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Official Study Title: **A randomized phase II study of pembrolizumab with or without defactinib, a focal adhesion kinase inhibitor following chemotherapy as a neoadjuvant and adjuvant treatment for resectable pancreatic ductal adenocarcinoma (PDAC)**

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Version 3.0, 5/31/2019
Version 4.0, 10/17/2019
Version 5.0, 02/27/2020
Version 6.0, 06/17/2020
Version 7.0, 09/01/2020
Version 8.0, 10/06/2020
Version 9.0, 01/27/2021
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Version 11.0, 10/13/2021
Version 12.0, 04/04/2022
Version 13.0, 05/16/2023
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Table of Contents

1.0 TRIAL SUMMARY

Abbreviated Title	A Randomized Phase II Study of Pembrolizumab With or Without Defactinib, a Focal Adhesion Kinase Inhibitor Following Chemotherapy as a Neoadjuvant and Adjuvant Treatment for Resectable Pancreatic Ductal Adenocarcinoma
Trial Phase	Phase II
Clinical Indication	High-Risk Resectable Pancreatic Ductal Adenocarcinoma
Trial Type	Interventional
Type of control	Historical Control
Route of administration	Intravenous (Pembrolizumab) and Oral (Defactinib)
Trial Blinding	Unblinded Open-label
Treatment Groups	**Arm A**: Two cycles of standard of care (SOC) neoadjuvant chemotherapy with gemcitabine and nab-paclitaxel. Followed by two cycles pembrolizumab (MK-3475) 200 mg IV every 3 weeks (Q3W) and focal adhesion kinase (FAK) inhibitor, defactinib, 400 mg twice daily (BID) throughout each immunotherapy (pembrolizumab) cycle, extending up until 2 days prior to surgery (last dose 48 hours prior to surgery). Followed by SOC surgery and adjuvant chemotherapy. Followed by eight cycles pembrolizumab (MK-3475) 200 mg IV every 3 weeks and defactinib, 400 mg twice daily (BID) throughout each immunotherapy (pembrolizumab) cycle. OR **Arm B**: Two cycles of standard of care (SOC) neoadjuvant chemotherapy with gemcitabine and nab-paclitaxel. Followed by two cycles pembrolizumab (MK-3475) 200 mg IV every 3 weeks (Q3W) only. Followed by SOC surgery and adjuvant chemotherapy. Followed by eight cycles pembrolizumab (MK-3475) 200 mg IV every 3 weeks alone.
Number of trial participants	36 subjects (18 per arm)
Estimated enrollment period	12-24 months
Estimated duration of trial	The trial will require approximately 36-48 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol specified contact. Eligible subjects will be randomized to either pembrolizumab and defactinib (Arm A) with SOC neoadjuvant chemotherapy, surgical resection and adjuvant chemotherapy or pembrolizumab only (Arm B) with SOC neoadjuvant chemotherapy, surgical resection and adjuvant chemotherapy. After enrollment, all subjects will receive two cycles (~2 months) of standard neoadjuvant chemotherapy with gemcitabine and nab-paclitaxel through local oncologist. Then subjects will undergo endoscopic ultrasound (EUS) with biopsy followed by on-study treatment with two cycles (~2 months) pembrolizumab and oral defactinib (Arm A) or two cycles of pembrolizumab alone (Arm B) until surgery. All

	subjects will undergo surgical evaluation and in the absence of systemic disease, pancreatectomy. Following surgery, all subjects will receive standard of care adjuvant chemotherapy at discretion of treating oncologist (~6 months; surgery followed by SOC adjuvant therapy together). Surgical resection and adjuvant chemotherapy will not be a part of the study protocol, as they are SOC therapies for resectable PDAC. After completion of SOC adjuvant chemotherapy, subjects will be treated on-study with immunotherapy and FAK inhibition or immunotherapy alone. Subjects in Arm A will be placed on maintenance pembrolizumab and oral defactinib twice daily every 3 weeks and subjects in Arm B will receive maintenance pembrolizumab only every 3 weeks for a total of 24 weeks (~6 months). After the end of treatment, which is the final administration of any study drug, pembrolizumab or defactinib, each subject will be followed for 30 days for AE monitoring, culminating with a post treatment visit 30 days after final administration. Serious adverse events (SAEs) will be collected for 90 days after the end of treatment or for 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects will have post-treatment follow-up for disease status, adverse events and survival, until initiating a non-study cancer treatment, experiencing disease recurrence/progression, death, withdrawing consent, or becoming lost to follow-up per protocol.
Estimated average length of treatment per patient	16 months (including SOC chemotherapies and surgery)

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multi-center, two-arm, randomized, open-label, phase II clinical trial of a combination of neoadjuvant and adjuvant immunotherapy with pembrolizumab (MK-3475) and defactinib, a focal adhesion kinase inhibitor (FAK), following neoadjuvant standard of care (SOC) chemotherapy in subjects with high-risk resectable pancreatic ductal adenocarcinoma (PDAC).

This immunotherapy and FAK inhibitor trial will primarily evaluate if reprograming the tumor microenvironment by targeting FAK following chemotherapy can potentiate anti-programmed death-1 (PD-1) antibody by modulating myeloid (tumor associated macrophages [TAM] & myeloid–derived suppressor cells [MDSC]) inflamed stroma and lead to an increase in CD8 T cell infiltration in PDAC. We will also assess for improvement of pathologic complete response. This trial will also assess for safety, disease free survival (DFS) and overall survival (OS) of immunotherapy and FAK inhibition combinatorial therapy and peritumoral immunologic implications through exploratory biologic endpoints.

Subjects who have newly diagnosed and surgically resectable PDAC, who will undergo a potentially curative resection and have an elevated CA 19-9 >200, are eligible to participate in this study. Criteria for determining resectability will strictly follow consensus guidelines issued by the Americas Hepatopancreatobiliary Association (AHPBA)/Society for Surgery of the Alimentary Tract (SSAT)/Society of Surgical Oncology (SSO)/National Comprehensive Cancer Network (NCCN). Eligible subjects will be randomized, stratified by age (≥65, <65), in a 1:1 fashion into either Arm A (pembrolizumab [MK-3475] 200 mg IV q3w following SOC neoadjuvant chemotherapy and eight cycles pembrolizumab 200 mg IV every 3 following SOC surgical resection and adjuvant chemotherapy with the addition of FAK inhibitor, defactinib, 400 mg twice daily [BID] throughout each immunotherapy [pembrolizumab] cycle in both the neoadjuvant and adjuvant settings) or Arm B (pembrolizumab 200 mg IV q3w following SOC neoadjuvant chemotherapy and eight cycles pembrolizumab 200 mg IV every 3 following SOC surgical resection and SOC adjuvant chemotherapy, only). 36 subjects (18 per arm) will be enrolled and randomized in the study. The study will consist of seven parts.

In part one, all subjects will undergo consent and pre-study screening procedures for eligibility in preparation for neoadjuvant therapy. An EUS-guided core biopsy for diagnostic, research purposes and organoid tissue culture will be obtained prior to the initiation of neoadjuvant chemotherapy, if a diagnostic biopsy has not been done prior to the enrollment. In part two, all subjects will receive two cycles of standard chemotherapy in the neoadjuvant setting with gemcitabine and nab-paclitaxel. Of note, patients can be enrolled and randomized up to 1 week after initiating chemotherapy as long as all screening procedures and eligibility criteria have been completed prior to starting treatment. In the SOC chemotherapy phase subjects will be able to receive chemotherapy through a local oncologist. A second EUS-guided core biopsy for research purposes and organoid tumor tissue production, is required prior to the administration of neoadjuvant immunotherapy and FAK inhibition in part three of the study. In part three, subjects will receive two cycles of pembrolizumab 200mg q3weeks and twice daily oral defactinib 400 mg for 3 weeks (Arm A) or pembrolizumab 200mg q3weeks alone (Arm B). Defactinib will be continued until 2 days before surgery (last dose 48 hours prior to surgery). In part four, all subjects will undergo surgical evaluation and in the absence of systemic disease, pancreatectomy. Standard surgical procedure will be determined by the operating surgeon. Pancreatectomy is considered standard of care for pancreatic cancer and therefore will not be a part of the study protocol. The surgery will be scheduled between day 10 to day 25 from the administration of cycle two of pembrolizumab. If the subject is found to have unresectable disease intraoperatively, core biopsies will be performed intraoperatively. Subjects who are found to have unresectable or metastatic disease intraoperatively will be excluded from continuing in the study. Following the surgery, subjects with R0 or R1 resection will continue to the next phase of the study. In part five, following surgery, all subjects will receive standard of care adjuvant chemotherapy at discretion of treating oncologist. Part four and five will not be a part of the study protocol, as pancreatectomy and adjuvant chemotherapy are standard therapies for resectable PDAC. In part six, subjects with no evidence of disease recurrence and who continue meet inclusion criteria after completion of SOC adjuvant chemotherapy will be treated on study with maintenance immunotherapy and FAK inhibition or immunotherapy alone.

Subjects will receive maintenance immunotherapy with pembrolizumab 200 mg q3weeks and defactinib 400 mg BID for 3 weeks (Arm A) or pembrolizumab 200 mg q3w (Arm B) alone, as one cycle for a total of 8 cycles/24 weeks. Part seven of the study will be the follow up phase.

Adverse events (AE) will be monitored from the first administration of any study drug (ie pembrolizumab or defactinib) and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Each subject will be followed for 30 days after last dose of any study drug administration for AE monitoring. Serious adverse events (SAEs) will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier.

This study will be conducted in conformance with Good Clinical Practices (GCP). Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - **Section 6.0**. Details of each procedure are provided in **Section 7.0** – Trial Procedures.

Details of each phase of the study are outlined below.

2.1.1 Part 1: Pre-study Consent, Screening, and Randomization

The pre-surgical staging of disease will be performed by the Department of Surgery. Pretreatment biopsy is necessary for enrollment in this study. If the subject is referred to the study without a diagnostic biopsy, a diagnostic core biopsy will be performed. If a diagnostic biopsy has already been done prior to enrollment, we will request the archived tissue in lieu of performing a core biopsy. If a subject is found to be eligible for this study based on pre-surgical staging and pre-study screening, they will be consented for this study and then randomized to either treatment Arm A or treatment Arm B.

2.1.2 Part 2: Neoadjuvant Chemotherapy

Following clinical trial enrollment, subjects will begin neoadjuvant therapy with planned two, 28-day cycles of gemcitabine and nab-paclitaxel. Gemcitabine and nab-paclitaxel are standard therapies for pancreatic cancer. As a standard of care therapy, subjects will be allowed to receive this portion of therapy with local oncologist. Adverse events monitoring will begin after the completion of standard of care therapy and with the first administration of study drugs pembrolizumab +/- defactinib.

2.1.3 Part 3: Neoadjuvant Pembrolizumab and Defactinib

A computed tomography (CT) scan will occur every 2 months or at the completion of cycle 2 of neoadjuvant chemotherapy. At the completion of two cycles of gemcitabine and nab-paclitaxel, subjects will undergo a second EUS-guided core biopsy for research purposes and organoid tissue procurement.

All subjects who have completed neoadjuvant chemotherapy will undergo re-screening in order to receive combination immunotherapy and FAK inhibition. Re-screening criteria can be found in **Section 5.1.3** and in **Section 5.1.4**.

Following second EUS-guided core biopsy and pre-immunotherapy imaging, subjects assigned to treatment Arm A will receive two cycles of pembrolizumab 200mg given every three weeks and oral defactinib 400 mg given twice daily every day up until 2 days preceding surgery (last dose 48 hours prior to surgery). Those subjects assigned to treatment Arm B will receive two cycles of pembrolizumab 200mg alone given every three weeks. The first dose of pembrolizumab will start within 1 week from second EUS guided biopsy. A second CT scan will occur at the end of the second cycle of pembrolizumab and prior to surgery. The surgery will be scheduled between 10 to 25 days following the start of the second cycle of pembrolizumab. If patient is unable to receive second cycle of neoadjuvant immunotherapy, patient's surgery can occur after the end of the first cycle of immunotherapy and after surgical evaluation has occurred. Surgical evaluation will include assessments as noted in section 6.2.

2.1.4 Part 4: Surgery

Subjects will undergo the pancreatectomy at the clinical trial site at which they are enrolled. The surgical procedure performed will result in either a R0, R1 or R2 resection as determined by final pathology. Perioperative outcomes will be recorded including the operation performed, whether vascular resection and reconstruction was required, completeness of the resection (R0, R1 or R2), duration of the operation, blood loss, the length of stay, the need for re-admission within 30 days of surgery, and intraoperative and postoperative complications. Pancreatectomy is the standard of care to which immunotherapy and FAK inhibition or immunotherapy alone will be added to. As standard of care therapy for PDAC, this part of the study will be conducted outside of the study protocol. Adverse events monitoring will still occur throughout the SOC surgery phase. If the subject is found to have unresectable disease, core biopsies will be performed intraoperatively. Resected specimens will be archived for research purposes. Tumor infiltrating immune cells will be isolated from resected tumor tissue.

2.1.5 Part 5: Adjuvant Chemotherapy

Following surgery, all subjects with R0 or R1 SOC resection will receive standard of care adjuvant chemotherapy with gemcitabine plus capecitabine or another standard of care chemotherapy at the discretion of the primary treating oncologist. As standard of care therapy for PDAC, this part of the study will be outside of the study protocol. While the subject is receiving the SOC adjuvant chemotherapy, she/he will not receive any immunotherapy. Because chemotherapy can have significant toxicities we will not be monitoring chemotherapy or adjuvant SOC treatment related toxicities during adjuvant SOC therapy. However, we will monitor and report toxicities that are not attributable to surgery, post-operative course, chemotherapy, radiation therapy and disease progression 90 days from administration of neoadjuvant immunotherapy.

2.1.6 Part 6: Adjuvant Immunotherapy Maintenance

All subjects who complete at least one cycle of neoadjuvant immunotherapy, undergo SOC surgical resection, complete SOC adjuvant therapy and have no evidence of recurrence will undergo re-screening in order to receive 8 additional cycles of adjuvant combination immunotherapy and FAK inhibition (arm A) or immunotherapy alone (Arm B). Re-screening criteria for adjuvant immunotherapy can be found in **Section 5.1.5** and **Section 5.1.6**.

After completion of adjuvant SOC chemotherapy, subjects will resume the study protocol for continuation of immunotherapy and FAK inhibition or immunotherapy alone. Subjects in Arm A will receive maintenance pembrolizumab 200mg every 3 weeks and defactinib 400 mg twice daily every 3 weeks for a total of 24 weeks (8 cycles). Subjects in Arm B will be placed maintenance 200mg pembrolizumab alone every 3 weeks for a total of 24 weeks (8 cycles).

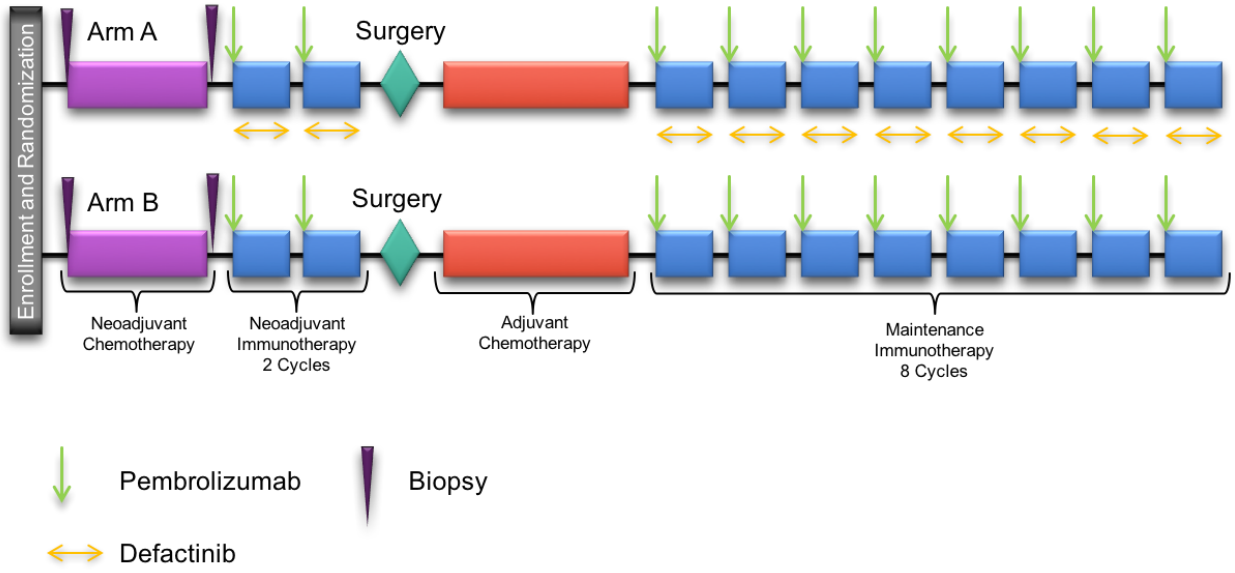
2.1.7 Part 7: Follow up

After subjects have completed all planned therapy, they are considered off treatment beginning 90 days after the last immunotherapy or FAK inhibitor (pembrolizumab or defactinib). All subjects will undergo an EOT evaluation 30 days after last dose of study drug, pembrolizumab or defactinib. Once off treatment, all subjects will undergo standard of care evaluations through their primary oncologist, consisting of history and physical, CT of the chest/abdomen/pelvis (or MRI abdomen/pelvis and non-contrast CT chest if do not tolerate contrast) every three to six months or as indicated to evaluate for local recurrence and metastatic disease. The study will collect the follow-up information including; disease status, adverse events and survival from primary oncologist and subjects.

Throughout the study, an internal and external real-time monitoring plan will be put in place to ensure that toxicities are captured and evaluated in a timely, appropriate, and non-biased manner. Subjects will be monitored at regular intervals for a broad range of toxicities, including enhanced inflammatory related complications prior to surgery, delayed surgery related healing, and immune-related adverse events (irAEs).

2.2 Trial Diagram:

The trial design is depicted in **Figure 1** below:



3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objectives & Hypotheses:

1. **Objective (1):** To assess changes in CD8 T cell intratumoral infiltration with pembrolizumab and defactinib or pembrolizumab alone, following neoadjuvant chemotherapy utilizing established multiplex IHC.

   Hypothesis: Pembrolizumab and defactinib or pembrolizumab alone increases CD8 T cell infiltration compared to chemotherapy alone.

2. **Objective (2):** To assess the pathologic complete response (pCR) rate of neoadjuvant pembrolizumab and focal adhesion kinase (FAK) inhibitor, defactinib or pembrolizumab alone following neoadjuvant chemotherapy.

   Hypothesis: Pembrolizumab and defactinib or pembrolizumab alone, improves pCR by 15%.

3.2 Secondary Objectives & Hypotheses:

1. **Objective (1):** To assess overall survival (OS).

   Hypothesis (1): Pembrolizumab and defactinib or pembrolizumab alone, following standard of care neoadjuvant therapy, surgical resection and adjuvant therapy improves OS as compared to historical outcomes with standard of care therapy.

Hypothesis (2): Pembrolizumab and defactinib improves OS compared to pembrolizumab alone.

2. **Objective (2):** To assess disease free survival (DFS).

   Hypothesis (1): Pembrolizumab and defactinib or pembrolizumab alone, following standard of care neoadjuvant therapy, surgical resection and adjuvant therapy improves DFS as compared to historical outcomes with standard of care therapy.

   Hypothesis (2): Pembrolizumab and defactinib improves DFS compared to pembrolizumab alone.

3. **Objective (3):** To assess safety: the proportion of subjects experiencing at least one grade 3/4 non-lymphopenia adverse events (AE).

3.3 Exploratory Objectives:

1. **Objective (1):** To assess immunogenic cell death (calreticulin IHC and signaling pathways following neoadjuvant chemotherapy/pre-immunotherapy and surgical biopsy specimens through immunohistochemistry and nanostring PCR analysis.

2. **Objective (2):** To assess CD68/CD8 ratio via multiplex IHC .

3. **Objective (3):** To assess expression of programmed death-ligand (PD-L1) and programmed death (PD-1) via IHC.

4. **Objective (4):** To assess immune signatures relevant to PD-L1/PD-1 activation and associated immunosuppressive pathways.

5. **Objective (5):** To assess pre- vs. post-treatment (pre-immunotherapy biopsy specimens and post-immunotherapy resected tumor specimens) intratumoral and peripheral blood T cell receptor (TCR) clonality.

6. **Objective (6):** To assess changes of TAM (tumor associated macrophages), myeloid–derived suppressor cells (MDSC) and T-reg cells with pembrolizumab and defactinib or pembrolizumab alone, following neoadjuvant chemotherapy utilizing established multiplex IHC.

7. **Objective (7):** To assess activity of pancreatic stellate cells via α-Smooth muscle actin (αSMA) and fibroblast activate protein (FAP) immunohistochemistry (IHC) with pembrolizumab and defactinib or pembrolizumab alone, following neoadjuvant chemotherapy.

8. **Objective (8):** To assess near pathologic CR rate and grade 3 pathologic response rate.

See **Section 7.3.2** for further information regarding analysis of exploratory objectives.

4.0 BACKGROUND AND RATIONALE

4.1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) is presently the third leading cause of cancer related death and is expected to surpass colorectal cancer to become second by 2030.[1,2] Despite advances in chemotherapy and radiotherapy over the last 10 years, the best clinical outcomes are appreciated in patients that undergo surgical resection. Yet among the 20% who are surgical candidates at the time of diagnosis, the rate of recurrence is nearly 80%. The median survival among this cohort is only 13-20 months.[3] The addition of adjuvant radiation and/or chemotherapy has demonstrated limited improvement in survival of resectable PDAC to 25-28 months.[4–6] Novel multidisciplinary and multimodal therapeutic approaches are needed for all stages of this aggressive disease.

4.2 Rationale for Neoadjuvant Chemotherapy

Presently the only the curative option for PDAC is surgical resection. Most patients recur after surgery and therefore adjuvant strategies have been investigated in the last decade to improve clinical outcomes. Multiple contemporary studies, including ESPAC-4 have clearly established the benefit of adjuvant chemotherapy.[5–9] However, the application of adjuvant therapy is not uniform across all resected patients. It is estimated that up to 50% of patients do not receive adjuvant therapy due to variety of post-operative circumstances.[10] Additionally, post-operative recovery delays time to adjuvant therapy and allows growth of potential micrometastatic disease. As a result of the high degree of recurrence and the potential of occult disease at time of diagnosis, neoadjuvant therapy has been investigated as a treatment approach among all stages of PDAC. Neoadjuvant therapy can lead to tumor regression, eradication of micrometastatic disease and increase the probability of achieving an R0 (no residual tumor) resection. Numerous studies have shown that neoadjuvant therapy can lead to a pCR in PDAC.[11] Pathologic complete response has significant clinical implications on local and distant recurrence, as well as overall survival.[12,13] Despite these benefits, there is no clear consensus on the role of neoadjuvant therapy. The utility of neoadjuvant therapy has predominantly been supported in studies looking at patients with borderline resectable or locally advanced disease.[14–16] Presently, multiple active clinical trials are evaluating neoadjuvant therapy for patients that are deemed resectable at time of diagnosis. Despite the paucity of data regarding the role of neoadjuvant therapy in upfront resectable PDAC, neoadjuvant therapy has been shown to confer a clinical benefit in patients with more aggressive or advanced disease.

Typically, radiographic assessment is utilized in determining the degree of advanced disease, appropriate management and the role of neoadjuvant therapy and/or surgical resection. Yet in patients with radiographically resectable disease, other biological

markers are needed to assist surgeons and oncologists in identifying the subset of patients who are at high risk of recurrence and who may benefit from neoadjuvant therapy. One prognostic marker that has been suggested as a tool for selection of high risk disease individuals, is cancer antigen 19-9 or sialylated Lewis antigen (CA 19-9). Perioperative CA 19-9 levels have been found to correlate with clinical outcomes and long term survival.[17] More importantly, a CA 19-9 >200u/ml has been associated with an increased risk of early recurrence after resection for PDAC as suggested by Tamburrino et al, *World J Gastroenerol*, 2014 and Shimizu et al, *American Surgeon*, 2018.[18,19] Higher CA 19-9 levels are correlated with advanced disease and have implications on resectability. Despite advancements in radiographic imaging for staging, up to 15% of patients with radiographically resectable disease are noted to have unresectable disease at time of surgery because of occult metastasis or locally invasive malignancy. CA 19-9 has been looked as a surrogate marker for resectability and disease stage, where significant elevations confer advanced and higher risk disease.[20] In order to improve clinical outcomes in patients with resectable disease, it is critical to move beyond radiographic assessment, as this does not take into account the biological aggressiveness of PDAC. The selection of patients who will benefit most from neoadjuvant therapy needs to take into account both patients who are resectable and those who have a substantially elevated CA 19-9.

4.3 Rationale for PD-1 Blockade (Pembrolizumab [MK-3475])

Immune surveillance is a critical aspect in the regulatory mechanism of cell growth and malignant transformation. The immune system has built in “checkpoints” to assist in differentiating “self” from “non-self” and more importantly in maintaining the homeostasis of inflammatory response. Neoplastic conversion of cells allows for the capture of cellular mechanisms in order to manipulate these checkpoints. Malignant cells are then able to avoid immune detection and diminish an anti-tumor inflammatory response.

Within the immune milieu, the adaptive T cell response, utilizing $CD8^+$ and $CD4^+$ T cells, plays a vital role in autoimmunity and acute inflammatory response. These same cells are involved in the adaptive immunity against tumor cells as tumor infiltrating lymphocytes (TILs). Over the last decade there has been a growing body of evidence suggesting that TILs play an important role in facilitating the response of standard chemotherapy and improving clinical outcomes in various tumors like breast cancer, melanoma and esophageal cancer.[21–23] Additionally, it has been suggested that many tumor antigens are “self” proteins and that the altered expression of these proteins increases tumor immunogenicity. However, self–tumor antigens may also induce the preferential propagation of $CD4^+$ $CD25^+$ $FOXP3^+$ T-regulatory (T-reg) cells. T-reg cells function to maintain immune homeostasis and limit acute inflammation.[24]

The degree of $CD8^+$ T-cell infiltration and the ratio of $CD8^+$ effector T-cells / $FoxP3^+$ T-reg has been shown to correlate with improved clinical outcomes and prognosis in solid malignancies such as ovarian, colorectal, urothelial, hepatocellular carcinoma, malignant melanoma, renal cell cancer and pancreatic cancer.[25–27]

Although historically pancreatic adenocarcinoma has been thought of a minimally immunogenic tumor, recent comprehensive genomic analysis provides evidence suggesting that a subtype of pancreatic adenocarcinoma can be highly immunogenic. This is thought to occur through the upregulation of the immune environment with TILs and increased immune checkpoint molecule expression, like programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1).[28]

PD-1 is expressed on activated T, B, NK and dendritic cells as well as monocytes and serves as an immune checkpoint.[29] It has a vital role in the development and regulation of the adaptive immune system via T cells. Under normal circumstances, PD-1 functions to inhibit effector T cells through downstream kinase inhibition, decreased signaling of T cell receptors (TCR), as well as decrease in INF-γ and IL-2 leading to immune suppression. This is done to modulate unwanted or excessive immune responses, including autoimmune reactions. However, this interaction between PD-1 and its ligands PD-L1 and PD-L2, is hijacked by tumors in order to suppress immune response. PD-L1 is expressed at diminished levels on numerous non-hematopoietic tissues, such as the vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or environments with chronic inflammation. PD-L2 is involved in immune T-cell activation within lymphoid organs, whereas PD-L1 serves to control mechanism for unwarranted T-cell function in peripheral tissues.[30]

Most normal healthy tissues express diminutive amounts of PD-L1. However a number of malignancies including ovarian, renal cell and hepatocellular carcinoma have been shown to express amplified levels of PD-L1 and consequently a diminished T cell response leading to poorer clinical outcomes and prognosis.[26,27,31] Even in pancreatic cancer, PD-L1 expression has been shown to be inversely correlated with TILs, particularly CD8+ cells and associated with a significantly poorer prognosis as suggested by Nomi et al, *Clinical Cancer Research*, 2007.[32] Since the discovery of PD-1 and its ligand in the early 90s, there has been increasing evidence to suggest that PD-L1 expression and the PD-1/PD-L1 pathway is a critical mechanism by which tumors like PDAC can evade immune detection. As a result of its integral role in immune modulation, blockade of PD-1 has been appealing and rational target for therapeutic intervention.

Pembrolizumab (MK-3475) is a potent and highly selective humanized monoclonal antibody of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab contains the S228P stabilizing mutation and has no antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity. Pembrolizumab strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T- cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. Pembrolizumab also modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T- cells.

Pembrolizumab is FDA-approved for unresectable or metastatic melanoma, metastatic non-small cell lung cancer, recurrent or metastatic head and neck squamous cell carcinoma and locally advanced or metastatic urothelial cancer at 200 mg flat dose every 3 weeks.

The observed correlation of clinical outcomes and prognosis with PD-L1 expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive and rational target for therapeutic intervention. However, the targeting of immune checkpoints alone are not ideal treatment strategies for pancreatic cancer, as other significant cellular and microenvironmental barriers remain.

4.4 Rationale for FAK Inhibition (Defactinib)

PD-1 blockade in lung cancer, colorectal cancer and melanoma has led to significant improvements of clinical outcomes.[33–35] However, pancreatic cancer has remained relatively refractory to checkpoint inhibition in comparison to other tumor types.[36] Immune modulation via upregulation of checkpoint molecules, like PD-1/PD-L1, is only one of many important barriers in an effective anti-tumor response. The tumor microenvironment (TME) serves as another critical barrier in pancreatic cancer treatment in general and immune checkpoint blockade. The reason that the TME in PDAC functions as critical barrier is twofold; 1) the pancreatic cancer is a significantly stroma rich tumor and 2) increased myeloid cell and immunosuppressive cell infiltration is noted within the TME.[37,38]

In order maximize the effect of traditional chemotherapy or any potential immune modulation via PD-1 blockade in favor of an anti-tumor response, the aforementioned obstacles of the TME must be overcome. Recently, a non-receptor tyrosine kinase, focal adhesion kinase (FAK) has been found to play an integral role modifying stromal fibrosis and TME immune suppression.[39]

In many malignancies, FAK is often upregulated with downstream signaling of integrins and growth factor receptors in order to maintain the neoplastic nature and survival of cancer cells. It does this by controlling a wide range of integral cellular functions from adhesion, migration, invasion, proliferation, and survival.[40] FAK has also been implicated in production of increased pathologic fibrosis, cytokine release and inflammation.[41,42]
FAK signaling is critically involved in various aspects of the TME, particularly immunosuppression and stromal alterations. Studies have shown that inhibition of FAK decreases the recruitment and migration of carcinoma associated fibroblasts (CAFs) and TAMs.[43] The tumor stromal environment is rich in CAFs which are implicated in the growth, drug resistance, angiogenesis and metastasis of cancer.[44] For example, in pancreatic cancer, the stromal and tumor microenvironment is characterized by increased collagen deposition with an elevated fibrotic response and infiltration of CAFs.[45] Additionally, CAFs have been shown to suppress CD8+ T cells and are associated with T cell dysfunction via mechanisms that involve immune checkpoints.[46] In a study by Stokes et al., pancreatic tumors from animals treated with PF-562,271 (a small molecule

inhibitor of FAK) led to a significant decrease in the number α-SMA-staining (CAFs) cells and a significant decrease in tumor cell proliferation.[43] Numerous preclinical studies have shown that FAK signaling is intimately involved in modulating MDSCs, TAMs, and T regulatory cells(T-Reg) within the TME.[41,43,47,48] In squamous cell carcinoma preclinical mouse models, small molecule FAK inhibitor VS-4718 was revealed to reduce immunosuppressive MDSCs, TAMs and T-Reg cells. This consequently led to increased CD8+ T-cells within the tumor environment and enhancement of CD8+ T cell mediated suppression of cancerous cells.[41]

Similarly, VS-4718 was evaluated in combination with standard cytotoxic chemotherapy employed in the treatment of PDAC and with immunotherapy by Jiang et al, 2016.49</sup> Jiang and colleagues have recently shown that by inhibiting the FAK pathway, pancreatic stellate cells can be modulated leading to a decrease in immune suppressive cells including MDSC, TAM, and Treg within the TME in PDAC of mouse models. They also noted that there was an increase in CD8+ T cells in FAK-depleted tumors and that inhibition of FAK decreased collagen deposition.[39] Together, these changes within the TME of pancreatic cancer lead to modulation of the immune system in favor tumor eradication. Jiang et al, also evaluated the role of FAK inhibition as synergistic modality along with immunotherapy and traditional chemotherapy. They found that mice treated with gemcitabine, anti-PD1 therapy and FAK inhibition had 2.5 fold increase in median survival time compared to those treated with gemcitabine and anti-PD1 therapy alone.

An additional benefit of FAK inhibition is its ability to reduce cancer stem cells (CSCs). Within a tumor, CSCs are capable of self-renewal, are able to generate more cancer cells with heterogenous differentiation and are typically resistant to standard therapies, resulting in tumor resistance, recurrence and metastasis.[5>,51] In preclinical malignant mesothelioma models, standard cytotoxic therapies such as pemetrexed, cisplatin, gemcitabine and vinorelbine have been shown to increase CSCs, but when FAK inhibition is added to the treatment backbone, CSCs are decreased.[52] CSCs are influenced by critical factors within the TME from cytokines, small RNAs, TAMs and fibroblasts which impact its unique niche.[38,53] These factors regulate the invasiveness, metastatic potential and differentiation of CSCs.

Defactinib is an oral, well tolerated, inhibitor of FAK, which is currently being investigated for the treatment of advanced solid tumors, including malignant pleural mesothelioma, ovarian cancer, pancreatic cancer and non-small cell lung cancer. Defactinib was found to be a potent and selective ATP- competitive, reversible inhibitor of recombinant human FAK kinase in biochemical and cell-based assays. A comprehensive evaluation of selectivity against a large panel of other kinases in enzyme assays demonstrated that defactinib was highly selective for FAK strongly suggesting that its predominant pharmacologic activity is mediated by inhibition of FAK. Additionally, utilizing cancer stem cell assays, both *in vitro* and *in vivo*, defactinib was observed to eradicate cancer stem cells. In a recent phase I study by Gilliam et al, defactinib was evaluated in combination with pembrolizumab and gemcitabine in advanced pancreatic adenocarcinoma. The triple drug regimen was shown to be well tolerated with the 400 mg BID determined to be the

RP2D dose. In patients who were heavily pre-treated one had (13%) partial response and 3 (38%) had stable disease. Additionally, paired biopsies showed an increase in proliferating CD8+ T cells and a reduction of T-reg cells and macrophages with treatment.[5]>

Findings from preclinical and clinical studies have elucidated the broad role of FAK inhibition as an important modulator of the immunosuppressive components and cancer promoting aspects of the tumor microenvironment. FAK inhibition is an appealing therapeutic target and adjunctive therapy that can potentially increase the effectiveness of traditional cytotoxic chemotherapy and immunotherapy, particularly for aggressive and refractory malignancies, like pancreatic adenocarcinoma.

4.5 Combination Therapy, Study Rationale and Biologic Markers

Despite the curative intent of surgery and the addition of adjuvant therapy, clinical outcomes in PDAC remain poor. Immunotherapy, TME modulation and chemotherapy each in their own right may serve as viable therapeutic options. However, each has its limitations as evidenced by the unfortunate outcomes appreciated in pancreatic cancer relative to many other malignancies that utilize similar therapies.

The aforementioned rationale for each therapeutic modality; its influence on other modalities and their interrelationship, suggests that sequential/combinatorial therapy in the neoadjuvant setting may provide a unique and novel avenue through which clinical outcomes can be improved.

Our previous studies demonstrated granulocyte-macrophage colony-stimulating factor gene transfected tumor cell vaccine (GVAX) can reprogram the tumor microenvironment (TME) in PDAC by inducing lymphoid infiltration.[5]> Additionally, we found that intratumoral CD68/CD8 ratio is a potential biomarker of myeloid-inflamed stroma that limits efficacy of immunotherapeutic responses despite induction of lymphoid infiltration (**Figure 2**).[56] Presently, we are developing a multiplex CD68/CD8 IHC into a CLIA biomarker assay using the tumor biospecimens from a clinical trial testing the synergistic activity of Nivolumab and GVAX as neoadjuvant and adjuvant therapy for PDAC (clinical trial design similar to this study) and using the tumor biospecimens from a clinical trial testing the synergistic activity of pembrolizumab, GVAX, SBRT in treating locally advanced PDACs (an ongoing Merck MISP study).

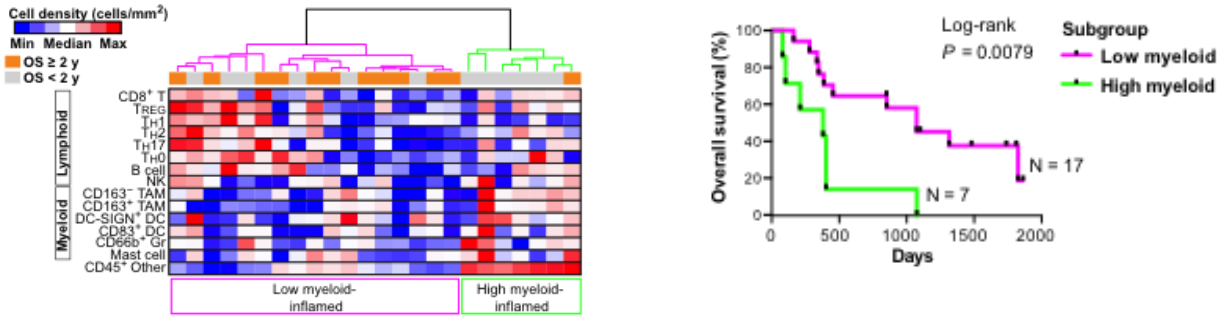


Figure 2 Left panel: Immune cell densities (cells/mm^2) of three leukocyte hotspots in intratumoral regions were assessed by sequential multiplex IHC/image cytometry. A heat map according to color scale is shown with a dendrogram of unsupervised hierarchical clustering, depicting low and high myeloid-inflamed subgroups. **Right panel:** Kaplan-Meier analysis of neoadjuvant GVAX-treated PDAC cohort (N = 24) stratified by subgroups. Statistical significance was determined via log-rank test. (From Tsujikawa et al. Cell Reports 2017).

Additionally our group also found that chemotherapy can reprogram the TME in PDAC. We found that lower level of CSF-1R TAM was associated with longer overall survival following neoadjuvant chemotherapy and surgical resection (**Figure 3**).

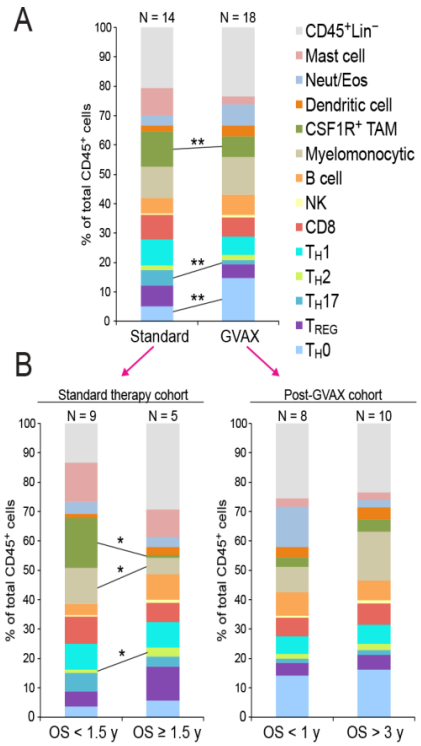


Figure 3 "Single Cell Based Cytometry" of cell populations expressing different phenotypic and functional markers in the PDA TME. This demonstrates the feasibility of analyzing the % of different immune populations within the TME for patients treated either with our vaccine or standard chemotherapy.

Note that lower level of CSF1R TAM was associated with longer overall survival (OS) following neoadjuvant chemotherapy and surgical resection (**Tsujikawa and Zheng, et al., unpublished**).

Although the appropriate sequencing of chemotherapy and immunotherapy in diseases where both therapies are known to be active remains unclear, there is emerging evidence that chemotherapy can modulate the host immune system. This can be achieved through the expression of cancer neoantigens leading to changes in expression and induction of PD-L1. Interestingly, work from our group has shown PD-L1 induction on tumor epithelium following neoadjuvant chemotherapy (**Figure 4**), suggesting a role for combinatorial therapy with immunotherapy and traditional cytotoxic chemotherapy. Yet this combination can be further augmented by modulating the TME.

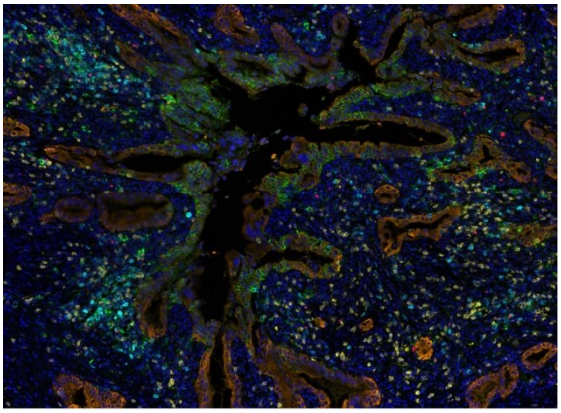


Figure 4: Multiplex immunofluorescence staining of PDACs following neoadjuvant gemcitabine/abraxane. CD 8 Yellow; FOXP3 Red; CD68 Magenta; PD-1 Cyan; PD-L1 Green; Keratin Orange; DAPI. Note that PD-L1 expression (in green) on tumor epithelium was induced following neoadjuvant chemotherapy. (**Zheng Lab, unpublished**)

As noted previously, inhibiting the FAK pathway is known to modulate pancreatic stellate cells and decrease the immune suppressive cells including MDSCs, TAMs, and T-regs within the TME in PDAC of mouse models (Jiang et al. Nature Medicine 2016). Therefore, by regulating the TME, FAK inhibition may serve as a further enhancer of the anti-tumor response of immunotherapy and traditional chemotherapy. This anti-tumor response can be appreciated both histologically and clinically, by observing pathologic response and disease related recurrence/survival, respectively.

Pathologic complete response, is clinically relevant prognostic indicator in many gastrointestinal malignancies, like rectal and esophageal cancer.[5>,58] In pancreatic cancer, patients with complete pathologic outcomes have superior outcomes.[59] Chemotherapy alone in the neoadjuvant setting results in a pathologic complete response rate of approximately 0-3%.[11] Chemotherapy followed by stereotactic body radiation potentially increases pCR to 13%.[60,61] Therefore, the standing hypothesis is that by adding FAK inhibitor to anti-PD-1 antibody following neoadjuvant chemotherapy will also enhance the pCR rate, modulate pancreatic stellate cells and sensitize PDAC to anti-PD-1 therapy. Additionally, by improving the pCR rate through immunotherapy and FAK

inhibition, systemic antitumor activity may be increased leading to an improvement in clinical outcomes and the survival in patients with PDAC.

This clinical trial will evaluate whether treatment that reprograms the tumor microenvironment by targeting FAK following chemotherapy can potentiate anti-PD-1 antibody by modulating myeloid (TAM&MDSC)-inflamed stroma and promote effector T cell infiltration in the PDACs, leading to a high rate of pathologic complete response and potentially an improvement in clinical outcomes.

5.0 METHODOLOGY

5.1 Study Population

Subjects with pretreatment biopsy-proven (or clinically suspected if the biopsy is not sufficient for diagnosis), surgically resectable (see **Section 5.1.7** for resectability criteria) and subsequently pathologically proven AJCC stage I or stage II adenocarcinoma of the head, neck, uncinate, body or tail of the pancreas (see 5.1.6 for staging criteria) and who have no radiographic evidence of metastatic or unresectable pancreatic cancer prior to the starting of immunotherapy. Subjects must also be defined as high risk by a CA 19-9 >200.

Our targeted accrual goal is 36 evaluable subjects, who will be randomly assigned to two treatment arms. Subjects are considered evaluable if they have a pretreatment biopsy demonstrating pancreatic ductal adenocarcinoma, an R0 or R1 resection of their tumors, their tumors are pathologically proven stage I/II adenocarcinoma of the pancreas and receive at least one dose of pembrolizumab/defactinib or pembrolizumab alone. These subjects are also considered evaluable for DFS and OS endpoints. All subjects who receive any dose of study therapy (ie pembrolizumab or defactinib) therapy will be monitored and evaluated for safety endpoints. These 36 subjects will be randomized to the two treatment arms via the Research Electronic Data Capture (REDCap) application to the two treatment arms in a 1:1 ratio. To ensure comparability of the two study arms, randomization will be stratified up-front by age (≥65, <65). The participants will be notified of their assigned arm after they have enrolled in the study.

Eligible participants will receive a total of two cycles of SOC neoadjuvant chemotherapy with gemcitabine and nab-paclitaxel. Each arm will receive 2 cycles of pembrolizumab in the neoadjuvant setting and then will be placed on maintenance pembrolizumab for a total of 8 cycles for a total of 24 weeks in the adjuvant setting following SOC surgery and SOC adjuvant chemotherapy. One investigational arm will receive defactinib throughout the cycles of immunotherapy with pembrolizumab.

- In **Arm A**, subjects will receive pembrolizumab 200mg IV every 3 weeks following neoadjuvant chemotherapy and every 3 weeks following adjuvant chemotherapy. Subjects in Arm A will also receive defactinib (FAK inhibitor) at 400 mg BID during immunotherapy cycles in both the neoadjuvant and adjuvant settings in addition to pembrolizumab.

- In **Arm B**, subjects will receive pembrolizumab 200mg IV alone every 3 weeks following neoadjuvant chemotherapy and every 3 weeks following adjuvant chemotherapy.

5.1.1 Participant Inclusion Criteria for Initial Enrollment (Pre-Neoadjuvant Chemotherapy)

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Are at least 18 years of age on the day of signing informed consent.

2. Has histologically confirmed diagnosis of pancreatic ductal adenocarcinoma will be enrolled in this study.

3. Has resectable disease at the time of diagnosis (see **Section 5.1.11**, for criteria of resectability).

4. Has received no systemic therapy for PDAC (prior symptomatic treatments such as pain medicines are acceptable).

5. Has stage $\leqslant$ IIb disease at time of diagnosis and trial enrollment (see **Section 5.1.10**, for disease staging).

6. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 14 days prior to the date of allocation/randomization. (**Appendix 1**)

7. Has CA 19-9 >200 in setting of a total bilirubin $\leqslant$1.5 $\times$ULN OR direct bilirubin $\leqslant$ ULN for participants with total bilirubin levels >1.5 × ULN. If total bilirubin levels are >1.5 x ULN, CA 19-9 must be >695 for patient to be included in the study. This criteria only applies at the time of initial pre study enrollment evaluation.

8. A male participant must agree to use a contraception as detailed in **Appendix 2** of this protocol during the treatment period and for at least 120 days after the last dose of any study treatment and refrain from donating sperm during this period.

9. A female participant is eligible to participate if she is not pregnant (in the case of a positive HCG test, a transvaginal ultrasound must be used to confirm lack of pregnancy, see **Appendix 2**), not breastfeeding, and at least one of the following conditions applies:

   a.) Not a woman of childbearing potential (WOCBP) as defined in **Appendix 2** OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in **Appendix 2**

during the treatment period and for at least 120 days after the last dose of any study treatment.

10. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

*If, after the participant has met the eligibility criteria, the participant is reevaluated for other indications either clinically or by laboratory tests, such re-evaluations will not be considered as the re-valuation of eligibility. However, whether or not to proceed with the study treatment is at the discretion of principal investigator or the designee. Decisions still can be made to take the participant off the study based on such re-evaluations. If the eligibility criteria for treatment are not met, the research participant may be re-evaluated if the Principal Investigators anticipates that the research participant may later meet the eligibility criteria. There is no time limit.

5.1.2 Participant Exclusion Criteria for Initial Enrollment (Pre-Neoadjuvant Chemotherapy)

Participants are excluded from the study if any of the following criteria apply:

1. Receiving, or previously received, any chemotherapy, radiation therapy or investigational agent for pancreatic cancer.

2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137).

3. Has received prior therapy with FAK inhibitor.

4. A WOCBP who has a positive urine pregnancy test within 72 hours prior to randomization and allocation (see **Appendix 2**). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

5. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

6. Has a known additional malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of this study's investigational drugs. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, low grade prostate cancer or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded. Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

7. Has known active metastasis, CNS metastases and/or carcinomatous meningitis.

8. 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.

9. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

10. Has an active infection requiring systemic therapy.

11. Has a known history of Human Immunodeficiency Virus (HIV).

12. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA qualitative detection) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

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

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

15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.

16. History of allergic reactions attributed to compounds of similar chemical or biologic composition to agents used in study: Pembrolizumab and Defactinib.

17. Received growth factors including, but not limited to, granulocyte-colony stimulating factor (G-CSF), GM-CSF, erythropoietin, within 14 days of study drug administration. Use of such agents while on receiving study treatments is also prohibited. Use of agents during SOC therapies, as long as they are >14 days from the administration of study therapies (pembrolizumab and defactinib) are allowed.

18. Is taking a medication that is a strong inhibitor or inducer of CYP3A4, CYP2C9, OATP1B1 or OATPIB3 (**Appendix 3**).

19. Has history of any organ transplant, including corneal transplants.

5.1.3 Participant Inclusion Criteria for Neoadjuvant Immunotherapy (Post-Neoadjuvant Chemotherapy)

Participants are eligible to continue in the neoadjuvant immunotherapy portion of the study only if all of the following criteria apply:

1. Have adequate organ function as defined in the following table (**Table 1**). Specimens must be collected within 3 days of dosing with investigational agent(s)

Table 1: **Adequate Organ Function Laboratory Values**

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000/μL
Platelets	≥80,000/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 (Except subjects with Gilbert syndrome, who may enroll as long as total bilirubin <3.0 mg/dL)
AST (SGOT) and ALT (SGPT)	≤3.0 × ULN

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.

5.1.4 Participant Exclusion Criteria for Neoadjuvant Immunotherapy (Post-Neoadjuvant Chemotherapy)

Participants are excluded from continuing in the study if any of the following criteria apply:

1. Evidence of metastatic disease on pre-immunotherapy CT or MRI imaging.

2. Unable to complete at least 1 cycle of neoadjuvant standard of care chemotherapy with gemcitabine and nab-paclitaxel (patient should have minimum of 3 doses over two cycles).

3. Unable to meet inclusion criteria number 8 and 9 in **Section 5.1.1**.

4. Received growth factors including, but not limited to, granulocyte-colony stimulating factor (G-CSF), GM-CSF, erythropoietin, within 14 days of study drug administration.

5. Is taking a medication that is a strong inhibitor or inducer of CYP3A4, CYP2C9, OATP1B1 or OATPIB3 (**Appendix 3**).

6. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

7. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

   Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

8. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

5.1.5 Participant Inclusion Criteria for Adjuvant Immunotherapy (Post-Surgery)

Participants are eligible to continue in the adjuvant immunotherapy portion of the study only if all of the following criteria apply:

1. Have adequate organ function as defined in the following table (**Table 1**). Specimens must be collected within 3 days of dosing with investigational agent(s)

Table 2: **Adequate Organ Function Laboratory Values**

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000/μL
Platelets	≥80,000/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 (Except subjects with Gilbert syndrome, who may enroll as long as total bilirubin <3.0 mg/dL)
AST (SGOT) and ALT (SGPT)	≤3.0 × ULN

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.

5.1.6 Participant Exclusion Criteria for Adjuvant Immunotherapy (Post-Surgery)

Participants are excluded from continuing in the study if any of the following criteria apply:

1. More than 90 days have elapsed since surgery (in the absence of adjuvant chemotherapy). The subject will be considered off treatment.

2. Subjects who were found to have unresectable or metastatic disease intraoperatively.

3. Subjects who develop disease recurrence in the adjuvant setting. These subjects will be monitored for the safety endpoint but will not continue to receive further immunotherapy and FAK inhibition or immunotherapy alone.

4. Are found to have an R2 resection following surgery.

5. Unable to meet inclusion criteria number 8 and 9 in **Section 5.1.1**.

6. Has severe hypersensitivity (⩾ Grade 3) to pembrolizumab and/or any of its excipients.

7. Has severe hypersensitivity (⩾Grade 3) to defactinib and/or any of its excipients.

8. Received growth factors including, but not limited to, granulocyte-colony stimulating factor (G-CSF), GM-CSF, erythropoietin, within 14 days of study drug administration.

9. Is taking a medication that is a strong inhibitor or inducer of CYP3A4, CYP2C9, OATP1B1 or OATPIB3 (**Appendix 3**).

10. Subjects who are unable to receive second cycle of neoadjuvant immunotherapy due to treatment related toxicity from pembrolizumab or defactinib.

5.1.7 Lifestyle Restrictions

5.1.7.1 Meals and Dietary Restrictions

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

5.1.7.2 Contraception

The investigation agents, pembrolizumab and defactinib may have adverse effects on a fetus in utero. Refer to **Appendix 2** for approved methods of contraception and further information on WOCBP, pregnancy and nursing.

Given the potential risk related to pharmacologically-mediated inhibition of the PD-1 pathway, no reproductive or developmental toxicity studies were conducted with pembrolizumab. Defactinib has also not been studied in pregnant women and must not be given to subjects who are pregnant. Additionally, no teratology studies with defactinib have been conducted. Safety for women of childbearing capacity cannot be implied from the existing data. Furthermore, animal reproduction studies have not been conducted with defactinib. Therefore, potential effects of defactinib use during pregnancy are not known and the potential for developmental toxicity cannot be excluded.

It is required for clinical studies that men and women of childbearing potential agree to use adequate contraception (double barrier birth control) for the duration of study therapy and for 3 months after the last dose of defactinib and pembrolizumab.

For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

5.1.8 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab and or defactinib, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. Verastem will be notified of the participants' pregnancy within 24 hours of investigator knowledge and Merck will be notified within 2 business days of investigator knowledge, and monthly updates will be relayed in a timely fashion. The outcome of the pregnancy will also be reported to Merck and Verastem within the same time frames listed above. If the outcome of the pregnancy is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn) it will be reported to Merck and Verastem within the same time frames noted above. The study 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 Merck and Verastem. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and Verastem and followed as described in **Section 7.6.2**.

5.1.9 Use in Nursing Women

It is unknown whether the investigational agents, pembrolizumab or defactinib are 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, participants who are breast-feeding are not eligible for enrollment.

5.1.10 Staging information

Staging criteria are from the “American Joint Committee on Cancer (AJCC) Staging Criteria for Pancreatic Cancer.” Subjects with stage <= IIb are eligible for this study.

Stage Grouping
- Stage Ia T1 N0 M0
- Stage Ib T2 N0 M0
- Stage IIa T3 N0 M0
- Stage IIb T1-3 N1 M0
- Stage III T4 Any N M0
- Stage IV Any T Any N M

Primary Tumor (T)
- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor limited to the pancreas 2 cm or less in greatest dimension
- T2 Tumor limited to the pancreas more than 2 cm in greatest dimension
- T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery.
- T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor).

Regional Lymph Nodes (N)
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

Distant Metastasis (M)
- MX Presence of distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

5.1.11 Criteria for Resectability

Resectability is determined by the study team based on spiral CT with intravenous contrast enhancement or MRI if the subject is allergic to contrast, according to the AHPBA/SSO/NCCN criteria.

Subjects with no arterial tumor contact (celiac axis, superior mesenteric artery or common hepatic artery) and no tumor contact with the superior mesenteric vein or portal vein or ≤ 180° contact without vein contour irregularity who are deemed to be resectable will be eligible for the study.

Subjects who would be considered borderline resectable per the study team according to the AHPBA/SSO criteria and the NCCN criteria include subjects with severe unilateral SMV/portal impingement, tumor abutment on the SMA, GDA encasement up to the origin at the hepatic artery, or colon invasion are not eligible for this study.

5.2 Trial Treatments

Treatments will be administered on an outpatient basis. Dosing delays are described in **Section 5.2.3, 5.2.4, and 5.2.5**. All subjects will receive two cycles of SOC neoadjuvant chemotherapy with gemcitabine and nab-paclitaxel during the SOC chemotherapy phase of the protocol. This will be followed by two cycles of pembrolizumab for all study subjects and with the addition of defactinib for those in treatment Arm A only. Surgery will be scheduled between 10 to 25 days following the start of the second cycle of immunotherapy. All subjects who undergo SOC surgical resection will receive SOC adjuvant chemotherapy and maintenance immunotherapy unless 1) more than 90 days have elapsed since surgery (in the absence of adjuvant chemotherapy), or 2) there was unresectable or metastatic disease intraoperatively, or 3) there has been recurrence of disease. Following surgery, all subjects will receive standard of care chemotherapy through local oncologist. This will be followed by on study maintenance pembrolizumab with the addition of defactinib in treatment Arm A only, whereas subjects in treatment Arm B will receive pembrolizumab only.

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

Table 3: **Trial Treatments**

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion, over 30 minutes*	Day 1 of each 3-week (21 day) cycle	Experimental
Defactinib (Arm A Only)	400 mg**	BID	PO administration	Each day of 3-week (21 day) cycle***	Experimental
*Infusion times are approximate and may be adjusted based on subject tolerability (-10/+25 minutes). **Defactinib comes as 200 mg tablet so patients will take 2 tablets for 400 mg ***Defactinib will be continued beyond the end of cycle two of pembrolizumab until 2 days preceding surgery (last dose of defactinib is 48 hours prior to surgery).					

Treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned.

Neoadjuvant Chemotherapy (Gemcitabine and Nab-Paclitaxel)

Gemcitabine and nab-paclitaxel is a standard treatment for PDAC. Patients will receive two cycles of neoadjuvant gemcitabine and nab-paclitaxel prior to immunotherapy and FAK inhibition. General recommendations for treatment with gemcitabine and nab-paclitaxel are provided here (see Von Hoff et al.[6]>) Subjects who are unable to receive gemcitabine and nab-paclitaxel or are intolerant to it may be switched to another standard chemotherapy regimen (ie, FOLFIRINOX [63]) for pancreatic cancer for the remaining portion of the standard neoadjuvant chemotherapy portion of the study. Subjects are considered to have completed the standard neoadjuvant chemotherapy portion of the study when they have completed at minimum three doses of gemcitabine and nab-paclitaxel. If tolerated patient should attempt to complete two 28-day cycles of gemcitabine and nab-paclitaxel, or at least two months of standard chemotherapy. This therapy can be given through local treating oncologist for a total of two cycles. Additionally dose and cycle modifications are allowed for gemcitabine and nab-paclitaxel at the discretion of the treating oncologist.

Pembrolizumab (KEYTRUDA®, MK-3475)

Pembrolizumab will be administered IV over 30 minutes at 200mg every 3 weeks (Q3W) in the neoadjuvant and adjuvant setting. The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg Q3W will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose Q3W, 2) will maintain individual subjects exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual subjects exposure in the exposure range established in melanoma that are well tolerated and safe.[6]> This is also FDA approved dose for other tumor types.

The Pharmacy Manual contains specific instructions for pembrolizumab administration. Antiemetic medications should not be routinely administered prior to dosing of pembrolizumab. See **Section 5.2.2** for subsequent premedication recommendations following a pembrolizumab-related infusion reaction. Subjects should be observed for a minimum of 30 minutes after administration of pembrolizumab.

Defactinib (Arm A Only)

Defactinib is an orally available, potent ATP-competitive, FAK inhibitor with a recommended phase II dose (RP2D) of 400 mg twice daily. The choice of 400 mg dose is based on preclinical studies, a first-in-human experience phase 1 study in subjects with advanced solid tumors and a subsequent Asian phase 1 dose-escalation study conducted to determine the MTD and overall safety.[65,66] Additionally, there is an ongoing phase 1/1b study of the combination of pembrolizumab, defactinib, and gemcitabine chemotherapy that has also escalated to 400 mg twice daily (NCT02758587). Across multiple studies PK analyses has shown that the 400 mg BID is a tolerable dose, with mild treatment related adverse events and confers adequate plasma concentrations for FAK activity suppression. Based on both preclinical and clinical data the recommended Phase 2 dose schedule is 400 mg BID for current clinical formulation of defactinib.[65,66]

The tablets should be taken twice daily approximately 10-12 hours apart (2 tablets twice a day) immediately (within 30 minutes) after a meal. Tablets should be swallowed whole with a full glass of water. It is acceptable to take Defactinib within 2 hours of a missed dose. In the event of emesis occurring after study drug ingestion, the participant should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Patient diary for defactinib can be found in **Appendix 4**.

Adjuvant Chemotherapy

Subjects may receive any standard of care adjuvant therapy for resected pancreatic cancer through local oncologist. The study team advocates for gemcitabine and capecitabine as a standard treatment for PDAC to be utilized, however any standard treatment can be given at the discretion of treating oncologist. Additionally, treatments may be modified based on local treatment standards and guidelines as appropriate. General recommendations for treatment with gemcitabine and capecitabine are provided here (Neoptolemos et al.[6]) Subjects who are unable to receive gemcitabine and capecitabine or are intolerant to it may be switched to another standard chemotherapy regimen at the discretion of the subject's treating oncologist for the remaining portion of the standard adjuvant chemotherapy portion of the study. Options for alternate therapy include FOLFIRINOX or other standard treatment options listed in the NCCN guidelines. This therapy will be given off protocol/study per treating oncologist.

5.2.1 Timing of Dose Administration

Pembrolizumab should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (**Section 6.0**). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Defactinib should be administered twice daily, beginning on Day 1 of each cycle, and should continue daily until the end of the cycle. During the final immunotherapy cycle prior to surgery, defactinib should continue until 2 days prior to surgery (last dose to be given 48 hours prior to surgery).

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks. 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).

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

5.2.2 Dose Modifications

In part two and part five of the study, dose or cycle modifications for standard of care chemotherapy (including gemcitabine, nab-paclitaxel, capecitabine or standard chemotherapy) will be allowed at the discretion of treating medical oncologist or study team.

Dose modifications, which include dose reductions or dose increases of pembrolizumab and defactinib, will not be permitted in individual subjects in any part of the study.

From part two of the study onwards, where study treatments are administered, pembrolizumab and defactinib related adverse effects will be closely monitored. Adverse events and toxicities, across all grades will be monitored and recorded for both defactinib and pembrolizumab. The first two subjects in each arm will be enrolled and treated in a staggered fashion in order to closely monitor for adverse events. For the first two staggered subjects in each arm, the subjects will be followed until the time of surgery or for two weeks, whichever occurs first following neoadjuvant immunotherapy/FAK inhibition, before the next subject will be treated with neoadjuvant immunotherapy and FAK inhibition. Subjects will be closely monitored for the number of grade 3 or higher toxicities through the first two cycles of immunotherapy in part three of the study. No dose reductions will be allowed, however if grade 3/4 adverse events attributable to pembrolizumab/defactinib or pembrolizumab or Grade 3 infusion-related reaction or cytokine release syndrome that lasts $\geqslant$ 12 hours occurs, the toxicity monitoring and stopping rule as outlined in **Section 8.2** will be assessed. Dose delays will be permitted.

In part six of the study, no dose reductions will be allowed for either defactinib or pembrolizumab. Dose delays will be permitted. The toxicity monitoring and stopping rule as outlined in **Section 8.2** will be invoked should subjects develop grade 3/4 adverse events attributable to pembrolizumab/defactinib or pembrolizumab or Grade 3 infusion-related reaction or cytokine release syndrome that lasts $\geqslant$ 12 hours occurs in this phase of the study.

5.2.3 Toxicity management for immune-related AEs associated with pembrolizumab

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 on 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 delays and toxicity management guidelines for irAEs associated with pembrolizumab are provided in **Table 3**.

Table 3: Dose delays and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

Immune-related AEs	Toxicity grade or conditions (CTCAEv5.0)	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 • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	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 (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).

	Grade 4 or recurrent Grade 3	Permanently discontinue		• 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.
AST / ALT elevation or Increased bilirubin	Grade 2[a]	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[b] or 4[c]	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[d]	• 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[d]		
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[d]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.

Nephritis and Renal dysfunction (Grading according to increased creatinine or acute kidney injury)	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		
Neurological Toxicities	Grade 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		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event[e]		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

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. Toxicity management guidelines on pembrolizumab associated infusion reaction are provided in **Table 4**.

Table 4: Pembrolizumab Infusion Reaction 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 (e.g., 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 (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be pre-medicated 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 pre-medicated 1.5h (± 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 (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids	No subsequent dosing

Grade 4: Life-threatening; pressor or ventilatory support indicated	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.**	
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 v5.0 (CTCAE) at http://ctep.cancer.gov		

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 IND Sponsor. The reason for interruption should be documented in the subject's study record.

5.2.4 Toxicity management for AEs associated with defactinib

Overall, defactinib has been found to be well tolerated in clinical studies. GI disorders were the most common type of treatment-related adverse events reported to date. Nausea with or without vomiting and diarrhea are commonly reported with defactinib. If subjects experience Prophylactic medications may be used as needed if nausea is found to occur with administration of defactinib and cannot be managed with small amounts of food.

Event Name	**Nausea**
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change
Grade 2	No change
Grade 3	Withhold until ≤ Grade 2. Discontinue defactinib if symptom lasts longer than 72 hours.
Recommended management: antiemetics.	

Event Name	**Vomiting**
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change
Grade 2	No change
Grade 3-4	Withhold until ≤ Grade 2. Discontinue defactinib if symptom lasts longer than 72 hours.
Recommended management: antiemetics.	

Event Name	**Diarrhea**
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change
Grade 2	No change
Grade 3-4	Withhold until ≤ Grade 2. Discontinue defactinib if symptom lasts longer than 72 hours.
Recommended management: Anti-diarrheal therapy	

Event Name	**AST / ALT elevation or Increased bilirubin**
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change
Grade 2	Withhold until ≤ Grade 1
Grade 3	Withhold until ≤ Grade 1. Discontinue defactinib if Grade 3 elevated LFTs do not improve to ≤ grade 2 after holding defactinib for two weeks.
Grade 4	Discontinue defactinib
Recommended management: Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable	

Event Name	**All other related AEs**
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change
Grade 2	No change for asymptomatic toxicities. Withhold until ≤ Grade 1 if toxicity is symptomatic.
Grade 3-4	Withhold or discontinue based on the type of event*
Recommended management: Ensure adequate evaluation to confirm etiology and/or exclude other causes. * The following toxicities do not require treatment discontinuation: ▪ Asymptomatic laboratory abnormalities or in the judgment of the investigator, are not clinically significant ▪ Grade 3 fatigue that improves to Grade 2 within 7 days ▪ Grade 3 dermatologic AEs that are considered mild in severity but only considered grade 3 because of >30% body surface involvement ▪ Grade 3-4 hyperglycemia or grade 3 endocrinopathies where symptoms are controlled on hormone replacement therapy	

5.2.5 Dosing Delays

Treatment delays for standard of care chemotherapy (e.g. gemcitabine, nab-paclitaxel and capecitabine or chemotherapy per treating oncologist preference for parts two and five of study) are at the discretion of the treating medical oncologist or study team. Subjects are considered to have completed neoadjuvant chemotherapy when they have completed two, 28-day cycles of chemotherapy in part two of the study, or have completed at least two months of standard chemotherapy. Adjuvant chemotherapy cycles are determined by treating oncologist and as tolerated by patient. Delays during adjuvant chemotherapy can occur at discretion of treating oncologist.

The first cycle of neoadjuvant immunotherapy and FAK inhibition, with pembrolizumab and defactinib or pembrolizumab alone should optimally be administered within one week of completing last cycle of neoadjuvant chemotherapy and second EUS biopsy. However, if necessary due to resolving adverse events related to chemotherapy or any other reason, the first cycle of pembrolizumab and defactinib or pembrolizumab alone can be delayed up to three weeks. If the first cycle of pembrolizumab and defactinib or pembrolizumab alone is delayed by more than three weeks from completion of neoadjuvant chemotherapy, the Principal Investigator must be contacted for further instructions on continued treatment versus preceding to definitive resection.

The second cycle of immunotherapy is to be administered within 7 days of completing last cycle of immunotherapy. If the second cycle is delayed by more than 1 week, due to adverse events relates to immunotherapy or FAK inhibition or any other reason, the Principal Investigator must be contacted for further instructions on continued treatment versus preceding directly to definitive resection. If delay is not due to FAK inhibition, defactinib can continue until next cycle of pembrolizumab.

Surgical resection should occur between 10 to 25 days from the administration of cycle 2 of immunotherapy. Defactinib should continue until 2 days preceding surgery (last dose of defactinib 48 hours prior to surgery). If surgery is delayed beyond the aforementioned treatment window, the Principal Investigator must be contacted for further instructions regarding defactinib, if the subject is on Arm A. Additionally, if patient does not receive second cycle of immunotherapy they can proceed to surgery following surgical evaluation and completion of cycle 1 of immunotherapy and will remain on study. Timing of this will be determined by Principal Investigator and treating surgeon but will occur as soon as possible. If patient is unable to receive one cycle of immunotherapy they will proceed directly to surgery off study.

In part six of the study, during maintenance immunotherapy each successive cycle of pembrolizumab and defactinib or pembrolizumab alone should be administered within one week from the completion of the preceding cycle. If the subsequent cycle is delayed by more than 1 week, the Principal Investigator must be contacted for further instructions on continued treatment on study versus discontinuation. If delay is not due to FAK inhibition, defactinib can continue until the next cycle of pembrolizumab. The first dose of immunotherapy following completion of adjuvant therapy in part five, should be administered within 6 weeks of completing last cycle of adjuvant therapy. However, if necessary due to resolving adverse events related to chemotherapy or for any other reason, immunotherapy is delayed by more than 6 weeks, the Principal Investigator must be contacted for further instructions on continued treatment.

Additional delays or modifications to the treatment schedule must be approved by the Principal Investigator or the IND Sponsor.

5.3 Trial Blinding and masking

This is an open-label trial; therefore, the IND sponsor, investigators and subjects will know the treatment administered. The subjects will be notified of their assigned arm after they have enrolled in the study.

5.4 Randomization or Treatment Allocation

36 subjects will be randomized to the two treatment arms via the Research Electronic Data Capture (REDCap) application in a 1:1 ratio to pembrolizumab and defactinib or to pembrolizumab alone.

5.5 Stratification

To ensure comparability of the two study arms, randomization will be stratified by age (≥65, <65).

5.6 General Concomitant Medication and Supportive Care Guidelines

5.6.1 Neoadjuvant Chemotherapy (Gemcitabine and Nab-Paclitaxel)

Acute reactions will be managed used standard therapy guidelines for acute drug reactions as per institutional guidelines. Neoadjuvant SOC therapy will be through local oncologist.

5.6.2 Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody. Subjects should be closely monitored for potential adverse reactions during antibody infusion and potential adverse events throughout the study.

Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.

5.6.2.1 Infusion Reactions

Pembrolizumab infusion reactions may consist of fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, rash, vomiting, myalgia, dizziness or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Subjects should be closely monitored for such reactions. Guidelines for subjects who experience an infusion related or allergic reaction during or after infusion with pembrolizumab are shown below in (**Section 5.2.2**, **Table 4).**

5.6.2.2 Immune-Related Adverse Events (IRAEs) for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous 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 the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis:**
  - For **Grade 2** events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4** events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis:**
  - Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All subjects who experience 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. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2** diarrhea/colitis, administer oral corticosteroids.
  - For **Grade 3 or 4** diarrhea/colitis, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (T1DM) (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

  - For T1DM or Grade 3-4 Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis:**

  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism:**

  - Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic:**

  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids

- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis:**

  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Elevated CK:**

  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **All other drug-related toxicity:**
  - For **Grade 3-4** events, treat with systemic steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

5.6.3 Defactinib

Defactinib is a potent and selective ATP-competitive, reversible inhibitor of recombinant human FAK.

Overall, defactinib has been found to be well tolerated in clinical studies at doses ranging from 2.5 mg to 750 mg BID (with 400 mg BID being the dose selected for further clinical development).

Gastrointestinal dysfunction symptoms were the most common type of treatment-related adverse events reported to date, with nausea being the most common individual study drug-related adverse event and diarrhea and vomiting being among the most common. Other common drug-related adverse events included fatigue, hyperbilirubinemia and decreased appetite.

Gastrointestinal Effects
Nausea with or without vomiting and diarrhea are commonly reported with defactinib. In clinical studies, nausea and diarrhea were reported more commonly in subjects on defactinib than in subjects who received placebo, whereas the incidence of vomiting was relatively similar. These events are generally mild or moderate (Grade 1 or 2) in intensity and non-serious, although serious cases have been reported. Prophylactic medications

may be used as needed if nausea is found to occur with administration of defactinib and cannot be managed with small amounts of food. Diarrhea should be managed per institutional guidelines.

Increased Bilirubin
Increased bilirubin has been observed with defactinib. These increases are generally asymptomatic and not associated with increases in AST or ALT. Increased bilirubin often resolves spontaneously, even with continued drug treatment.

Significant Drug Interactions

Defactinib is a potent inhibitor of OATP1B1 and OATPIB3 with IC50 values of 0.2 and 8.5 uM. Therefore, drugs that are substrates of these hepatic uptake transporters may be subjected to DDI. The blood levels of these substrate drugs might increase to unsafe levels. (Example – sartans) (see Appendix 3 for comprehensive list).
Defactinib may have the potential to increase warfarin exposure due to a potential drug-drug interaction affecting warfarin's metabolism. Based on a review of information from all clinical studies, an increased level of caution is recommended. If subjects can safely stop taking warfarin, they will be asked to do so. If subjects require anti-coagulation, an alternative to warfarin will be considered. Subjects who require anti-coagulation but cannot discontinue warfarin, will be monitored closely and have their INRs checked more frequently whilst on defactinib. For subjects requiring the start of anti-coagulation therapy during the course of the study, alternatives to warfarin will be recommended.

Additionally, concomitant use of strong inhibitors and inducers of CYP3A4 or CYP2C9 should be avoided. For strong inhibitors and inducers of CYP3A4 or CYP2C9 (**Appendix 3**).

5.6.4 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 therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator.

5.6.5 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), 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 28 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 recorded for SAEs and ECIs as defined in **Section 7.6**.

5.6.6 Prohibited and Restricted Therapies

Subjects may not use any of the following agents during the study:

- Any non-study anticancer or immunotherapy agent (investigational or non-investigational)

- Any other investigational agents, other than defactinib and pembrolizumab.

- Any other immunotherapy treatment, including, but not limited to: IL-2, interferon, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti-CTLA-4 antibodies.

- Systemic glucocorticoids 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 IND Sponsor. Steroid treatment should be completed at least 14 days prior to resuming study-related treatments. Further, if patients require high dose steroids, while on study, pembrolizumab can be re-administered if the steroids are tapered over a 12-week period.

- Filgrastim (Neupogen® or G-CSF) or sargramostim (Leukine® or GM-CSF). Use of these agents during SOC therapies, as long as they are >14 days from the administration of study therapies (pembrolizumab and defactinib) are allowed.

- Live vaccines (examples of live vaccines include, but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid [oral] vaccine). Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

- Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any

medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the IND Sponsor, and the participant.

- Strong inhibitors or inducers of CYP3A4, CYP2C9, OATP1B1 or OATPIB3 (**Appendix 3**).

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

5.7 Unacceptable Toxicities

Unacceptable toxicities are defined as any AE that is related to study drug administration (pembrolizumab and defactinib) and is not due to the subject's underlying malignancy and for which there is no clear evidence for an alternative etiology and meets one of the following NCI CTCAE criteria:

1. Hematologic toxicities deemed an unacceptable toxicity are:
   - Grade 4 anemia
   - Grade 3 or 4 neutropenia lasting $\geqslant$ 14 days
   - Grade $\geqslant$ 3 febrile neutropenia
   - Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with clinically significant bleeding

2. Any $\geq$ grade 3 non-hematologic toxicities. Exceptions include:

   - Asymptomatic laboratory abnormalities or in the judgment of the investigator, are not clinically significant
   - Grade 3 fatigue that improves to Grade 2 within 7 days
   - Grade 3 dermatologic AEs that are considered mild in severity but only considered grade 3 because of >30% body surface involvement
   - Diarrhea, nausea, or vomiting that resolves to < grade 3 within 72 hours of intervention
   - Grade 3-4 hyperglycemia or grade 3 endocrinopathies where symptoms are controlled on hormone replacement therapy
   - Grade 3 elevated LFTs that improve to $\leq$ grade 2 after holding defactinib for two weeks.

3. Grade 3 transaminase elevation in the presence of a total bilirubin elevation greater than 2x ULN

4. Grade ⩾ 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to ⩽ grade 1 severity within 2 weeks of starting therapy, or requires systemic therapy

Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.

The proportion of unacceptable toxicities will be monitored. If the toxicity levels are unacceptable (high probability that it is >33% of subjects), then enrollment will be suspended until further review and consideration by the IND Sponsor.

Events meeting unacceptable toxicity criteria should be reported via email to the IND Sponsor (lzheng6@jhmi.edu) and GIsafetyreporting@jhmi.edu within 24 hours.

5.8 Criteria for Removal from Study Treatment

Subjects will be removed from study treatment when any of the criteria listed below applies. The reason for study treatment removal and the date the subject was removed must be documented in the Case Report Form.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent, or
- Subject is lost to follow-up.

A subject must be discontinued from treatment (but may continue to be monitored in the post-treatment follow-up portion of the trial) for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment,
- Subject completes all cycles of planned treatment and assessments,
- Development of local recurrence or distant metastatic disease,
- Subjects who were found to have unresectable disease intraoperatively,
- ⩾ Grade 3 infusion-related or hypersensitivity reaction,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) (see **Section 5.7**),

- Severe or life-threatening pembrolizumab or defactinib-related AE(s) (**Section 5.2.3** and **5.2.4**).

- Subject meets the exclusion criteria listed in **Sections 2.13 and 2.1.6**,

- Need for >2 dose delays due to the same toxicity as per the dose delay guidelines.

- Inability to reduce corticosteroid dose for immune-related adverse reactions to ⩽10 mg prednisone or equivalent per day,

- More than 90 days have elapsed since the last immunotherapy treatment in the adjuvant setting. >90 days between neoadjuvant and adjuvant immunotherapy does not apply.

- Subjects who do not proceed to surgery within four weeks from completion of second cycle of pembrolizumab (21 day cycle) (for patients who receive only 1 dose of neoadjuvant therapy, if they do not proceed to surgery within 4 weeks from end of cycle),

- If in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the patient. The IND Sponsor should be included in this decision,

- Noncompliance with trial treatment or procedure requirements, or

- Subject becomes pregnant.

5.9 End of Treatment (EOT) Visit

After a subject is discontinued from treatment or has completed all study related therapies, a mandatory EOT Visit should be performed 30 days (± 7 days) after the last dose of any study medication (pembrolizumab or defactinib, or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first). An in-person visit is preferred, however, if the patient is unable to return for an EOT visit (e.g. disease/clinical progression, poor health, intercurrent illness, or initiation of a new anti-cancer therapy), or if the EOT visit occurs early, an assessment of adverse events should be made by telephone or telemedicine visit on day 30 (± 7) after the last study drug in place of the PE/PS/vitals. Clinical laboratory values should still be collected. Additionally, for those subjects who do not have scans within 6 weeks prior to EOT a repeat scan should be collected and an in-person EOT visit is recommended. Procedures and assessments performed at this visit should follow the respective guidelines described in **Section 6 and 7.5.3.1** as appropriate.

The patient will be monitored for adverse events up to the mandatory EOT Visit or to resolution of toxicity to Grade 0-1, whichever occurs later.

5.10 Duration of Follow Up

5.10.1 Safety Follow-up

Subjects who discontinue treatment should be contacted by telephone or email at 90 days (+ 14-day reporting window) from their last dose of study drug or within 7 days before initiation of a new antineoplastic treatment (whichever comes first) to assess for treatment related toxicities. Serious Adverse Events (SAEs) that occur within 90 days of the last infusion of pembrolizumab, administration of defactinib or before initiation of a new antineoplastic treatment should also be followed and recorded.

Subjects who are discontinued from the study treatment due to an unacceptable drug-related AE will be monitored for safety until the resolution of the AE to $\leqslant$ grade 1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first.

5.10.2 Survival Follow-up

Subjects who complete or discontinue from treatment will be contacted directly or their treating oncologist or designee (by phone, email, telemedicine, medical record search, or scheduled visit) per standard of care after completion of the EOT Visit for up to 2 years or study closure to monitor overall survival. Information of disease status, survival, other cancer therapies after discontinuation from the study treatment and adverse events will also be collected.

All subjects should continue to be monitored for disease status by radiologic imaging. Disease monitoring should continue to be assessed per standard of care until: 1) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) until death, 3) withdrawal of consent, or 4) study closure, whichever occurs first.

If serious adverse events in the survival follow-up phase (beyond 90 days from last study drug administration) are determined to be secondary to study drugs (pembrolizumab or defactinib), they will also be followed, reported, and recorded.

6.0 TRIAL FLOW SHEET

1) Consent - Study consent should be obtained prior to the initiation of any therapy for pancreatic cancer. Randomization will occur after consent and eligibility are verified. Eligibility determination, randomization and enrollment can occur up to 1 week after initiating SOC chemotherapy, as long as all screening procedures were completed prior to starting therapy.

2) Standard of Care Neoadjuvant chemotherapy - After consenting to the study and eligibility is verified, the subject will receive two, 28 day cycles of neoadjuvant

standard of care chemotherapy with gemcitabine and nab-paclitaxel. This phase will occur through local oncologist.

3) Pre-immunotherapy (after neoadjuvant chemotherapy) - within two weeks after the last dose of standard of care chemotherapy, the subject should receive a CT scan and EUS guided Core Biopsy. Before proceeding to next phase on study, eligibility criteria as outlined in **Section 2.1.3** must be satisfied.

4) Neoadjuvant Immunotherapy and FAK inhibition – The subject will begin neoadjuvant immunotherapy within three weeks of completing neoadjuvant chemotherapy and after EUS guided biopsy (within 1 week from biopsy). They will receive two, three-week cycles of immunotherapy with pembrolizumab and FAK inhibition with defactinib or pembrolizumab alone. FAK inhibition will continue up until 2 days prior to surgery (last dose 48 hours prior to surgery).

5) Surgical evaluation - After the last dose of neoadjuvant pembrolizumab the subject will be reassessed for surgical resection. If the subject is still deemed to be a surgical candidate, they will proceed to surgery outside of the study protocol. Surgical resection will occur between 10-25 days from the administration of second dose of immunotherapy. If patient does not receive second dose of immunotherapy in neoadjuvant setting, patient can still proceed to surgery on study after surgical evaluation, which can occur after end of first cycle of immunotherapy. At the time of surgery, if the subject is found to have unresectable disease intraoperatively, core biopsies will be performed intraoperatively for research purposes.

6) Standard of Care Adjuvant Chemotherapy – The subject may choose to receive this standard chemotherapy through a local oncologist. All follow-up visits, blood work, and interval surveillance scans during this portion of the study will be scheduled at the discretion of the subject's local oncologist. This portion of the study will be off protocol. Before proceeding to next phase on study, eligibility criteria as outlined in **Section 2.1.6**, must be satisfied.

7) Adjuvant Maintenance Immunotherapy and FAK inhibition – The subject will begin neoadjuvant immunotherapy within 6 weeks of completion of standard of care adjuvant chemotherapy. They will receive eight, three-week cycles of immunotherapy with pembrolizumab and FAK inhibition with defactinib or pembrolizumab alone.

8) End of Treatment (EOT) – A mandatory EOT Visit should be performed 30 days (± 7 days) after last dose of study drug (pembrolizumab or defactinib). An in-person visit is preferred, however, if the patient is unable to return for an EOT visit (e.g. disease/clinical progression, poor health, intercurrent illness, or initiation of a new anti-cancer therapy), or if the EOT visit occurs early, an assessment of adverse events should be made by telephone or telemedicine visit on day 30 (± 7) after the last study drug in place of the PE/PS/vitals. Clinical laboratory values should still be collected. Additionally, for those subjects who do not have scans within 6 weeks prior to EOT a repeat scan should be collected and an in-person EOT visit is

recommended. After the EOT visit, subjects or treating oncologists will be contacted (by phone, email, telemedicine, medical record search, or scheduled visit) oer standard of care to monitor OS until death, adverse events, disease status, withdrawal of consent, or study closure.

6.1 Screening, Standard of Care Neoadjuvant Chemotherapy/Pre Immunotherapy Phase Study Calendar

Procedure	Screening/ Baseline Procedures and Enrollment	Neoadjuvant SOC Chemotherapy	Post-SOC Neoadjuvant Chemotherapy/ Pre-immunotherapy Evaluation
Visit Window[1]	-21 to 1	-	21 days[2]
Standard Neoadjuvant Chemotherapy Gemcitabine/Nab-Paclitaxel		X[3]	
Inclusion/exclusion criteria	X		X[4]
Randomization and Enrollment	X[19]		
Demographics	X		
Medical History[5]	X		X[6]
Medications	X		X
Physical Exam[7]	X		X
Vital Signs and pulse ox[8]	X		X
Height[9]	X		
Weight	X		X
Performance Status	X		X
Hematology profile[10]	X		X
Complete Metabolic Profile[10]	X		X
TSH[11]			X
Serum/Urine Pregnancy[12]	X		X
CEA	X		X
CA 19-9	X		X
Total Bilirubin	X		
CT or MRI[14]	X		X
Pathology Review	X		
Whole blood for PBMC[15, 18]	X		
Whole blood for serum[15, 18]	X		
Whole blood for plasma[15, 18]	X		
EUS Core Biopsy[18]	X[16]		X[17]
Surgical Evaluation	X		

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for inperson clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

1: Longer delays to be approved by the IND sponsor.

2: This visit should occur within 21 days from C2D15 of chemotherapy with gemcitabine/nab-paclitaxel (cycle length 28 days). Ideally day +7-14 from last dose of chemotherapy.
3: Eligibility determination, enrollment and randomization can occur up to 1 week after initiating neoadjuvant chemotherapy as long as all screening procedures were completed before starting treatment. Longer delays will need will require notification of the IND sponsor and continuation on study will be at discretion of the IND sponsor.
4: Criteria defined in **Sections 5.1.3 and 5.1.4**.
5: Includes history of autoimmune disease, lung disease, HIV, hepatitis B or C infection, and complete cancer history, including primary site of cancer, gross location of primary tumor, histology, histologic grade, date of initial diagnosis, and prior cancer therapy regimens.
6: This can be a focused history, and should include ongoing symptoms from neoadjuvant chemotherapy.
7: Complete physical exam will be completed at baseline; focused physical examinations will be conducted thereafter. Exams, concomitant medication, AE assessments can be made up to 3 days prior to study visit.
8: Temperature, respiration rate, blood pressure, pulse, and pulse oximetry.
9: Height will be obtained at or prior to baseline only.
10: See **Table 5**.
11: Total T3 and FT4 to be checked reflexively if TSH is abnormal and clinically indicated.
12: For WOCBP: serum pregnancy test is required at screening; urine pregnancy tests are required thereafter. Pregnancy tests must be done within 7 days of the first treatment and then will be repeated with each subsequent therapy (collected within a window of up to 3 days prior to dosing).
13: Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, color, protein, RBC and WBC count, and specific gravity.
14: Radiologic evaluations (CT pancreas protocol, Chest, abdomen, and pelvis with contrast). Non-contrast CT Chest and MRI Abdomen/pelvis will be done for those with contrast allergies. Imaging will occur: 1. at time of diagnosis, 2. after the completion of neoadjuvant chemotherapy and prior to start of immunotherapy (window 21 days, from last dose of neoadjuvant SOC chemotherapy), and 3. following the last dose of neoadjuvant immunotherapy before surgical resection
15: See **Section 7.3.2** on correlative studies. These studies only apply after time of consent.
16: If a diagnostic biopsy has been already done prior to enrollment we will request the archival tissue. If no biopsy has been completed, we will obtain EUS diagnostic core biopsy.
17: EUS Guided biopsy (4-6 core biopsies) if amenable and safe to do so, will be obtained for research purposes and archival tissue collection for organoid culture. Biopsy will occur within 21 days from last dose of standard of care neoadjuvant chemotherapy.
18. Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff.
19. Eligibility determination, enrollment and randomization can occur up to 1 week after initiating neoadjuvant chemotherapy as long as all screening procedures were completed before starting treatment.

6.2 Neoadjuvant Immunotherapy Phase Study Calendar

Procedure	Cycle 1 Pembrolizumab ± Defactinib		Cycle 2 Pembrolizumab ± Defactinib		Post Immunotherapy/ Pre-surgical Evaluation[3]
	C1D1	C1D2-21	C2D1	C2D-21[17]	
Visit Window[1]	+21 Days[2]	-	+7 days	-	
Pembrolizumab	X[4]		X[5]		
Defactinib (Arm A Only)[18]	X	X	X	X[6]	X
Medications[7]	X		X		X
Physical Exam[7]	X		X		X
Vital Signs, pulse ox[8]	X		X		X
Weight	X		X		X
Performance Status	X		X		X
Hematology Profile[9]	X[10]		X[11]		X
Complete Metabolic Profile[9]	X[10]		X[11]		X
TSH[12]	X[10]		X[11]		X
Urine Pregnancy[13]	X[10]		X[11]		X
CEA	X[10]		X[11]		X
CA19-9	X[10]		X[11]		X
Phone Call				X[17]	
Adverse event evaluation[7]	X		X		X
CT or MRI[14]					X
Whole blood for PBMC[15, 19]	X				X
Whole blood for serum[15, 19]	X				X
Whole blood for plasma[15, 19]	X				X
Surgical Evaluation[16]					X

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for inperson clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

1: Longer delays to be approved by the IND sponsor.
2: C1D1 can occur on the same day following post SOC neoadjuvant chemotherapy visit, as long as imaging studies and EUS have also been completed prior to immunotherapy.
3: This visit will occur as close as possible to the second cycle of immunotherapy, however can occur any time prior to surgical resection.
4: The first cycle of pembrolizumab will begin within 21 days of C2D15 even if patient does not receive dose on D15. If delayed further, please see **Section 5.2.5.** Pembrolizumab can only be administered after imaging scans, EUS biopsy, and post-SOC neoadjuvant chemotherapy visit are complete.
5: The second cycle of pembrolizumab will begin within 7 days of completing the last cycle of pembrolizumab. If delayed further, please see **Section 5.2.5**.
6: Defactinib will continue up until 2 days prior to surgery (last dose given 48 hours prior to surgery) and surgery will occur 10-25 days from the administration of the second cycle of pembrolizumab. If second cycle of immunotherapy is not administered due to toxicity or other reasons, patient can proceed with surgical evaluation and be considered for surgery. If delayed further, please see **Section 5.2.5.**
7: Focused physical examination for Cycle 1 and 2. Complete physical exam during the pre-surgical evaluation. Exams, concomitant medication, AE assessments can be made up to 3 days prior to infusion.
8: Temperature, respiration rate, blood pressure, and pulse should be taken prior to and at the end of the pembrolizumab infusion. Pulse oximetry should be taken prior to each pembrolizumab infusion.
9: See **Table 5**.
10: If these labs were obtained at the post SOC neoadjuvant chemotherapy visit and are not >7 days old, they do NOT need to be repeated. If lab parameters are not met on earlier labs at post neoadjuvant chemotherapy visit they can be repeated on C1D1.
11: Labs may be collected within a window of up to 3 days prior to dosing. Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.
12: Total T3 and FT4 to be checked reflexively if TSH is abnormal and clinically indicated.
13: For WOCBP. Urine pregnancy tests must be done within 7 days of the first treatment and then will be repeated with each subsequent therapy (collected within a window of up to 3 days prior to dosing).
14: Radiologic evaluations (CT pancreas protocol, Chest, abdomen, and pelvis with contrast). Non-contrast CT Chest and MRI Abdomen/pelvis will be done for those with contrast allergies. Imaging will occur: 1. at time of diagnosis, 2. after the completion of neoadjuvant chemotherapy and prior to start of immunotherapy (window + 14 days, from completion of neoadjuvant chemotherapy) and 3. following the last dose of neoadjuvant immunotherapy and before surgical resection (i or after cycle 1 of immunotherapy and before surgical evaluation for those patients who do not receive second dose of immunotherapy) If surgical evaluation is <4 weeks from last scan, it does not need to be repeated.
15: See **Section 7.3.2** on correlative studies. These research studies can be obtained earlier +/- 7 days from C1D1, but should ideally be obtained on C1D1. Prior to surgery, these labs can be obtained +/-14 days from day of surgery, but ideally should be obtained at preoperative visit regardless of receiving one or two cycles of neoadjuvant immunotherapy.
16: An option surgical initial planning visit as part of standard of care may occur at any point during immunotherapy treatment and after chemotherapy, at discretion of surgical team.
17: Subjects are planned to receive 21 days of defactinib. However, administration of defactinib can be prolonged until 23 days or discontinued prior to 21 days depending on planned date

of surgery. Defactinib will continue up until 2 days prior to surgery (last dose given 48 hours prior to surgery). Study team will notify patient when to stop drug.

18: Defactinib should be administered within 30 minutes of a meal.

19. Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff.

6.3 Surgery, Standard of Care Adjuvant Chemotherapy Phase Study Calendar

Procedure	Surgery[1]	Adjuvant chemotherapy	Post Standard of Care Adjuvant Chemotherapy/Pre-Maintenance Immunotherapy Evaluation
Visit Window	-	-	X[2]
SOC Chemotherapy		X	
Medications			X
Inclusion/Exclusion Criteria			X[3]
Complete Physical Exam			X
Vital Signs and pulse ox[4]			X
Weight			X
Performance Status			X
Hematology profile[5,6]			X
Complete Metabolic Profile[5,6]			X
TSH[6,7]			X
Urine Pregnancy[8]			X
CEA[6]			X
CA19-9[6]			X
Surgical Tumor Specimen[12, 13]	X		
Pathology Review			X
Adverse Event Evaluation	X[9]	X[9]	X[9]
CT or MRI[10]			X
Whole blood for PBMC[11, 13]			X
Whole blood for serum[11, 13]			X
Whole blood for plasma[11, 13]			X

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for inperson clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

1: Surgery will be scheduled within 10-25 days from the second dose of neoadjuvant pembrolizumab.
2: Post Standard of Care Adjuvant Chemotherapy/Pre-Maintenance Immunotherapy evaluation should occur within 6 weeks from completion of standard of care adjuvant chemotherapy or after final administered dose of adjuvant therapy. This visit can coincide with the first dose in the maintenance immunotherapy phase (C3D1).
3: Criteria defined in **Sections 5.1.5 and 5.1.6**.
4: Temperature, respiration rate, blood pressure, pulse, and pulse oximetry.
5: See **Table 5**.
6: Labs may be collected within a window of up to 3 days prior to dosing. Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.
7: Total T3 and FT4 to be checked reflexively if TSH is abnormal and clinically indicated.
8: For WOCBP. Urine pregnancy tests must be done within 7 days of the first treatment and then will be repeated with each subsequent therapy (collected within a window of up to 3 days prior to dosing).
9: Collection of pembrolizumab and defactinib related toxicities. See **Section 7.6.5 and 8.2.1** for the surgical toxicities that will be collected.
10: CT Chest, abdomen, pelvis with pancreas protocol with contrast or Non-contrast CT chest and MRI Abd, pelvis for those with contrast allergies. CT at the start of immunotherapy in the adjuvant phase will need to occur before start of C1 of pembrolizumab. This should occur at the end of adjuvant SOC chemotherapy and prior to the first cycle of pembrolizumab (6 week window) but as close as possible to administration of first dose of immunotherapy in the maintenance phase (cycle 3).
11: See section on correlative studies, **Section 7.3.2.** If research bloods are collected at the Post SOC Adjuvant Chemotherapy/Pre-Maintenance Immunotherapy Evaluation they do not need to be collected again at C3D1.
12. If patient is a surgical candidate, resected specimen will be obtained intraoperatively for research. If patient is noted to have metastases at the time of surgery, a research biopsy will be performed. If it is determined at the pre-surgical evaluation that the patient is not a candidate for surgery, a research biopsy will be performed via EUS if safe and amenable to do so.
13. Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff.

6.4 Maintenance Immunotherapy Phase Study Calendar

Procedure	Combination immunotherapy[1] on 3-week cycles																EOT[2]	90 Day Safety FU Visit
	Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9		Cycle 10			+14
	D1	D 2-21	D1	D 2-21	D1	D 2-21	D1	D 2-21	D1	D 2-21	D1	D 2-21	D1	D 2-21	D1	D 2-21		
Visit Window	+7[3]		+7		+7		+7		+7		+7		+7		+7		X[2]	
SOC Chemotherapy																		
Defactinib (Arm A) Only[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab	X		X		X		X		X		X		X		X			
Medications	X		X		X		X		X		X		X		X		X	
Focused Physical Exam	X		X		X		X		X		X		X		X		X	
Vital Signs, pulse ox[4]	X		X		X		X		X		X		X		X		X	
Weight	X		X		X		X		X		X		X		X		X	
Performance Status	X		X		X		X		X		X		X		X		X	
Hematology profile[5,6]	X[7]		X		X		X		X		X		X		X		X	
Complete Metabolic Profile[5,6]	X[7]		X		X		X		X		X		X		X		X	
TSH[6,8]	X[7]		X		X		X		X		X		X		X		X	
Urine Pregnancy[6,9]	X[7]		X		X		X		X		X		X		X			
CEA[6]	X[7]		X		X		X		X		X		X		X		X	
CA19-9[6]	X[7]		X		X		X		X		X		X		X		X	
Adverse Event Eval	X		X		X		X		X		X		X		X		X	X
CT or MRI[10]	X						X								X		X	
Whole blood for PBMC[11, 13]	X						X								X		X	
Whole blood for serum[11, 13]	X						X								X		X	
Whole blood for plasma[11, 13]	X						X								X		X	

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for inperson clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

1: Subjects will receive combination immunotherapy and defactinib or pembrolizumab alone on a 21-day cycle. Each subsequent cycle of pembrolizumab should start within 7 days after the completion of the last cycle on a 21-day cycle with visit (window + 7 days) occurring prior to administration of pembrolizumab. If delayed further, please see **Section 5.2.5**. Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.
2: End of Treatment (EOT) Evaluation: 30 days (±7 days) after their last dose of study drug or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first. An in-person visit is preferred, however, if the patient is unable to return for an EOT visit (e.g. disease/clinical progression, poor health, intercurrent illness, or initiation of a new anti-cancer therapy), or if the EOT visit occurs early, an assessment of adverse events should be made by telephone or telemedicine visit on day 30 (± 7) after the last study drug in place of the PE/PS/vitals. Clinical laboratory values should still be collected. Additionally, for those subjects who do not have scans within 6 weeks prior to EOT a repeat scan should be collected and an in-person EOT visit is recommended. The EOT scan and research labs do not need to be repeated if they occurred within 6 weeks of the EOT evaluation. Patients who discontinue from treatment should be contacted (by phone, email, telemedicine, medical record search, or scheduled visit) per standard of care for up to 24 months or study closure to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected.
3: Patients must have eligibility reconfirmed prior to initiation of Cycle 3 of adjuvant immunotherapy (Please see **Sections 5.1.1, 5.1.2 and 2.1.6** for criteria). Cycle 3 of adjuvant immunotherapy should begin within 6 weeks from completion of standard of care adjuvant chemotherapy. Further dosing of study medications will be based on visits prior to each adjuvant immunotherapy cycle. This visit can coincide with the post-surgery/SOC adjuvant chemotherapy visit.
4: Temperature, respiration rate, blood pressure, and pulse should be taken prior to and at the end of the pembrolizumab infusion. Pulse oximetry should be taken prior to each pembrolizumab infusion.
5: See **Table 5**.
6: Labs may be collected within a window of up to 3 days prior to dosing. Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.
7: If these labs were obtained at the post-surgery/SOC adjuvant chemotherapy visit and are not >7 days old, they do NOT need to be repeated.
8: Total T3 and FT4 to be checked reflexively if TSH is abnormal and clinically indicated.

9: For WOCBP. Urine pregnancy tests must be done within 7 days of the first treatment and then will be repeated with each subsequent therapy (collected within a window of up to 3 days prior to dosing).
10: CT Chest, abdomen, pelvis with pancreas protocol with contrast or non-contrast CT chest and MRI Abd, pelvis for those with contrast allergies. Imaging at the start of immunotherapy in the adjuvant phase will need to occur before start of C1 of pembrolizumab. The first scan in the immunotherapy maintenance phase can occur at the post-surgery/SOC adjuvant chemotherapy visit. Subsequent scans will approximately on C6D1 and C10D1, with a window of -14 day window.
11: Research blood should coincide with imaging studies, and are to occur on C3D1, C6D1 and C10D1, with a window of -14 day window. See section on correlative studies, **Section 7.3.2.**
12: Defactinib should be administered within 30 minutes of a meal.
13. Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff.

7.0 TRIAL PROCEDURES

The Trial Flow Chart - **Section 6.0** summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. 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 IND Sponsor and/or Merck/Verastem for reasons related to participant 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 participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1 Administrative Procedures

7.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial.

7.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant'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 participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

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

7.1.2 Inclusion/Exclusion Criteria

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

7.1.3 Registration Guidelines and Procedures

Eligible patients will be entered on study centrally at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University by the Coordinating Center. All sites should email GITrialRegistration@jhmi.edu to verify ongoing study enrollment status. The Registration Form and Eligibility Checklist will be supplied to each participating site.

If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

To register a patient, the following de-identified documents should be completed by the Research Nurse or Study Coordinator at the participating site and e-mailed to GITrialRegistration@jhmi.edu:

- Fax cover sheet
- Registration Form
- Signed patient consent form
- HIPAA authorization form
- Eligibility Screening Checklist
- Copy of required screening tests and scans

The Research Nurse or Study Coordinator at the participating site will then e-mail GITrialRegistration@jhmi.edu to verify eligibility. To complete the registration process, the Coordinating Center at JHU will:

- Assign a patient study number
- Register the patient on the study
- Fax or e-mail the patient study number to the participating site
- Call or e-mail the research nurse or data manager at the participating site and verbally confirm registration.

7.1.4 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 subjects PDAC, for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

7.1.5 Prior and Concomitant Medications Review

7.1.5.1 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 participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in **Section 7.6**.

7.1.6 Disease Details and Treatments

7.1.6.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding subjects PDAC.

7.1.6.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.6.3 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 participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

7.1.7 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in **Section 7.6.1**.

7.1.8 Assignment of Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.9 Trial Compliance (Medication/Diet/Activity/Other)

Interruptions from the protocol specified treatment for greater than 4 weeks between study treatment of pembrolizumab for non-drug-related or administrative reasons require consultation between the investigator and the IND Sponsor and written documentation of the collaborative decision on subject management. Interruptions from the protocol specified treatment for greater than 2 weeks between study treatment pembrolizumab for non-drug-related or administrative reasons require consultation between the investigator and the IND Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medications will be witnessed by the investigator and/or trial staff when administered in the outpatient setting.

7.2 Clinical Procedures/Assessments

7.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.
Please refer to **Section 7.6** for detailed information regarding the assessment and recording of AEs.

7.2.2 Complete 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. Additional complete physical exams should be performed as specified in the Trial Flow Chart – **Section 6.0**. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

7.2.3 Focused Physical Exam

For cycles that do not require a complete physical exam per the Trial Flow Chart – **Section 6.0**, the investigator or qualified designee will perform a focused physical exam as clinically indicated prior to dosing ±3 days of Day 1 of each treatment cycle. New clinically significant abnormal findings should be recorded as AEs.

7.2.4 Vital Signs and Pulse Oximetry

The investigator or qualified designee will take vital signs and pulse oximetry at screening, prior to and after the administration of each dose of pembrolizumab, and at treatment discontinuation as specified in the Trial Flow Chart (**Section 6.0**). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured prior to or at screening only. New clinically significant abnormal findings should be recorded as AEs.

7.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (**Appendix 1**) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.2.6 Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT) using JHH pancreatic protocol. For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

7.2.6.1 Tumor Imaging During the Study

The first on-study imaging assessment should be performed within ±4 weeks from the date of randomization. Subsequent tumor imaging should be performed every 8 weeks (56 days ±14 days) in the neoadjuvant setting or more frequently if clinically indicated. In the adjuvant setting imaging will occur prior to immunotherapy or C3D1, C6D1 and C10D1/EOT Visit with window of - 14 day. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until progression indicating unresectability of disease in the neoadjuvant phase, recurrence in the adjuvant phase or metastatic disease at any point in the study is identified by the Investigator.

7.2.6.2 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study treatment for any reason, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 6 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory.

In participants who discontinue study treatment without documented disease progression, recurrence or metastatic disease, every effort should be made to continue monitoring their disease status by tumor imaging per standard of care to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

7.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

7.3.1 Basic Laboratory Testing

Laboratory tests for hematology, chemistry, and others are specified in **Table 5**.

Table 5: Laboratory Tests

Hematology	Chemistry	Other
Hematocrit	Albumin	Serum β-human chorionic gonadotropin†; (β-hCG)
Platelet count	Alanine aminotransferase (ALT)	Urine pregnancy test †
WBC (total and differential)	Aspartate aminotransferase (AST)	Total thriiodothyronine (T3)
Red Blood Cell Count	Carbon Dioxide ‡	Free thyroxine (T4)
Absolute Neutrophil Count	*(CO_2 or biocarbonate)*	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Calcium	CEA
	Chloride	CA 19-9
	Glucose	
	Potassium	
	Sodium	
	Total Bilirubin	
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*	
	Total protein	
	Blood Urea Nitrogen	

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Serum pregnancy test required at time of intitial enrollment, urine pregnancy test acceptable subsequently.

‡ If considered standard of care in your region.

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of trial treatment. New clinically significant abnormal findings should be recorded as AEs. Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.

7.3.2 Tumor Tissue Collection and Correlative Studies

7.3.2.1 Tissue Studies

Four to six core tumor biopsies will be collected during scheduled endoscopies (at diagnosis (baseline) and after neoadjuvant chemotherapy [part 2 of study]). Archival tumor samples will also be collected for every subject (10 slides and/or blocks). Detailed instructions for tissue collection, processing, and shipment are provided in the Laboratory Manual.

The tissue samples will be banked for the evaluation of CD8+ T Cell effectors, MHC 1 expression, PD-L1 expression on tumor and PD-L1 on tumor-infiltrating immune cells, and their associated immune suppressive pathways and other immune activation pathways to assess the effect of treatment upon the tumor microenvironment and the correlations between these immune parameters and clinical response. Immunohistochemistry, flow cytometry, quantitative PCR assays and microarray analysis will be employed. Peripheral Blood Lymphocytes (PBL) and tumor infiltrating lymphocytes (TIL), either directly from FFPE tumor sections or following isolation from fresh surgical tumor specimen, will be used for the TCR repertoire analysis by next-generation sequencing.

7.3.2.2 Translational Immune Biology Analysis

Peripheral blood mononuclear cells (PBMC), plasma, and serum will be collected before and after chemotherapy, each cycle of immunotherapy and surgery at participating sites. Whole blood for PBMCs (up to 100cc) will be collected at the specified timepoints (See **Section 6.0**). Detailed instructions for blood collection, processing, and storage are provided in the Laboratory Manual. Peripheral MDSCs will also be assessed before and after study treatments. Resected tumor specimens will be archived for research purpose. Tumor infiltrating immune cells will be isolated from resected PDACs. Biopsy and surgical resected biospecimens will be archived for tumor/stroma DNA/RNA sequencing. Tumor infiltrating immune cells will be isolated from resected tumors, phenotypically analyzed and also sorted to immune subpopulations including CD4, CD8, CD4+, CD25+, B cells, myeloid cells for RNA sequencing. All biospecimens will be subjected to multiplex immunostaining analysis and nanostring PCR analysis.

- TAM, MDSC, and Treg will be particularly analyzed through multiplex IHC based methods. In addition, M1 vs. M2, Th1, Th2, Th17, vs. Treg, immune checkpoint pathways, T effector, memory, and activation markers will be analyzed by multiplex

IHC. The role of FAK inhibitor on the change of immune suppressive cells and immune effector cells will be assessed.

- Chemokine/cytokines and their receptors will be analyzed by RNA sequencing and nanostring PCR.
- Tumor signaling, immune signaling and stroma signaling pathways will be analyzed through RNA sequencing and nanostring PCR. In particular, dissected stroma will be analyzed for the FAK signaling pathways and TCR clonality.
- Genetic alterations in the tumor will also be analyzed. Immune response or change in immune parameters will be correlated to the subtypes of PDACs as defined by genetic alterations and transcriptome.
- Stromal fibroblast density, activity (SMA expression) and FAP expression will be assessed by immunohistochemistry.
- Immunogenic cell death markers (calreticulin) and signaling pathways will be assessed in the post-chemo and pre-immunotherapy biopsy specimens through immunohistochemistry and nanostring PCR analysis.
- TCR clonality analysis will be assessed in the pre-immunotherapy biopsy specimens and post-immunotherapy resected tumor specimens, pre- and post-immunotherapy peripheral blood.
- Plasma will be collected for ctDNA analysis; serum will be collected for serum proteomic analysis for predictive biomakers
- Microsatellite instability (MSI), a form of genomic instability, occurs through the insertion or deletion of repeating nucleotides during DNA replication and failure of the mismatch repair system to correct errors in nucleotide repeat markers. This can confer tumor responses to anti-PD1 therapy. All MSI testing will be performed retrospectively for mismatch repair deficiency (MRD) or MSI using IHC, PCR, or next generation sequencing (NGS) in all study subjects. MMRd or MSI status is determined by examining either 1) protein expression by IHC of 4 MMR enzymes (MLH1/MSH2/MSH6/PMS2) or 2) 3-5 tumor microsatellite loci using PCR-based assay, respectively.

Genomic sequencing library construction, whole genome/exome sequencing, whole transcriptome sequencing, T cell receptor and B cell receptor sequencing, neoepitope prediction, mutation burden, CITE-seq, ChIP-seq, ATAC-seq, and MBD-seq, and bioinformatic analysis will be performed either at an on-campus laboratory or at an off-campus sequencing service. These assays will allow us to explore the effects of therapy on tumor and tumor infiltrating immune cells.

All the samples will be de-identified before sending to any laboratory for sequencing. The FASTQ files, BAM files and VCF files will be generated and analyzed. Genomic sequencing data will be stored and computations conducted using a JH IT managed subscription of Azure.

Results from the sequencing studies will not be released to the patients. These studies are for research purposes only and are not using a clinically validated platform.

7.3.2.3 Serum and Plasma Marker Studies

Sera (up to 10 cc in neoadjuvant setting and 5cc in the adjuvant setting) and plasma (up to 10cc) will be collected at the specified time points (**Section 6**) detailed in the study schedule to identify potential therapeutic targets, biomarkers, and predictors of response and autoimmune toxicity. Detailed instructions for blood collection, processing, and shipment are provided in the Laboratory Manual.

7.3.2.4 Diagnostic Tissues Samples

Tissue, fluid, or blood may be collected from standard of care procedures used to treat or diagnoses immune related toxicities.

7.3.2.5 Tumor Modeling for Molecular Characterization

Tissue collected at the time of diagnostic biopsy, 2nd research biopsy and surgical specimen will also be utilized to create organoid models of each subject's tumor. For the purposes of this work, one to three core needed biopsies of the tumor will be obtained during endoscopy. This tissue cores will be transported to the laboratory and used to generate organoid culture models of each subject's tumor. In this manner, each tumor's organoid model may then be utilized for gene mutation, gene expression and immune biology analysis as in **Section 7.3.2.2-7.3.2.4**. For further details, please refer to the laboratory analysis.

7.4 Other Procedures

7.4.1 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial 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 7.6** - Assessing and Recording Adverse Events.

7.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.5 Visit Requirements

Visit requirements are outlined in **Section 6.0** - Trial Flow Chart. Specific procedure-related details are provided above in **Section 7.0** - Trial Procedures.

7.5.1 Screening

Approximately 14 days prior to treatment randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in **Section 5.1**. Screening procedures may be repeated after consultation with the IND Sponsor.

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. CA19-9 level will be determined for eligibility at the time of diagnosis.

- Laboratory tests and ECOG performance status are to be performed within 14 days prior to randomization.
- Baseline scan is to be performed within 21 days prior to randomization.
- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met. Subjects may not rescreen more than 1 time without consulting with the IND Sponsor. Subjects who are rescreened will retain their original screening number.

7.5.2. Treatment Period

Visit requirements are outlined in the Trial Flow Chart (**Section 6.0**). Specific procedure-related details are provided above in the Trial Procedures (**Section 7.0**)

7.5.3 Post-Treatment Follow-up Visits

7.5.3.1 End of Treatment (EOT) Visit

The mandatory EOT Visit should be conducted 30 days (± 7 days) after the last dose of study treatment (pembrolizumab or defactinib) or within 7 days before the initiation of a new anti-cancer treatment, whichever comes first. Procedures and assessments performed at this visit should follow the respective guidelines described in **Sections 5.9 and 6.4**.

7.5.3.2 Safety Follow-up Visit

See **Section 5.10.1**.

7.5.3.3 Survival Follow-up

See **Section 5.10.2**.

7.6 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant 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 pre-existing condition that is temporally associated with the use of the study treatments, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events.

Study treatments include any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck or Verastem for human use.

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

- All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the event caused the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.
- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
    - Chemotherapy is considered standard of care (SOC). Patients will be considered off investigational therapy/ies during neoadjuvant chemotherapy. Patients will also be off investigational therapy/ies during adjuvant chemotherapy. Only AEs and SAEs related to pembrolizumab or defactinib that occur during this off treatment period will be recorded and reported.
    - Surgery is also considered SOC. Adverse events will be reviewed to ensure that pembrolizumab and defactinib are not contributing to postoperative complications. **Section 7.6.5** outlines which surgical complications will be recorded as adverse events. Adverse events and serious adverse events related to either pembrolizumab or defactinib will also be recorded and reported.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following

cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

- Events of clinical interest as defined in **Section 7.6.3.2**.
- All pregnancies and exposure during breastfeeding, that occur from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator. All pregnancies will be followed through pregnancy completion or termination.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck and Verastem.

7.6.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the IND Sponsor, Merck, and Verastem

Pembrolizumab:

For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 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, pembrolizumab should be stopped and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other serious criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect" on the ECI Reporting Form (**Appendix 5**) to the IND Sponsor (e-mail: lzheng6@jhmi.edu **and** GIsafetyreporting@jhmi.edu) within 24 hours and to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-661-6229) within 2 business days.

All reports of overdose with an adverse event must be reported using the SAE Reporting Form (**Appendix 6**) to the IND Sponsor (e-mail: lzheng6@jhmi.edu **and** GIsafetyreporting@jhmi.edu) within 24 hours and to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-661-6229) within 2 business days.

Defactinib:

For purposes of this study, if the subject was given (accidentally or intentionally) a dose of 1600 mg or greater ($\geqslant$4 times the indicated dose) of defactinib, it is considered an overdose. No specific information is available on the treatment of overdose of defactinib. In the event of overdose, defactinib should be stopped and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse experience(s) is associated with ("results from") the overdose of test drug, the adverse experience(s) is reported as a serious adverse experience, even if no other serious criteria are met.

If a dose of defactinib meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect" on the ECI Reporting Form (**Appendix 5**) within 24 hours to the IND Sponsor (e-mail: lzheng6@jhmi.edu **and** GIsafetyreporting@jhmi.edu) and Verastem local safety representative (drugsafety@verastem.com or faxed to +1 781 465 7936).

All reports of overdose with an adverse experience must be reported using the SAE Reporting Form (**Appendix 6**) within 24 hours to the IND Sponsor (e-mail: lzheng6@jhmi.edu **and** GIsafetyreporting@jhmi.edu) and Verastem local safety representative (drugsafety@verastem.com or faxed to +1 781 465 7936).

7.6.2 Reporting of Pregnancy and Lactation to the IND Sponsor, Merck, and Verastem

Although pregnancy and infant exposure during breast feeding are not considered adverse events unless there is cause to believe that the investigational product may have interfered with the effectiveness of a contraceptive medication or if the outcome of the pregnancy meets serious criteria, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.
Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant 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 infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of the investigational product, or 30 days following cessation of treatment if the participant 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 adverse events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported using the SAE Reporting Form (**Appendix 6**) within 24 hours to the IND Sponsor (e-mail: lzheng6@jhmi.edu **and** GIsafetyreporting@jhmi.edu), Verastem (drugsafety@verastem.com or faxed to +1 781 465 7936), and to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-661-6229) within 2 business days.

7.6.3 Immediate Reporting of Adverse Events to the IND Sponsor, Merck, and Verastem

7.6.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of study product that:

- Results in death;
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization $\geqslant$ 24 hours (see note below for exceptions);
- Is a congenital anomaly/birth defect;
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.);

- **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 IND Sponsor, Verastem, and Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the IND Sponsor, Verastem, and Merck for collection purposes:

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose
- Is a pregnancy or pregnancy outcome of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, or stillbirth.

Events **not** considered to be SAEs are hospitalizations for:

- Visits to the emergency room or other hospital department for <24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

Refer to **Table 6** 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 that occurs to any participant must be reported within 24 hours to the IND Sponsor and Verastem, and within 2 business days to Merck Global Safety if it causes the participant 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 participant 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 whether or not related to the study product, must be reported to the IND Sponsor and Verastem within 24 hours, and to Merck Global Safety within 2 business days.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to study product 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 IND Sponsor, Verastem, and Merck Global Safety.

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

SAE reports and any other relevant safety information are to be forwarded to the IND Sponsor (lzheng6@jhmi.edu), GIsafetyreporting@jhmi.edu, Merck Global Safety (facsimile number: +1-215-661-6229) and to Verastem (email address: drugsafety@verastem.com or faxed to +1-781 465 7936) using the SAE Reporting Form found in Appendix 6.

Investigators will submit a copy of any Expedited Safety Reports submitted to the FDA (**Section 7.6.5.3.1**) to Verastem (email: drugsafety@verastem.com) and Merck (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

7.6.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the IND Sponsor (lzheng6@jhmi.edu), GIsafetyreporting@jhmi.edu, and Verastem (email: or faxed to +1 781 465 7936) within 24 hours, and to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-661-6229) within 2 business days using the ECI Reporting Form in **Appendix 5.**

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 participant must be reported to the IND Sponsor and Verastem within 24 hours and to Merck Global Safety within 2 business days if it causes the participant 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 participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the IND sponsor and Verastem, and to Merck Global Safety within 2 business days.

Events of clinical interest for this trial include:

1. an overdose of Verastem or Merck product, as defined in **Section 7.6.1**, 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.

7.6.3.3 Unacceptable Toxicities

Any event meeting unacceptable toxicity criteria as defined in **Section 5.7** should be reported via email to the IND Sponsor (lzheng6@jhmi.edu) and GIsafetyreporting@jhmi.edu within 24 hours.

7.6.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. 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.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

The relationship of an AE to the administration of the study drug is to be assessed by the investigator according to the following definitions:

- No (unrelated, not related, no relation): The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

- Yes (related): The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The expectedness of an AE is to be assessed by the investigator according to the following definitions:

- Unexpected AE: An AE, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the product IB, package insert or safety reports. Any AE that is not included in the IB, package insert, safety reports or informed consent is considered “unexpected”.

- Expected (known) AE: An AE, which has been reported in the IB, package insert or safety reports. An AE is considered “expected”, only if it is included in the IB document in the Reference Safety Information.

Table 6: Evaluating Adverse Events

An investigator, who is a qualified physician, will evaluate all adverse events against CTCAE if no adverse event grading is assigned:

V5.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck or Verastem product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the IND Sponsor and Verastem within 24 hours and to Merck within 2 business days; **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the IND Sponsor and Verastem and to Merck within 2 businesss days.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Verastem or Merck product to be discontinued?	
Relationship to Merck or Verastem Product	Did the Merck or Verastem product cause the adverse event? The determination of the likelihood that Merck or Verastem product 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 test drug and the adverse event based upon the available information.	

	The following components are to be used to assess the relationship between Merck or Verastem product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck or Verastem product caused the adverse event (AE):	
	Exposure	Is there evidence that the participant was actually exposed to Merck or Verastem product 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 Merck or Verastem product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	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

Relationship to Merck or Verastem Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck or Verastem product 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 investigational product; or (3) the trial is a single-dose drug trial); or (4) investigational product(s) is/are only used one time.)
	Rechallenge	Was the participant re-exposed to Merck or Verastem product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Investigational product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK OR VERASTEM PRODUCT, OR IF REEXPOSURE TO MERCK OR VERASTEM PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE IND SPONSOR, MERCK, AND VERASTEM.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck or Verastem product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**	
Yes, there is a reasonable possibility of Merck or Verastem product relationship.	There is evidence of exposure to Merck or Verastem product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.	
No, there is not a reasonable possibility of Merck or Verastem product relationship	Participant did not receive the Merck or Verastem product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)	

7.6.5 Special considerations for adverse events that occur during the surgery and postoperative course

Pancreatic surgery is one of the highest-risk procedures, requires prolonged hospitalization, has significant toxicities and is commonly associated with complications and comorbidities. It is deemed to be standard of care, therefore, is not part of this research study. From the day of surgery through day 0 of the third immunotherapy, participants will be primarily followed by their primary surgeons for monitoring and managing the complications and comorbidities attributable to the surgery. **Table 7** summarizes complications commonly associated with the pancreatic surgery based on several published analyses of more than 1000 patients at Johns Hopkins Medicine and other institutions.[6]> A normal, uncomplicated postoperative course is still commonly associated with laboratory abnormalities (grade 1/2 AEs and occasionally grade 3 AEs) without need of therapeutic interventions. At least one complication was associated with 58.5% of patients based on a recent analysis of a consecutive series of 633 patients undergoing pancreaticoduodenectomy at Johns Hopkins Medicine between February 2003 and August 2005. Grade I, II, III complications were common, in 10%, 30%, 13.5% of the patients, respectively. These complications and comorbidities are commonly associated with toxicities and laboratory abnormalities of CTCAE grade 3 and even grade 4. By contrast, Grade IV and V complications are relatively uncommon, in 3.0% and 2.0% of the patients, respectively (**Table 8**).

Table 7: Complications after Pancreaticoduodenectomy

Anastomotic leak, pancreas	Anastomotic leak, intestinal
Wound infection	Gastrointestinal bleeding
Delayed gastric emptying	Pleural effusion
Hemorrhage, immediate postoperative or delayed	Pneumonitis
Intraabdominal abscess	Sepsis
Fascial dehiscence or evisceration	Acute respiratory distress syndrome
Supraventricular arrhythmia	Angina, cardiac ischemia
Urinary tract infection	Aspiration
Anastomotic leak, biliary	Cardiopulmonary arrest
Pancreatitis	Catheter-related infection
Hypotension, shock	Constipation
Cellulitis	Delirium tremens
Clostridium difficile colitis	Fever
Congestive heart failure, left ventricular dysfunction	Fluid imbalance
Myocardial infarction	Gastroesophageal reflux disease
Renal failure	Congestive heart failure
Apnea or hypoxia	Ileus
Atelectasis	Interstitial pneumonitis and fibrosis
Catheter-related infection	Prolonged intubation
Deep venous thrombosis	Salivary gland infection
Dehydration	Small bowel obstruction

Table 8: Classification of Surgical Complication Adopted for Pancreatic Surgery

Grade	Definition
I	Any deviation from the normal postoperative course without pharmacologic treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacologic treatment with drugs other than ones allowed for grade I complications. Blood transfusion and total parenteral nutrition* are also included.
III	Requiring surgical, endoscopic, or radiologic intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications)† requiring IC/ICU management
IVa	Single-organ dysfunction (including dialysis)
IVb	Multiorgan dysfunction
V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of the discharge, the suffix "d" (for disability) is added to the respective grade of complication (including resection of the pancreatic remnant). This label indicates the need for a follow-up to fully evaluate the complication.

*Note regarding DGE: The insertion of a central line for TPN or nasojejunal tube by endoscopy is a grade IIIa. However, if a central line is still in place or a feeding tube has been inserted at the time of surgery, then a TPN or enteral nutrition is a grade II complication.

†Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks.

CNS indicates central nervous system; IC, intermediate care; ICU, intensive care unit.

Pancreatic surgery is commonly associated with laboratory abnormalities in blood cell counts, serum electrolytes, liver function, and renal function, etc., with a range of severity from grade 1 to grade 4 by CTCAEv3.0 criteria. Grade I-III complications are common; therefore, laboratory abnormalities associated with a normal postoperative course or Grade I-III complications are considered to be within the commonly expected range of grades of severity (**Table 9**). Laboratory abnormalities beyond these commonly expected ranges of severity should be considered uncommon. Although Grade IV and V complications have still occurred, any SAE including laboratory abnormalities associated with Grade IV/V complications should be considered uncommon.

Table 9: Laboratory abnormalities commonly associated with pancreatic surgery

Lab test Abnormality	Ranges of severity by CTCAEv3.0 criteria	
Amylase	Elevated	Grade 1-4
Lipase	Elevated	Grade 1-4
Bilirubin	Elevated	Grade 1-4
AST	Elevated	Grade 1-4
ALT	Elevated	Grade 1-4
Albumin	Decreased	Grade 1-3
Glucose	Elevated	Grade 1-4
Glucose	Decreased	Grade 1-4
Alk Phosphatase	Elevated	Grade 1-4
Creatinine	Elevated	Grade 1-3
Glomerular filtration rate	Decreased	Grade 1-3
Bicarbonate	Decreased	Grade 1-4
Acidosis	Elevated	Grade 1-4
Alkylosis	Elevated	Grade 1-4
CPK	Elevated	Grade 1-4
WBC	Elevated	Not graded by CTCAE
Hemoglobin	Decreased	Grade 1-3
Platelets	Elevated	Not graded by CTCAE
Platelets	Decreased	Grade 1-3
Sodium	Elevated	Grade 1-3
Sodium	Decreased	Grade 1-3
Potassium	Elevated	Grade 1-3
Potassium	Decreased	Grade 1-3
Magnesium	Elevated	Grade 1-3
Magnesium	Decreased	Grade 1-3
Phosphate	Elevated	Grade 1-3
Phosphate	Decreased	Grade 1-4
Calcium	Elevated	Grade 1-3
Calcium	Decreased	Grade 1-4

Therefore during this period, first, the study will be focused on monitoring and reporting the complications with uncommon grades of severity such as Grade IV and Grade V complications by criteria used at Johns Hopkins (**Table 8**). The severity of any SAEs associated with such grades of complications should be considered uncommon. Second, any unusual complications not seen commonly with this operation will be reported. Third, the study will also be focused on monitoring and reporting any laboratory abnormality beyond the common ranges of severity (**Table 9**). Fourth, the study will also be focused on monitoring and reporting any type of toxicity not commonly attributable to the surgery or postoperative course. These events will be recorded as described in **Section 7.6** and their severities will still be categorized by NCI CTCAEv5.0 criteria. Relationship of these events to the investigational drug will be determined by the principal investigator together

with surgical co-investigators of the study team and, if necessary, with primary surgeons, and will be categorized as described in **Section 7.6.4**. Reporting of these events will follow the same guidelines described in **Sections 7.6** and **7.6.6**.

7.6.6 IND Sponsor Responsibility for Reporting Adverse Events

All serious adverse events that meet immediate reporting criteria will be reported by the IND Sponsor to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, and sent to both Verastem and Merck.

7.6.6.1 Handling of Expedited Safety Reports

In accordance with local regulations, the IND Sponsor (or designee), Verastem, and Merck will notify investigators of all SAEs that are unexpected (i.e., not previously described in the IB), and related to pembrolizumab or defactinib. An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an Investigator Safety Letter that is to be e-mailed to the principal investigator and designee as requested. Upon receiving such notices, the investigator must review and retain the notice with the IB and where required by local regulations, the investigator will submit the SUSAR to the appropriate IRB. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information.

7.6.6.2 Institutional Review Board (IRB)

SAEs will be reported to the IRB per institutional guidelines. The following SAEs will be reported to the Johns Hopkins Medicine IRB per institutional guidelines:

1. Deaths, regardless of causality
2. Serious adverse events that are both related and unexpected

Follow-up information will be submitted to the IRB as soon as relevant information is available.

7.6.6.3 Food and Drug Administration (FDA)

All reporting to the FDA for the trial will be completed by the IND Sponsor.

7.6.6.3.1 Expedited IND Safety Reports

7 Calendar-Day Telephone or Fax Report:

The IND Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to be emailed to the regulatory project manager

and faxed (301-796-9849) to the FDA within 7 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

15 Calendar-Day Written Report:

The IND Sponsor is required to notify the FDA of any SAE that is unexpected and assessed by the investigator as possibly related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

7.6.6.3.2 IND Annual Reports

In accordance with the regulation 21 CFR § 312.33, the IND Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the AEs and progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.33 for a list of the elements required for the annual report. All IND annual reports will be submitted to the FDA by the IND Sponsor.

8.0 STATISTICAL METHODS

This is a multi-center, randomized, phase II open label study to evaluate the clinical activity and safety of a combination of neoadjuvant immunotherapy with pembrolizumab and focal adhesion kinase inhibitor, defactinib or pembrolizumab alone following standard chemotherapy in subjects with resectable PDAC. The primary endpoint will be pathologic complete response. The primary correlative endpoint is immune response, defined as >80% increase of intratumoral infiltration of CD8+ cells for each patient. Additionally, will also be assessing the activity and changes in TAM (tumor associated macrophages), myeloid–derived suppressor cells (MDSC) and T-reg cells, as well as the activity of pancreatic stellate cells via α-Smooth muscle actin (αSMA) and fibroblast activate protein (FAP).

8.1 Study Design and Sample Size

We wish to determine whether the percent of pCR subjects after neoadjuvant pembrolizumab/defactinib or pembrolizumab following standard chemotherapy exceeds 3%. A clinically meaningful improvement would be a 15% increase over that, i.e. 18% of subjects with pCR after neoadjuvant pembrolizumab/defactinib or pembrolizumab

following standard chemotherapy. Additionally, we wish to assess change in intratumoral expression of CD8+ cells with pembrolizumab and defactinib or pembrolizumab alone, following neoadjuvant chemotherapy. The primary efficacy endpoint is pathologic complete response (pCR). The primary correlative endpoint is immune response, defined as >80% increase of intratumoral infiltration of CD8+ cells for each patient. Secondary endpoints include safety, disease-free survival (DFS), overall survival (OS), near pathologic CR rate and Grade 3 pathologic response rate. We will also perform correlative studies (expression of TAMs, MDSCs, T-reg cells and effector T cells, as well activity of pancreatic stellate cells via αSMA and FAP) to evaluate the effect of FAKi with anti-PD1 therapy on myeloid cell modulation and impact on effector T cell infiltration in the TME of PDAC.

Approximately 16 evaluable subjects in each arm will be enrolled. Subjects will be considered efficacy evaluable if they have surgically resectable, biopsy proved adenocarcinoma of the pancreas with a CA19-9>200 at the time of randomization and they go to surgery after neoadjuvant treatment. The study will have 81% power to detect an increase of 15% in the number of pCR subjects with neoadjuvant pembrolizumab/defactinib or pembrolizumab treatment at the trial's completion based on a one-sided Fisher's exact test with a type I error of 0.082. It also gives 90% power to detect an increase of immune response rate from 5% to 30%. Adjusting for 10% unevaluable patients, the trial will recruit 18 patients each arm.

8.2 Interim Monitoring for Toxicity

In each arm, toxicity will be monitored closely and continuously. Any grade-3/4 local reactions attributable to pembrolizumab/defactinib or pembrolizumab or Grade 3 infusion-related reaction or cytokine release syndrome that lasts $\geqslant$ 12 hours will be considered AEs for purposes of this stopping rule. If the risk of these adverse events appears to be higher than 33%, we will temporarily halt the study pending dose modification. Specifically, we apply a Bayesian toxicity monitoring rule that suspends the enrollment if the posterior probability of risk being larger than 0.33 is 65% or higher. The monitoring rule uses beta (1.5, 5.5) as prior distribution. This means that our prior guess at the proportion of toxicity is 21%, and there is 90% probability that this proportion is between 3% and 49%. The decision rule for toxicity stopping is as follows:

Study termination if:	3 AEs	4 AEs	5 AEs	6 AEs	7 AEs	8 AEs
In number of patients between:	3 - 4	5 - 7	8 - 10	11 - 12	13 - 15	16 - 18

For example, we will interrupt the accrual if 3 subjects have AEs among the first 4 receiving treatment. If 4 or more out of the first 5-7 subjects have AEs, we will suspend accrual.

The operating characteristics of the stopping rule are shown below and are based on 5000 simulations:

Risk of AE	0.20	0.25	0.30	0.33	0.40	0.45
% of Time study stops	6.7%	14.1%	24.7%	31.8%	52.1%	65%
Expected sample size	15.4	14.7	13.9	13.3	11.5	10.3

8.2.1 Surgical Complications/Toxicity

Surgical complications will be defined based on Clavien-Dindo classification. In addition to toxicity monitoring, we will monitor for post-operative complications. The stopping rule will focus on Grade IIIa surgical complication or above, which is beyond what may be expected for chemotherapy or resection without immunotherapy or defactinib, and that may be attributable to these drugs. If the risk of Grade IIIa or higher surgical complications appears to be greater than 40%, the study will temporarily be halted pending feasibility evaluations. The study may resume after discussion between the principal investigator and the IND sponsor if the surgical co-investigators do not deem there is an association of an increased rate of high grade postoperative complication with any of the study treatments. Specifically, we apply a Bayesian monitoring rule that suspends the enrollment if the posterior probability of risk being greater than 40% is 0.5 or higher. The previous study showed 26% Grade IIIa or above post-operative complications in patients receiving neoadjuvant stereotactic body radiation therapy or chemoradiation therapy. Thus, a Beta (2.5, 5.5) prior, representing the prior guess of a post-operative complications (Grade IIIa or above) rate of 31%, will be used. Starting from the 30th randomized patient, surgical complications will be monitored continuously according to the protocol amendment. The table below shows the number of post-operative complications (Grade IIIa or above) that would need to be observed in order to trigger the stopping for each arm:

Study termination if number of complications	2	3	4	5	6	7	8
In number of patients between:	2-3	4 - 5	6 - 8	9 - 10	11 - 13	14 - 15	16 - 18

The operating characteristics of the stopping rule are shown below and are based on 5000 simulations:

Risk of surgical complications	0.2	0.25	0.3	0.35	0.4	0.45	0.5	0.6
% of Time study stops	16%	25%	38%	51%	67%	79%	87%	97%
Expected sample size	15.7	14.7	13.2	11.8	9.9	8.4	7.1	4.8

8.3 Interim Analysis for Futility

No interim analyses for efficacy are planned for this study. The participating Investigators, the IND Sponsor, and the independent safety physician will review the safety profile of all subjects in the run-in phase and determine that the defined dose and regimen are acceptable for Phase 2.

8.4 Data Analysis

The primary objective is to assess the pCR rate of neoadjuvant pembrolizumab and defactinib or pembrolizumab alone following chemotherapy. Pathologic response will be graded and defined as follows: 0: No viable residual tumor (complete response[pCR]) 1: Marked response (minimal residual cancer with single cells or small groups of cancer cells) 2: Moderate response (residual cancer outgrown by fibrosis) 3: Poor or no response (extensive residual cancer).The primary outcome of efficacy will be pCR. The pCR rate will be estimated as the proportion of subjects who have pCR after neoadjuvant pembrolizumab and defactinib or pembrolizumab alone following chemotherapy. Subjects who drop out of the study due to disease progression, death, or limiting toxicity before surgery may be considered as not evaluable in estimating the pCR rate. Exact binomial test will be used to test the increase in pCR rate compared with the null hypothesis 3% pCR rate. The 95% confidence interval (CI) of the pCR rate will be computed. The primary correlative endpoint is immune response, defined as >80% increase of intratumoral infiltration of CD8+ cells for each patient. We will estimate the proportion of patients who achieve immune response, along with 95% CI. We will also evaluate the changes of TAM, MDSC & T-reg, pre- vs. post-treatment.

The secondary objectives include accessing the proportion of patients experiencing at least one grade 3/4 non-lymphopenia AE, OS, DFS, near pathologic CR rate and Grade 3 pathologic response rate, explorative immunology endpoints (αSMA, FAP IHC), immunogenic cell death (calreticulin IHC) induced by different types of chemotherapy, CD68/CD8 ratio, changes of TAM, MDSC & T-reg, PD-L1, PD-1, pre- vs. post-treatment intratumoral and peripheral blood TCR clonality. Summary statistics and percentages will be reported for AE and toxicities. The rate of near pathologic CR rate and Grade 3 pathologic response rate along with 95% confidence interval (CI) will be computed for each arm. Changes from pre- to post-treatment will be assessed using paired-sample t tests or Wilcoxon signed rank tests as appropriate. Summary statistics and plots for OS, DFS will be computed using the Kaplan Meier estimate of the survival function. Comparisons between arms will be made using the log-rank test. Cox proportional hazards models will be used to evaluate the impact of different groups on OS and DFS.

9.0 LABELING, PACKAGING, STORAGE, AND SUPPLIES

9.1 Investigational Product

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.

Pembrolizumab will be provided by Merck and defactinib will be supplied by Verastem as summarized in **Table 10**.

Table 10: Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection
Defactinib 200 mg IR Tablet	Tablet (white, oval) for Oral Administration

9.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the IND Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage, Stability, and Handling Requirements

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

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

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

Refer to the Pharmacy Manual for storage, stability, and handling conditions.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck, Verastem, or designee, the amount dispensed to and returned by the participants, and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, 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.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

AE guidelines and instructions for AE reporting can be found in **Section 7.6** (Adverse Events: List and Reporting Requirements).

Dr. Zheng will be holding the IND for this study. He will comply with all regulated reporting requirements to the FDA. The Sponsor-Investigator will comply with FDA Regulations: Good Clinical Practice and Clinical Trials, 21 code federal regulations (CFR) parts 50, 54, 56, 312.

10.1 Data Collection and Processing

All information will be collected on study-specific CRFs by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator at each site.

CRFs will be used to capture study results and data. The study coordinator or other authorized study personnel will transcribe data from source documents onto eCRFs. At any time, the IND Sponsor or designee may request copies of the CRFs for preliminary medical review. Once the CRFs are complete and source-verified, the investigator must sign and date all required pages, verifying the accuracy of all data contained within the CRF.

<u>Protocol Chair</u>
The Protocol Chair and/or designee is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of SAE
- Reviewing data from all sites.

<u>Coordinating Center (Johns Hopkins University)</u>
The Coordinating Center (or its representative) is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first subject registration at that site, and maintaining copies of IRB approvals from each site.
- Monitoring subject registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Consent subjects promptly and randomize eligible subjects in EDC.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

10.2 Meetings

Scheduled meetings will take place weekly and will include the protocol principal investigator, study coordinator(s), research nurse(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

Monthly teleconferences will be scheduled to include the Coordinating Center and the clinical trial sites. During these meetings, the Coordinating Center and clinical trial sites shall discuss the following: study protocol updates, safety data, enrollment status, and progress of data for objectives.

10.3 Monitoring

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring. Data monitoring of this protocol will occur on a regular basis with the

frequency dependent on the rate of subject accrual and the progress of the study. Eligibility for all sites will be monitored by the Protocol Chair. The protocol will be internally monitored by the Principal Investigator at each site. The PI shall internally monitor the progress of the trial, including review and confirmation of all safety/treatment-related outcomes, response assessments, safety reports and/or any related source documentation. IND-sponsor is ultimately responsible for external monitoring of the trial. External monitoring will occur according to the following guidelines:

Johns Hopkins SKCCC: The protocol will be monitored externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at SKCCC.

Participating site(s): The protocol will be monitored by authorized representatives of the Coordinating Center.

Authorized representatives of the Coordinating Center may visit the satellite sites to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

Additional data and safety monitoring oversight will also be performed by the SKCCC Safety Monitoring Committee (SMC - as defined in the DSMP) and a Data Safety Monitoring Board as detailed below.

Interim analysis of toxicity, outcome and ongoing scientific investigations will be performed every 6 months by the Sidney Kimmel Comprehensive Cancer Center Data Safety Monitoring Board (SKCCC DSMB). The SKCCC DSMB will review aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Board (DSMB) Guidance. If the committee decides that amendments should be made to this trial, recommendations will be made in writing to the Study Principal Investigator. The study team will submit modifications to the IRB within 60 days of receipt from the DSMB. The Associate Director of Clinical Research, will arbitrate any disagreements between the DSMB and the study Principal Investigator. These changes may include early termination of accrual if deemed appropriate.

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Appendix 1: Performance Status Criteria

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

Appendix 2: Contraceptive Guidance and Pregnancy Testing

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 time frame from first visit through 120 days after the final administration of any study therapy.

- 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 11** 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 consistently and correctly as described in **Table 11** during the protocol-defined time frame from first visit through 120 days after the final administration of any study therapy.

Table 11: Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● 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) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly).

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 60 days.
c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the Schedule of Activities, and as required locally.

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

Appendix 3: Substrates, Inhibitors, Inducers of CYP2C9, CYP3A4, OATP1B1 and OATPIB3

Examples[1] of Substrates of CYP2C9 and CYP3A4

Substrates of CYP2C9	Substrates of CYP3A4
Celecoxib	Alprazolam
Phenytoin	Astemizole
Tolbutamide	Buspirone
Warfarin	Calcium Channel Blockers
	Carbamazepine
	Cisapride
	Cyclosporine
	Doxorubicin
	Erythromycin
	Etoposide
	Felodipine
	Fentanyl
	HIV protease inhibitors
	Ifosphamide
	Lovastatin (not prevastatin)
	Midazolam
	Nifedipine
	Pimozide
	Quinidine
	Quinine
	Simvastatin
	Tacrolimus
	Terfenadine
	Triazolam

[1]Note that this is not an exhaustive list. Additional information on drugs and possible interactions can be found at http://www.drugs.com.

Examples[1] of Strong Inhibitors and Inducers of CYP2C9 and CYP3A4

Inhibitors of CYP2C9	Inhibitors of CYP3A4
fluconazole miconazole amentoflavone (constituent of Ginkgo biloba and St. John's Wort) sulfaphenazole valproic acid	boceprevir clarithromycin conivaptan grapefruit juice indinavir itraconazole ketoconazole lopinavir/ritonavir mibefradil nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole
Inducers of CYP2C9	**Inducers of CYP3A4**
rifampicin secobarbital	carbamazepine phenytoin oxcarbazepine phenobarbital St. John's wort rifampicin rifabutin efavirenz nevirapine pioglitazone troglitazone glucocorticoids modafinil

[1]Note that this is not an exhaustive list. Additional information on drugs and possible interactions can be found at http://www.drugs.com.

Examples of Substrates for OATP1B1 and OATPIB3

Substrates of OATP1B1	Substrates of OATPIB3
Atorvastatin	Atrasentan
Atrasentan	Bosentan
Benzylpenicillin	Digoxin
Bosentan	Docetaxel
Caspofungin	Enalapril
Cerivastatin	Erythromycin
Enalapril	Fexofenadine
Ezetimibe glucuronide	Fluvastatin
Fexofenadine	Imatinib
Fluvastatin	Methotrexate
Methotrexate	Olmesartan
Olmesartan	Ouabain
Pitavastatin	Paclitaxel
Pravastatin	Pitavastatin
Rifampicin	Pravastatin
Rosuvastatin	Rifampicin
SN-38	Rosuvastatin
Temocapril	Telmisartan
Troglitazone sulfate	SN-38
Valsartan	Thyroxine
	Valsartan

These are referenced from: Kalliokoski, A., & Niemi, M. (2009). Impact of OATP transporters on pharmacokinetics. *British journal of pharmacology*, *158*(3), 693–705. doi:10.1111/j.1476-5381.2009.00430.x, and can be cross referenced in Lexicomp

Appendix 4: Adverse Event of Clinical Interest (ECI) Reporting Form

Please notify: Dr. Lei Zheng (lzheng6@jhmi.edu AND GIsafetyreporting@jhmi.edu) within 24 hours
Merck within 2 business days (FAX: +1-215-661-6229)
Verastem within 24 hours (drugsafety@verastem.com or faxed to +1 781 465 7936)

Protocol Title:	A randomized phase II study of pembrolizumab with or without defactinib, a focal adhesion kinase inhibitor following chemotherapy as a neoadjuvant and adjuvant treatment for resectable pancreatic ductal adenocarcinoma (PDAC)		
Protocol Number: J18140	**Signature of PI:**	**Principal Investigator:**	**Date:**
Report Type: ☐**Initial** ☐**Follow-up** ☐**Final Follow-up** ☐**Addendum to:**			
Section A: Subject Information			
Subject ID:	**Subject Gender:** ☐**Male** ☐**Female**	**Subject Age:**	
Section B: Event Information			
Event diagnosis or symptoms:	**Date of First Dose:**	**Action taken with the study drug:** ☐**None** ☐**Interrupted** ☐**Discontinued** ☐**Delayed**	
	Date of Last Dose prior to Event:		
Event Grade:	**Number of Total Cycles:**		
Event Onset Date:	**Event End Date:**	**Date Event Discovered:**	
Section C: Study Drug Information:			
Investigational Products: Arm A: Pembrolizumab 200 mg IV every 3 weeks (21 days), Defactinib 400 mg BID Arm B: Pembrolizumab 200 mg IV every 3 weeks (21 days) **Indication:** High-Risk Resectable Pancreatic Adenocarcinoma			

Treatment Arm:
☐ Arm A
☐ Arm B

Relationship to:	Pembrolizumab	Defactinib	Underlying Disease
Unrelated	☐	☐	☐
Related	☐	☐	☐

Section D: Brief Description of the Event: (please include relevant procedures and laboratory values)

Section E: Relevant Medical History

Section F: Concomitant Drug (Not related to ECI)

Name of the Drug	Start Date	Stop Date	Route	Dose	Frequency

Section F: Comments

Additional Documents: ☐ Please specify

Appendix 5: SAE Reporting Form

Please notify: Dr. Lei Zheng (lzheng6@jhmi.edu AND GIsafetyreporting@jhmi.edu) within 24 hours
Merck within 2 business days (FAX: +1-215-661-6229)
Verastem within 24 hours (drugsafety@verastem.com or faxed to +1 781 465 7936)

<table>
<tr><td>Protocol Title:</td><td colspan="3">A randomized phase II study of pembrolizumab with or without defactinib, a focal adhesion kinase inhibitor following chemotherapy as a neoadjuvant and adjuvant treatment for resectable pancreatic ductal adenocarcinoma (PDAC)</td></tr>
<tr><td>Protocol Number:
J18140</td><td>Signature of PI:</td><td>Principal Investigator:</td><td>Date of Report:</td></tr>
<tr><td>Report Type:
☐Initial
☐Follow-up
☐Final Follow-up
☐Death
☐Addendum to:</td><td>Serious Criteria (check all that apply):
☐Death
☐Life-threatening
☐ Hospitalization or Elongation of Existing Hospitalization
☐ Other Important Medical Event
☐ Cancer
☐ Overdose
☐ Other:_____</td><td>Hospital Admission Date:

Hospital Discharge Date:</td><td>Date Event Discovered:</td></tr>
<tr><td colspan="4">Section A: Subject Information</td></tr>
<tr><td colspan="2">Subject ID:</td><td>Subject Gender:
☐Male
☐Female</td><td>Subject Age:</td></tr>
<tr><td colspan="4">Section B: Event Information</td></tr>
<tr><td>Event diagnosis or symptoms:</td><td>Event Grade:</td><td>Cause of death (if applicable):</td><td>Event Outcome:

☐ Recovering
☐ Recovered
☐ Recovered with sequelae
☐ Death
☐ Unknown</td></tr>
<tr><td colspan="2">Event Onset Date (or Date of Death):</td><td colspan="2">Event End Date:</td></tr>
<tr><td colspan="4">Section C: Study Drug Information:</td></tr>
</table>

Investigational Products:
Arm A: Pembrolizumab 200 mg IV every 3 weeks (21 days), Defactinib 400 mg BID
Arm B: Pembrolizumab 200 mg IV every 3 weeks (21 days

Indication: High-Risk Resectable Pancreatic Adenocarcinoma

Treatment Arm: ☐ Arm A ☐ Arm B	**Number of Total Cycles:**	**Action Taken with Study Drug:** ☐ None ☐ Interrupted ☐ Delayed ☐ Discontinued
Date of First Dose:	**Date of Last Dose prior to Event:**	

Relationship to:	**Pembrolizumab**	**Defactinib**	**Underlying Disease**
Unrelated	☐	☐	☐
Related	☐	☐	☐

Section D: Brief Description of the Event

Section E: Relevant Tests/Laboratory Data

Section F: Relevant Medical History

Section G: Concomitant Drug (Not related to SAE)

Name of the Drug	**Start Date**	**Stop Date**	**Route**	**Dose**	**Frequency**

Section H: Comments

Additional Documents: ☐ Please specify

END OF PROTOCOL