of 0.05. A one-sided test was selected as we are only interested in the combination if it decreases the percentage of patients progressing at 6 months. This sample size estimate was obtained using binomial enumeration of all possible outcomes to compare two independent binomial proportions (Pearson's chi-squared test) using PASS 15.[18] A statistical concern is that the Pearson chi-squared test does not guarantee the alpha level. We confirmed that we have adequate statistical power using the Miettinen & Nurminen [19] exact likelihood score method (89% power) using Pass 15.

8.3 Statistical Analysis Plan

8.3.1 Analysis of the Conduct of the Trial

Enrollment, major protocol violations, and discontinuations for the trial will be summarized using a CONSORT diagram.

8.3.2 Analysis of Patient Characteristics

Demographic and baseline characteristics, such as age, race, BSA, duration of pancreatic cancer, site(s) of metastatic disease, prior cancer treatment, and baseline ECOG performance status will be summarized using means (± standard error) or medians (range) for continuous variables and proportions for categorical variables.

8.3.3 Analysis of Pembrolizumab and Paricalcitol Administration

Pembrolizumab + Paricalcitol (or placebo) dose administration will be listed and dose modifications will be flagged. Mean and standard deviations will be used to summarize the average dose received.

8.3.4 Analysis of Primary Endpoint - Disease progression at 6 months

All patients that receive trial treatment will be included in the analysis to determine the percentage of patients progressing by RECIST 1.1 criteria at 6 months when maintained on a combination regimen of paricalcitol plus pembrolizumab versus pembrolizumab alone. The 6-month time-point will be defined as 6 months (180 days) from the initial treatment (cycle 1/day 1). Statistical analysis will compare the proportion progression free at 6 months 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, we will analyze the data using Barnard's exact unconditional test of equality, as implemented in StatXact.[20]

8.3.5 Analysis of Secondary Endpoints

8.3.5.1 Analysis of Toxicities

All adverse events occurring on or after Cycle 1/day 1 will be summarized by body systems and per grade according to NCI-CTCAE Version 4. Additionally, all serious adverse events and events of clinical interest (ECI) as defined in section 6.2.3.2 will be listed separately and tabulated. All patients who receive any amount of trial treatment will be included in the analysis.

8.3.5.2 Comparison of Overall Survival

Duration of survival will be defined as the time from initial treatment (cycle1/day1) until death. Overall survival will be estimated 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.

8.3.5.3 Analysis of Tumor Mutational Landscape and Transcriptional Programs

The change in the biomarkers in the pre- versus 6-week biopsies will be estimated for each patient. A two-sample t test will be used to compare the continuous changes between the two treatment arms, assuming that the differences are normally distributed. If they are non-normal, a Wilcoxon Rank Sum Test will be used. A sensitivity analysis will use a linear regression model to compare the two treatment arms, adjusted for the baseline level.

8.3.5.3 Analysis of Cellular VDR targets with PD1 Blockade

Analysis of the specified cellular VDR targets will be assessed using the change in the pre- versus 9-week biopsies. A two-sample t test or Wilcoxon Rank Sum Test, and a sensitivity analysis using linear regression will be performed as outlined previously.

8.3.6 Analysis of Exploratory Endpoints

8.3.6.1 Comparison of RECIST 1.1 and iRECIST criteria

Given that pembrolizumab is an immunotherapy agent, disease progression will be defined by RECIST and iRECIST criteria (Appendix 5). Comparison of the proportion progression-free at 6 months using iRECIST will be performed using the same method as for the primary endpoint of RECIST 1.1. Additionally, McNemar's Test will be used to estimate the concordance between the two outcome measures.

8.3.6.2 Compliance to Use of a Phone-Based Application for Assessing Patient Defined Symptoms

The planned statistical analysis is included in Appendix 6.

8.3.6.3 Patient Personalized Clinical Benefit

The symptoms identified by each patient and the change across time will be evaluated graphically. The most severe ranking across the three items will be compared at baseline and the EOT visits to determine whether each patient's symptoms have improved across time. The relationship between progression at 6 months by RECIST 1.1 versus the change in rankings from baseline to EOT will be assessed using a Wilcoxon Rank Sum test.

8.3.6.4 Quantitative Textural Analysis (QTA)

The planned analysis for QTA is included in Appendix 7.

8.3.6.5 16S Gut Microbiome rRNA Analysis

The planned analysis for 16S Gut Microbiome is included in Appendix 8.

9.0 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Institutional Review Board/Ethics Committee Approval

Before trial initiation, this protocol and informed consent form will be submitted for review and approval to the IRBs charged with oversight for the clinical sites. In addition, any form of proposed advertising and advertising text for patient recruitment must be reviewed and approved by the Sponsor prior to submission to the IRB. The Investigator will forward to the Sponsor a copy of the IRB's approval of this protocol, any amendments, informed consent form, and any modifications to the informed consent, based on the FDA regulations set forth in 21 CRF 56 of the *Code of Federal Regulations.*

In addition, the Investigator will be responsible for forwarding to the Sponsor a description of the IRB members (including profession and affiliation) or a United States (US) Department of Health and Human Services (DHHS) General Assurance number and expiration date. If neither of these is available, the chairperson must submit a statement indicating that the members of the board responsible for the review meet the FDA and other appropriate regulatory requirements. In addition, the labeling for all approved trial medications should be submitted to the IRB for information purposes.

Clinical supplies will not be shipped to the clinical site until IRB approval is obtained for the protocol. Any existing amendments, informed consent, and photocopies of the approved documents must be received by the Sponsor prior to drug shipment.

9.2 Investigators protocol agreement

The Investigator must sign the Investigator's Protocol Agreement. The original must be kept on file by the Sponsor and the Investigator must retain a copy. The completed Investigator's Protocol Agreement signifies agreement to comply with all procedures outlined by this protocol by the Investigator. An Investigator's Protocol Agreement must be signed if and when a protocol amendment is issued.

9.3 Remaining Samples

Any samples remaining after the trial specified analyses is completed will be transferred to and stored at TGen if the patient consented for use of their remaining samples for future research purposes at TGen's discretion. This includes the original specimen collected from the patient [blood, tumor tissue, or fecal swabs]) as well as derivatives created from the original specimen (DNA, RNA, blocks or slides). Documentation of the transfer of all specimens will be recorded on the Sample Destruction/Return Request Form- refer to Trial Laboratory Manual.

If a patient has not consented for their remaining samples to be used for future research purposes, remaining samples and derivatives will be destroyed and documented on the Sample Destruction/Return Request Form- refer to Trial Laboratory Manual.

9.4 Confidentiality

The Investigator and any other personnel involved in this trial shall not disclose, or use for any purposes (other than for the performance of this trial any data, records, or other information (hereinafter collectively “information”) disclosed to the Investigator or other trial personnel. Such information shall remain the confidential and proprietary property of the TGen and SU2C, and shall be disclosed only to the Investigator or other designated trial personnel.

Patient confidentiality will be ensured by using assigned site-specific Screening and Randomization numbers (refer to Section 6.1) throughout the trial.

9.5 Publication

As a general rule, no trial results should be published without prior approval of the Sponsor. The rights of the investigator and the Sponsor with regard to publication of the results of this trial are described in the investigator contract.

9.6 Compliance with Financial Disclosure Requirements

All Investigators will be required to submit written financial disclosures to the Sponsor prior to participating in this clinical trial and any changes in disclosures during the course of the trial as per 21 CFR part 54.

9.7 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are patient to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

9.8 Quality Management System

9.8.1 Data Monitoring Plan

Data monitoring procedures will be carried out by [redacted] for all participating sites, and will be performed on a regular basis to comply with Good Clinical Practice guidelines.

Review of the case report forms, cross-reference with source documents (including radiology review), review of trial related regulatory documents and logs (e.g. enrollment, trial site staff), would be monitored on an ongoing basis during monitoring sessions. The monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

At the conclusion of the monitoring visit, the monitor will meet with the site staff to discuss and request specific corrections to the case report forms, and/or request clarification, and/or additional source documentation. The site Clinical Research Coordinator responsible for the trial will be provided with a copy of the written monitoring notes for resolution of the findings.

The monitor will complete a written monitoring report and provide to the Sponsor and [redacted]. The report will include a summary of what the site monitor reviewed and the site monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to ensure compliance. The site Principal Investigator will be expected to submit any Corrective Action Plans, in writing, to the Sponsor. A copy of the monitoring forms, final monitoring reports, and Corrective Action Plan will be kept in the site monitor's trial file follow up at the next monitoring session.

For drug accountability an independent unblinded monitor will be assigned to monitor the Pharmacy file containing all information on preparation and dispensing of trial medication. Monitoring will occur on an ongoing basis to determine that the medication is being prepared and dispensed in accordance with the protocol design.

A *blinded* report documenting the visit and any findings will be written and provided to the Sponsor.

9.8.2 Data Safety Monitoring

A trial specific Data Safety Monitoring Plan (DSMP) will be implemented for this trial. The Trial Principal Investigators and an independent Medical Monitor will review the safety and progress of the trial on a regular interval and provide documentation of their review and any recommendations that will then be shared with the trial team.

The trial progress reports will be prepared by [redacted] in aggregate and provide blinded trial data pertaining to: patient recruitment, retention/attrition, data collection status, and adverse events. The progress reports will not provide data on the primary or secondary endpoints of the trial as there is no interim analysis planned for this trial.

In additional a separate unblinded trial report will be generated by the unblinded trial monitor and provided only to the independent medical monitor to review.

An annual trial progress report will be generated by [redacted] and sent to the Independent Monitor, Consulting Investigator, funding organization (SU2C), and each site Principal Investigator for submission to their governing IRB.

9.9 Data Management

9.9.1 Case Report Forms

All the clinical data will be captured by the site on electronic case report forms (eCRFs). The eCRFs will be used for all consented patients. The investigator and trained trial personnel will enter and edit the data via a secure network, with secure identification and

password requirement. A complete electronic audit trial will be maintained. The investigator will be required to provide approval of all data to confirm accuracy. Copies of the eCRFs will be provided to the investigator at the conclusion of the trial.

9.9.2 Source Documents

Source documents serve as the evidence of the existence of the patient and the data collected for this trial. Source documents will be the responsibility of the Investigator and will be filed at the site and available as needed by the Sponsor, [redacted], or assigned clinical monitor.

Data captured on the eCRF is to be transcribed from source document and must be consistent with any discrepancies explained and documented.

REFERENCES

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APPENDICES

Appendix 1 - Pembolizumab (Keytruda®) Package Insert

The pembrolizumab (Keytruda®) package insert can be accessed at the following link:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125514s012lbl.pdf

Appendix 2 - Paricalcitol (Zemplar®) Package Insert

The paricalcitol (Zemplar®) injection package insert can be accessed at the following link:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/20819se5-014_zemplar_lbl.pdf

Appendix 3 - NCI CTCAE version 4.0

The CTCAE Version 4.0 can be accessed and downloaded from the CTEP website at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Appendix 4 - ECOG Performance Status

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

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Appendix 5 - Protocol Criteria for Measurement of Trial Endpoint RECIST 1.1 and iRECIST

1. Definitions

1.1. Evaluable for adverse events. All patients will be evaluable for adverse event evaluation from the time of their first treatment.

1.2. Evaluable for response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee as well as the modified iRECIST guidelines. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria.

See section 6.1.2.6 for criteria for continuing treatment past RECIST 1.1 disease progression.

2. RECIST 1.1 Response and Evaluation Endpoints

2.1. Measurable Disease. Measurable tumour lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest x-ray and as ≥10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

2.2. Non-measurable Disease. All other lesions (or sites of disease), including small lesions are considered non- measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

2.3. Target Lesions. When more than one measurable tumour lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be 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. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed (see 8.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

2.4. Non-target Lesions. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

2.5. Response.

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of target and non-target lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases[4] before CR can be accepted. Confirmation of response is only required in non-randomised studies.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is only required in non-randomised studies.

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

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new

lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table S1: Integration of target, non-target and new lesions into response assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumour markers, tumour nodes <10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documented at least once ≥4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumour markers, tumour nodes <10 mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes*	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

*Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments – see table 2.

3. iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those

of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumour burden, or the appearance of new lesions, does not reflect true tumour progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

3.1. Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumour burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumour burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
  - Continued unequivocal progression in non-target disease with an increase in tumour burden
  - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in table 2, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

3.2. New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Table S2: Time-point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: o further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD SOM ≥5 mm and / or o NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD ≥5 mm and / or o previously identified NT lesion iUPD (need not be unequivocal) and /or o size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on o increase in size or number of new lesions previously identified
* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.				

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

Table S3:iRECIST Best Overall Response (iBOR)

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

1. Table assumes a randomised study where confirmation of CR or PR is not required.
2. NE = not evaluable that cycle.
3. Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
4. For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

5. Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

6. Methods of Measurement

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. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

6.1. Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

6.2. Chest X-ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

6.3. CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case.[4] For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

6.4. Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

6.5. Endoscopy, Laparoscopy. The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

6.6. Tumour Markers. Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

6.7. Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

Appendix 6 - Patient Personalized Clinical Benefit APP

BACKGROUND AND SIGNIFICANCE
Standard paper based questionnaires are typically filled out only during office visits and the questions are predefined by the study or clinic. This reduces the number of data points that are collected during a study and relies heavily on a patient's ability to recall specifics from days to weeks prior to the questions being asked. In addition, many of the questions may be irrelevant to that specific patient. Paper based questionnaires also require a patient or healthcare provider to fill out the forms with identifiable information so the data can be correlated to that patient. The healthcare provider is then required to enter the data into an electronic database after completion, which provides for more chance of error.

The Patient Personalized Clinical Benefit (PPCB) App not only simplifies data entry, by alleviating the need to enter a patient's name or other info, but also limits questions to the three main symptoms bothering each individual patient. In addition, data is automatically uploaded to an electronic database, removing the need for a healthcare provider to input data. This can significantly reduce costs associated with collecting and analyzing data, as well as decrease the chance for error. These questions will be asked once a week (patients will have a reminder setup via the app as to increase adherence) for the entire study duration or until the patient elects to stop taking the questionnaire.

INSTRUCTIONS
The patient will be provided the following instructions for downloading the app.

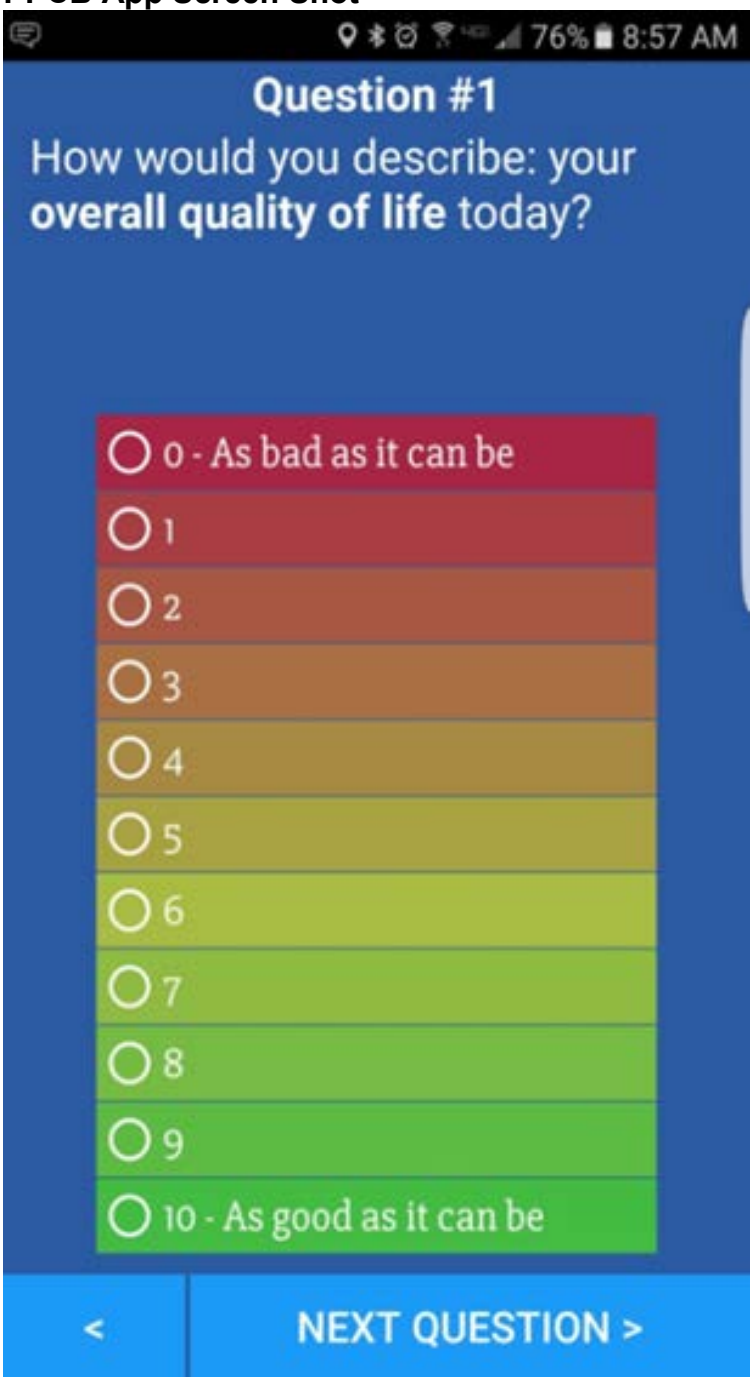
Patient Instructions for Downloading the PPCB Phone App

iPhone Users
1. Go to the App Store on your iPhone or iPad and search for [insert APP name]:
2. Tap the app.
3. Tap GET on the right side of the screen, then tap Install.
4. If asked, enter your password. You can also use Touch ID for app purchases.
5. The app then downloads to your device.
6. Find the app once it has downloaded and tap on the app icon to open the app
7. Enter the assigned UserID that your study team has provided to you.
8. Then tap START QUESTIONNAIRE

Android Users
1. Go to the Play Store on your Android device and search for [insert APP name]:
2. Tap the app.
3. Tap INSTALL, read access needs and tap ACCEPT.
4. The app then downloads to your device.
5. Click OPEN, or find the app on your device and tap on the app icon to open the app
6. Enter the assigned UserID that your study team has provided to you.
7. Then tap START QUESTIONNAIRE

QUESTIONNAIRE
The 3-item phone-based app uses a Likert scale for the patient to rate general symptoms The app will be accessed and completed weekly to assess self-defined symptoms in cancer patients. In the event that a patient does not have the type of mobile device required to access the APP, the patient will be provided the paper version of the questionnaire (printed in color as per screen shots) to complete. Examples of both the PCBB APP- screen shot and the hard copy PPCB Questionnaire are included below.

PPCB App Screen Shot



Personalized Patient Clinical Benefit Questionnaire- Hard Copy
Instructions for Site: Complete the three patient reported symptoms in provided form and print in color for the patient to complete.

Pt Initials _____ **Paper Based PPCB Form** Week # _____
Date:

How would you describe your …over the past week?	How would you describe your …over the past week?	How would you describe your …over the past week?
0 - As bad as it can be	0 - As bad as it can be	0 - As bad as it can be
1	1	1
2	2	2
3	3	3
4	4	4
5	5	5
6	6	6
7	7	7
8	8	8
9	9	9
10 - As good as it can be	10 - As good as it can be	10 - As good as it can be

COMPLIANCE
The compliance rate will be estimated as the number of days in which a report was completed, out of the total number of days in which a report was expected. Usability metrics will include the average duration for each daily assessment. These data may be compared to other lab values or treatment information collected while on study. The results of this questionnaire will not affect the patient's current treatment.

SECURITY
Data security and integrity is maintained through multi-layered encryption of the communication pathways and tokens using leading industry standards. Communication between the mobile device and the backend service utilizes a Restful interface using HTTPS encryption and authentication tokens. Additionally, no communication to the backend can be achieved without the clientID, which is unique to each user. Data collected from the application is stored within a secured database on the backend. No encryption is performed on data at rest currently, however, this can be enabled as needed. Please note, that even though multiple protocols are being employed to secure the communication pathways, no

personal user information is stored in the database. There is no name, email or any other information that is stored in the database that could be used to identify the individual utilizing the application.

ACCESS AND SUPPORT

The link to the app in the Android "Play Store" or Apple "App Store" can be provided via email or directly searched for using the app name. Initial usability support would be provided by the app support staff. An email distribution list will be set up for any support issues. Any technical issues would be emailed to that distribution list with an expected turnaround time of <24 hrs.

When the app is run on either Android or iOS platforms, the only identifiable information that is sent and used to identify the end user is the initial “ID” that is entered to start the app. The user’s IP address, phone model, or phone number are not collected by the app.

DATA ANALYSIS

Frequency distributions and descriptive statistics will be computed on all variables. Any continuous variable with a markedly non-normal distribution will be transformed to more closely approximate a normal distribution.

The compliance rate to weekly reporting will be computed as the number of assessments completed divided by the number of expected assessments. Number of questions completed, duration of each reporting session, and time of day of each reporting session will be analyzed using descriptive statistics. Statistical analysis will employ both daily scores for individual items as well as summary measures (e.g., mean scores computed per item per patient over each 8 week period in which at least 4 surveys are completed). Patient weekly and monthly scores for individual items will be graphically displayed longitudinally using stream plots and mean plots. Mean scores with standard deviations will be computed at each time point (weekly as well as monthly). Mean scores for each individual item over time (weekly and monthly) will be modeled using a generalized linear mixed model with a covariate for time (weeks or months since registration) and a random intercept term per patient. Correlations between items will be assessed using Pearson correlations at fixed time points. The threshold for feasibility is estimated at 70%. Finally, coordinator feedback will be collected via interviews and qualitatively analyzed.

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Appendix 7 - Quantitative Textural Analysis

A Quantitative Radiomics Approach

Recent data acquisition and analytical advances have expanded the traditional role of medical imaging beyond subjective/qualitative arenas. Radiomics refers to the comprehensive analyses of tumor phenotypes based on quantifiable image features (1). Quantitative CT-based tumor and tissue texture analysis (QTA) provides comprehensive, 3-dimensional and temporal analyses of tumor heterogeneity (1). This approach represents an emerging technology that can conceivably monitor tumor development, progression, immune cell activity and response to treatment. Tumor heterogeneity on cross-sectional imaging is manifested by histopathological differences in cell density, necrosis, and hemorrhage (2,3). Image texture analyses assess tumor heterogeneity in accordance to the distribution and relationship of pixel or voxel-gray levels in the image (4). Findings from several studies have suggested that imaging texture reflects tumor-host interactive status within the tumor microenvironment (5,6). CT tumor texture analysis has shown promise in predicting pathologic features, overall survival, and response to therapy in NSCLC (1,7-9), colorectal cancers (3,5), esophageal cancer (10), head and neck cancers (11) and metastatic renal cell cancer (13). For, example, Aerts have examined 440 quantitative features that define tumor image intensity, shape and texture extracted from CT scans of 1,019 patients with NSCLC or head and neck cancers and has shown an association between tumor patterns and outcomes through unsupervised clustering analyses of Radiomic expression patterns and demonstrated associations with primary tumor stage (T stage), overall stage, and histology in 422 Stage I/II NSCLC patients (1). Using a prognostic signature that comprised the top features of tumor image intensity, shape, texture, and multiscale wavelet findings, QTA were better than tumor volume and TNM staging in survival prediction by Kaplan Meier analyses. Features describing heterogeneity in the primary tumor were associated with worse survival, whereas patients with more compact/spherical tumors had better survival probability. In separate studies, we have shown prognostic QTA signature that differentiated K-ras mutant NSCLC tumors from pan-wild type NSCLCs (9). We have recently demonstrated that using QTA, a specific imaging QTA signature of kurtosis and entropy is associated with interchromosomal aberrations in mPDA as determined by NGS and that these imaging features are associated with PFS and OS (12). Furthermore, preliminary work from our core lab by QTA analysis from the standard of care baseline CT scans from 28 subjects with metastatic solid tumors treated with PD-1 therapy demonstrated a distinct texture signature that distinguished which tumors were going to respond to PD-1 therapy. Finally, an analysis of the texture of tissue and tumors from subjects treated with paracalcitol showed a distinct texture pattern in the liver and pancreas of mPDA subjects on both the pre treatment and early post treatment scans leading to texture differences that may be distinctive based on vitamin D levels measured in patient serum. These encouraging results provide the rationale for using QTA to explore differences in tumor and tissue texture between the two arms of this study using baseline to and post treatment scans. Such information would be informative and provide a basis for establishing a complementary diagnostic biomarker that could 1) predict disease stability in the maintenance environment 2) provide an imaging signature that is associated with immune infiltrative activity, 3) allow a non invasive method for detecting tumor and tissue texture changes related to vitamin D exposure and 4) identify other correlations of imaging to tumor biology, response, laboratory assessments.

In order to perform Quantitative Textural Analysis (QTA) the following steps are required- De-identified dicomm encoded CT scans will be sent to [redacted] for analysis. Images will be reviewed to ensure appropriate series, images and anatomic coverage is available and that all PHI has been removed. Only query free studies will be forwarded for analysis. Query-free scans will be loaded onto [redacted] QTA analysis platform for textural analysis. Standard reconstructed algorithm generated image series will be evaluated for presence or absence of evaluable tumor, i.e. tumor ≥10mm containing clearly defined tumor margins on at least two consecutive slices. Polygon ROI tools will be selected and an ROI will be posited around the mid-slice section of the tumor lesion or tissue of interest such as the liver, pancreas, lung, and muscle.

QTA will be applied to regions of interest which uses an image filtration-histogram technique whereby the filtration technique applies a Laplacian of Gaussian band-pass filter enhanced algorithm leading to extracted features of different sizes based on the spatial scale filter (SSF) value varying from fine-texture (SSF2, 2 mm in radius), medium texture (SSF3, 3 mm in radius), and coarse-texture (SSF4, 4 mm in radius). This is followed by quantification of tumor texture from the filtered histogram based texture maps producing the following quantitative parameters

a) Mean (a measure of average brightness within the ROI)
b) Kurtosis (K, a measure of peakedness and tailedness)
c) Skewness (S, a measure of asymmetry of the histogram)
d) Standard-deviation (SD, a measure of variation or dispersion that exists from the mean)
e) Mean Positive Pixel (MPP, a measure of pixels that contain non-fat/air densities)
f) Entropy (a measure of orderliness based upon co-occurrence matrix principles)

A Sample Output from QTA Analysis of Lung Metastasis Lesions is shown below

The resulting Signature Readout file will be forwarded to IE's data management site and entered into a secure database for marker analysis. Additional IE published Radiomics features may be extracted on the imaging slice (e.g. DVP signs, feature convergence, AB index, etc) as appropriate for tumor size, location and pattern features. Clinical team will supply IE with appropriate data to perform bioinformatics linkage with clinical and genomic data for surrogate marker testing. IE Data Management Team will perform full QC on entered data and manage query resolution process. The expected statistical analysis of the data will involve a non-parametric Mann Whitney test used to assess the ability of the QTA, clinical, and patient characteristics to differentiate between early disease relapses, immunoinfiltration, vitamin D levels, molecular characterization and relapse risk. We anticipate using a recursive-type decision tree (or similar) approach to determine whether the differentiation between these outcomes could be improved by sequential application of QTA parameters. The QTA parameter that most accurately identifies the selected dependent variable will be used in the entire patient cohort as the first node, thereby generating two branches. The abilities of additional QTA parameters to identify outcomes will then be separately tested for each branch, adding further nodes to the tree. The diagnostic threshold values for the QTA parameters used at each node will be optimized using Receiver Operator Characteristic (ROC) analysis to maximize diagnostic accuracy. QTA parameters will be applied in order of overall accuracy for determination between early disease relapses, immunoinfiltration, molecular characterization and relapse risk. If two modalities have the same accuracy, the modality with the highest sensitivity will be applied first. No further node will be added to a branch if the misclassification rate in that branch is less than 15%. The final decision tree will be applied to the whole cohort to determine the

overall sensitivity, specificity, and accuracy. Since this is an exploratory study, General mixed linear modeling and/or computer simulation analysis will be sought to link early disease relapses, immunoinfiltration, vitamin D levels, molecular characterization and relapse risk with QTA results. In our prior work a Monte Carlo analysis using 1,000 iterations of the decision tree was used to assess the impact of uncertainty in the sensitivity and specificity for each QTA parameter (expressed as their 95% confidence intervals [CI]) on the overall diagnostic performance of the decision tree. For early disease relapses and relapse risk, univariate Kaplan-Meier survival (KM) analysis will assess the relationship between the above. An iterative procedure will also be applied to identify the optimal cut off for each marker that provides the best separation of the population into 'good' and 'poor' prognosis groups (indicated by the best p-value from log-rank test). Due to small numbers, we might need to censor reporting results for significant features yielding less than 10 patients per group for comparison to avoid overstating significant results. Additionally, we will focus on analysis for SSF0 through 4, because we believe that there will be a small numbers of cases having QTA measures for SSF 5 mm in radius and above in cases of tumors that are approximately 1 cm. Multivariate Cox regression will be used to determine which significant univariate parameters along with their interactions are independent predictors of recurrence, metastasis and relapse, along with the hazard ratio (HR) and the CI. A two-tailed P value of less than 0.05 will be considered to indicate a significant difference.

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Appendix 8 - 16S Gut Microbiome rRNA Analysis

The bacterial communities living in and on our bodies interact with our epithelial cells and can influence adaptive immunity, metabolic functions, and inflammation at a local and systemic level. The gut microbiota has been particularly well-studied and regulates the barrier functions of the gut epithelium, prevents pathogen or pathobiont overgrowth, facilitates metabolism of dietary fibers, and regulates metabolism. The gut microbiota may also influence the initiation, progression, and treatment of cancer. Monitoring the microbiota in patients may enhance our ability to predict the likelihood of a positive patient response to therapy as well as indicators of adverse treatment effects and sensitive metrics of general patient health. Given the possibility of altering the microbiome of a patient, future research is likely to include manipulating microbiotic communities to maximize the effectiveness of other therapies.

Fecal samples are relatively easy to collect and non-invasive. They provide an indication of the gut microbiome which may be an indicator of general health, impact drug availability, and indicate the presence of communities associated with inflammation, digestive inefficiencies, and pathogens. Monitoring the gut microbiome may allow us to predict the risk of possible side effects of pembrolizumab (colitis and decreased appetite) and paricalcitol (decreased appetite).

Sample processing. Quantitative TaqMan PCR assay will be used that targets Variable Regions 3 and 4 of the 16S rRNA sequence. This assay will provide a rough estimation of the overall bacterial load per sample. It is important to recognize that different species have different copy numbers of the rrs gene that encodes the 16S rRNA, however this assay will still provide a rough estimation of bacterial load for inter-sample comparisons. For whole community surveys, 515F/806R 16S rRNA primers will be used to amplify Variable Regions 4 and 5. This primer pair achieves nearly universal coverage across bacteria and archaea7. These amplicons will be sequenced using the Illumina MiSeq, NextSeq, or HiSeq next generation sequencing platforms. For the purposes of this work, the throughput, cost, and depth of coverage provided by the Illumina MiSeq currently make this sequencing platform better suited than other technologies. Moreover, the read lengths of up ~300bp allows approximately genus, and sometimes even species-level discrimination of taxa.

Sequence Analyses. The microbial communities will be compared using phylogenetic beta diversity metrics based on 16S rRNA reads. The 515F/806R 16S rRNA primers will amplify a 292bp region containing variable regions 4 and 5. Sequences will be processed using the open source Quantitative Insights Into Microbial Ecology 2 (QIIME2) software package to demultiplex, quality filter, and cluster sequences into operational taxonomic units (OTUs). Taxonomy will be assigned to OTUs by classification against the Greengenes database using the RDP Classifier (unless a better approach is available at the time of analysis). These data will be used to understand the differences in taxonomic composition.

Measuring diversity within and between samples. Beta diversity is a measure of the relative similarity of samples (i.e., the between-sample diversity), while alpha diversity is a measure of the diversity within a sample. Thus beta diversity will provide an estimate on how different

microbial communities are, while alpha diversity provides information on the richness or evenness of a single community. Both alpha and beta diversity measures can be qualitative, considering only presence/absence of taxonomic groups in a community, or quantitative, considering the abundance of taxonomic groups. Qualitative measurement of beta diversity, for example, may be simply the fraction of shared taxa, but differences may be overlooked if the same set of taxa are present but in different abundances. However, quantitative diversity metrics may be misleading as community profiling based on amplicon sequence data is not necessarily quantitatively accurate. Additionally, diversity metrics are either taxon-based or phylogenetic-based. Taxon-based diversity considers all taxa to be equally related, ignoring the likelihood that closely related taxa are phenotypically similar. Phylogenetic diversity accounts for the evolutionary relationships between taxa, and has been shown to improve the resolution of differences between microbial communities.

Appendix 9 - Fecal Swab Sample Collection Instructions (To be included in Fecal Swab Collection kit)

You have been provided a Fecal Swab Collection kit.
The collection kit includes the following items:

1. Disposable Gloves
2. A stool collection bowl (toilet hat), as pictured below.

3. A bio-specimen bag

4. A pre-labeled CultureSwab tube, as pictured below. The tube has already been labeled with your assigned subject ID. **Please DO NOT write your name on the label.**

In order to ensure the best results, please follow the instructions below.

You will need to collect **two different** stool samples during each treatment cycle:

1. The **first** stool sample is to be collected up to 72 hours **before** your study treatment on day 1 of each treatment cycle.

2. The **second** stool sample is to be collected from your first or second bowel movement within 24-72 hours **after** receiving your study treatment on day 1 of each treatment cycle.

A **final** stool sample will be collected approximately 30 days after your last dose of study treatment.

To Collect a Stool Specimen:

1. Raise the toilet seat and place the stool collection container (toilet hat) on the back of toilet bowl. Place the toilet seat down.
2. Pass stool into the stool collection container. Do not urinate into the container.
3. Put the provided disposable gloves on before collecting the stool sample. Use the provided CultureSwab to remove a portion of the stool, as follows:
    a. Remove the CultureSwab tube from the plastic bag.
    b. Remove the sterile swab from the tube while handling only the cap and not touching the swab or shaft.
    c. Wipe the sterile swab across the stool to collect a pea size amount of stool on the tip of the swab. Do not touch the swab on the sides of the collection bowl or on any other surface.
    d. Carefully re-insert the swab with the fecal sample back into the CultureSwab tube and close with the cap.
4. Write the date and time of collection on the label that is affixed to the tube. DO NOT write your name on the tube.
5. Dump the remaining stool in the toilet and flush. The stool collection bowl and the disposable gloves may be disposed in the regular trash. Wash your hands thoroughly with soap and water.
6. Store the CultureSwab tube in the bio-specimen bag in the FREEZER.
7. Return the sample to the study team within 24-72 hours of collection. This should correspond with your next study visit. Sample can be transported in the car without need for ice packs, if the car is air-conditioned. If the car is not air-conditioned please transport the specimen on ice to keep cool.

IMPORTANT: If for some reason you cannot make your scheduled appointment within 72 hours of the fecal collection, please contact your study site at (site to specify contact tel number) to make arrangements for return of the sample.

If you have any questions please call (site to specify contact tel number)

Thank you for your participation!