Academic and Community Cancer Research United (ACCRU)

A Multicenter Phase II Study of Pembrolizumab (MK-3475) in Patients with Advanced Small Bowel Adenocarcinomas

For any communications regarding this protocol, please contact the person listed on the Protocol Resource page. This is a stand-alone document found on the ACCRU website (www.ACCRU.org).

Study Chairs

ACCRU: Robert R. McWilliams, M.D.
Mayo Clinic
Rochester, MN 55905
mcwilliams.robert@mayo.edu

FDA IND Sponsor/Investigator: Robert R. McWilliams, M.D.

Study Co-chairs: [redacted]

[redacted]

Statistician: [redacted]
Mayo Clinic
[redacted]

Drug Availability

Drug Company Supplied: Pembrolizumab (MK-3475Commercial supply provided by Merck) IND #130955

√ Study contributor(s) not responsible for patient care.

NCI: NCT02949219
Merck MISP# 52192

Research Coordinating Center
Academic and Community Cancer Research United
200 First Street Southwest
Rochester, MN 55905
FAX# 507-538-0906

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Index

Schema

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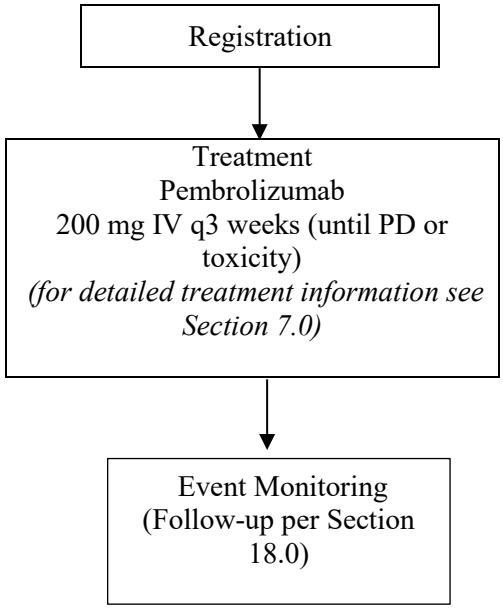
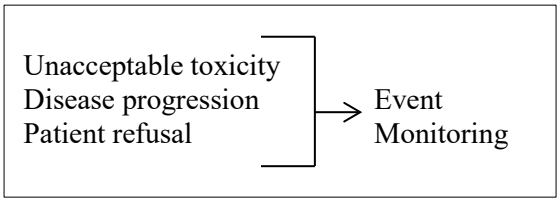
Schema





Primary outcome is response based on RECIST criteria. Secondary endpoints are PFS, OS, and adverse events.
*To permit continued study treatment beyond initial radiographic disease progression, see section 7.6 Treatment Continuation.
Cycle length = 21 days

Generic name: Pembrolizumab Brand name(s): Keytruda ACCRU Abbreviation: Availability: Clinical Research Services, a division of Rx Crossroads by McKesson

1.0 Background

Trial Summary

Abbreviated Title	Pembrolizumab in advanced small bowel adenocarcinoma
Trial Phase	Phase II
Clinical Indication	Treatment of subjects with advanced small bowel adenocarcinoma after first-line treatment
Trial Type	Interventional
Type of control	None
Route of administration	Intravenous
Trial Blinding	Unblinded, open-label
Treatment Groups	All patients receive pembrolizumab 200 mg every 3 weeks.
Number of trial subjects	41 patients
Estimated enrollment period	The sponsor estimates that the trial will require approximately 17 months from the first patient enrolling until the final patient signs informed consent.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 20 months to allow full accrual and at least the first 4 cycles of pembrolizumab.
Duration of Participation	Until disease progression, drug intolerance, or 24 months of pembrolizumab therapy.

1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+

and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.
Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

1.2 Preclinical and Clinical Trial Data

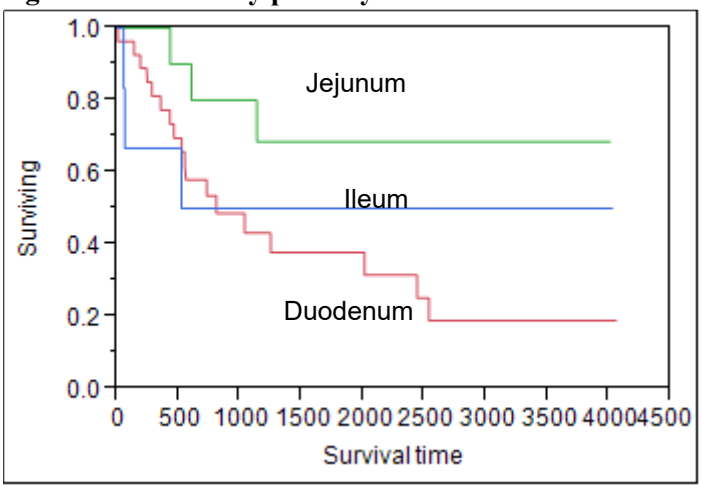
Refer to the Investigator's Brochure for Preclinical and Clinical data.
Small bowel adenocarcinoma (SBA) is a rare malignancy that is often diagnosed in its late stages. Due to its rarity, it is historically understudied. As such, there is no clear, consistent standard of care. This is further complicated by a noted heterogeneous response to standard chemotherapy regimens. To date, small prospective clinical studies have evaluated chemotherapy for SBA the first of which examined the use of mitomycin C, Adriamycin, and 5-fluorouracil with minimal therapeutic effect. (Gibson, Holcroft et al. 2005). This study was performed in the early 1980s but not reported until 2005. More recently oxaliplatin-based therapies have been demonstrated to have activity and have emerged as a standard of care in the front line setting. Overman et al. demonstrated a high response rate (50%) with combination therapy of oxaliplatin and capecitabine although the trial also included patients with ampullary carcinoma.(Overman, Varadhachary et al. 2009) This study showed that small bowel carcinoma is a chemosensitive disease with response rates and sensitivity profile similar to other GI malignancies, namely fluoropyrimidine and oxaliplatin-based therapy. A Chinese study using FOLFOX showed similar response rates, progression free survival, and overall survival to the XELOX study (Table 1).(Xiang, Liu et al. 2012) A recently completed multicenter trial, N0543 is a small bowel adenocarcinoma study using a triplet combination of irinotecan, oxaliplatin, and capecitabine, with UGT1A1 genotype-based therapy. This study has demonstrated the feasibility of performing a small adenocarcinoma study within a cooperative group, in this case the North Central Cancer Treatment Group, now part of the Alliance for Clinical Trials in Oncology. (McWilliams, Mahoney et al. 2012) While oxaliplatin-based therapy is widely considered the standard for first line therapy, there is no clearly established therapy beyond first line treatment for SBA, as no prospective trials have been performed to date.

Table 1. Prospective Trials for Oxaliplatin-based therapy in Metastatic SBA

Study	Regimen	# patients	PFS (mo.)	OS (mo.)	RR (%)
Overman et al. (2009)	XELOX	30	9.4	15.5	50
McWilliams et al (2012)	XELIRINOX	29	8.7	13.2	39
Xiang (2012)	FOLFOX	33	7.8	15.2	48

Similar to patterns seen in colorectal cancer (Gonsalves, Mahoney et al. 2014; Missiaglia, Jacobs et al. 2014), there appears to be genetic heterogeneity among sites of small bowel adenocarcinoma primary tumor origination. This may correspond with differences in overall survival, as we have noted in examining outcomes of 50 small bowel patients seen at the Mayo Clinic (**Figure 1**). (Unpublished data) For instance, tumors deficient in DNA mismatch repair and having resulting high microsatellite instability (dMMR/MSI-H) appear more often in proximal tumors, and KRAS mutations are more common in duodenal cancers (57% vs. jejunum (29%) and ileum (14%).(Aparicio, Svrcek et al. 2013) Her-2 expression levels appear to be lowest in proximal tumors and highest in ileal tumors. While several of these genetic mutations that have been noted in small bowel adenocarcinomas are potentially targetable with therapy, the frequency is too low, even when attempting screening by the above known tumor site characteristics, in this rare cancer to allow for feasible clinical study.

Figure 1. Survival by primary tumor site



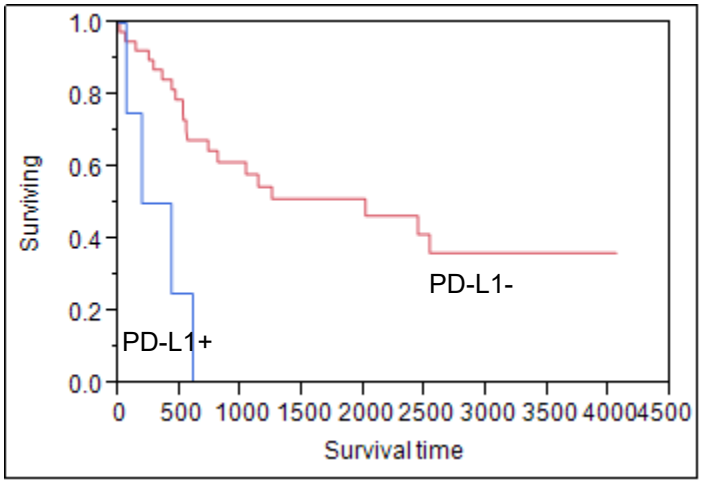
1.3 Rationale for the Trial and Selected Subject Population

Beyond conventional chemotherapy for these tumors, there are no known SBA-specific genetic targets that have been investigated for treatment efficacy. Genetic analyses have revealed similar molecular characteristics to colorectal cancer. Recently, a European coalition investigated 46 commonly altered cancer genes in 83 cases and found that the most common mutations are not therapeutically targeted: KRAS, TP53, APC, and smad4 (Laforest, Aparicio et al. 2014). There may be a population of Her2, BRAF, or PI3KCA patients who may benefit from signaling pathway blockade, but with the rarity of those mutations (≤15.8%) in a rare disease, trials will be difficult to accrue. There is an urgent need to perform larger, coordinated international studies to establish further evidence-based therapeutic options.

The relative rarity of adenocarcinoma of the small bowel compared to the colon or stomach is postulated to be related to increased immune surveillance in the small intestine(Lowenfels 1973) suggesting that, in those tumors that do develop in the small bowel, immune checkpoint therapies may be widely useful in re-establishing anti-tumor immune function.

We performed a pilot study of PD-L1 staining of 50 archived small bowel adenocarcinoma tumors. In this study, 4 patients (8%) had strong cellular staining for PD-L1, while 21/50 (42%) had 3+ or greater staining of intratumoral stroma. In an unadjusted survival analysis, tumors that showed cellular staining for PD-L1 were associated with a poorer survival (median survival 10 months vs 5.5 years, p = 0.0009 by Log-Rank), though the cohort size was too small to draw general conclusions (**Figure 2**). There was no difference in outcome by stromal stating 3+/4+ vs 0, 1+, 2+ (p=0.51). The poor survival of PD-L1 staining tumors is similar to what is reported for renal cell carcinoma, suggesting impaired immune surveillance and providing the rationale for PD1 targeted therapy in this disease.(Thompson, Gillett et al. 2004).

Figure 2. Survival by tumor cell staining for PD-L1



It has recently been suggested that dMMR/MSI-H patients may have a superior response to anti-PD1 therapy. (Le, Uram et al. 2015) In our preclinical study, seven of the 50 tumors (14%) were already known clinically to be dMMR/MSI-H. These had a superior prognosis to tumors not known to be dMMR/MSI-H (median survival not reached vs 2.5 years, p=0.028 by Log-Rank), suggesting a unique biology at baseline and is in keeping with survival data on Lynch syndrome patients with cancer of the large intestine. While the response to PD-1 inhibitors was most prominent in the dMMR cohort of the Le et al. study (ORR 40%), a small number of patients with proficient MMR and microsatellite stability (pMMR/MSS) did achieve a small response or stable disease, indicating potential efficacy in both cohorts.
Our goal is to evaluate whether pembrolizumab administered to patients with advanced small bowel adenocarcinoma in second- or later lines of therapy demonstrates antitumor activity as measured by confirmed response rate. Secondary endpoints would include response in dMMR vs. pMMR patients, response in PD-L1 (+) vs, PD-L1 (-) expressers, progression-free survival (PFS), overall survival (OS), and tolerability.

1.4 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity(Daud, Ribas et al. 2015).

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.
A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The

relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.
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 every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe. A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce waste.

2.0 Goals

2.1 Primary Objective and Endpoint

2.11 To determine whether pembrolizumab administered to SBA patients demonstrates antitumor activity as measured by the confirmed response rate

2.2 Secondary Objectives and Endpoints

2.21 To assess survival endpoints (OS, PFS), including stratified analysis by tumor site.

2.22 To assess whether pembrolizumab is safe in SBA patients by assessing adverse events.

2.3 Correlative Research

2.31 To determine whether PD-L1 expression, as measured by IHC, or MSI status is associated with the response rate overall.

2.32 To determine if Bim levels in tumor-reactive CD11ahighPD-1+CD8+ peripheral

blood T cells can objectively monitor responses to pembrolizumab and to determine if excessive release of soluble B7-H1 (sPD-L1) by the tumor leads to Bim upregulation and treatment resistance in SBA.

2.33 To determine if other tissue-based factors, such as total mutational burden, correlate with response to pembrolizumab.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Patients must have biopsy-proven adenocarcinoma of the small bowel at any site (duodenum, jejunum, ileum), excluding ampullary and appendiceal tumors.

3.12 Have locally advanced (unresectable) or metastatic small bowel adenocarcinoma.

3.13 Willing and able to provide written informed consent for the trial.

3.14 Age ≥ 18 years.

3.15 Measurable disease based on RECIST 1.1.

3.16 Had at least one prior line of systemic chemotherapy for metastatic disease. Adjuvant therapy would not count toward first-line therapy unless patient recurs less than 6 months after completion of that regimen.

3.17 Willing to provide blood and tissue (can be archival) samples for mandatory research purposes (see sections 4.0, 14.0 and 17.0).

3.18 ECOG Performance Status (PS) 0 or 1. (Form is available on the ACCRU web site)

3.19a The following laboratory values obtained ≤28 days prior to registration.

- Absolute neutrophil count (ANC) ≥1500/mm3 (1.50 x 10^9/L)
- Platelet count ≥100,000/mm3 (100 x 10^9/L)
- Hemoglobin ≥9.0 g/dL (5.6 mmol/L or 90 g/L) without transfusion or EPO dependency (within 7 days of assessment)
- Serum total bilirubin ≤1.5x upper limit of normal (ULN) **OR** direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5x ULN
- Aspartate transaminase (AST) and alanine aminotransferase (ALT) ≤2.5x ULN **OR** ≤ 5x ULN for subjects with liver metastases
- Serum creatinine ≤1.5x upper limit of normal (ULN)

OR

- Measured or calculated creatinine clearance must be ≥60 mL/min for subjects with creatinine levels > 1.5 X ULN using the Cockcroft-Gault formula below (Glomerular Filtration Rate [GFR] ≥60 mL/min (1.0 mL/s/m^2) can also be used in place of creatinine or CrCl):

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$

Creatinine clearance for females = $\frac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$

3.19b Female subject of childbearing potential have a negative urine or serum pregnancy ≤7 days prior to registration. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
Note: Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

3.2 Exclusion Criteria

3.21 Non-adenocarcinoma histology.

3.22 Adenocarcinoma originating in the ampulla or appendix. (Duodenal Tumors that involve the ampulla but originate in the duodenum are eligible).

3.23 Currently participating and receiving study therapy, or have participated in a study of an investigational agent and received study therapy, or used an investigational device ≤4 weeks of registration.

3.24 Diagnosis of immunodeficiency or be receiving systemic steroid therapy or any other form of immunosuppressive therapy ≤7 days prior to registration.

3.25 History of active TB (Bacillus Tuberculosis).

3.26 Hypersensitivity to pembrolizumab or any of its excipients.

3.27 Any of the following:

- Prior anti-cancer monoclonal antibody (mAb) ≤4 weeks prior to registration

3.28 Prior chemotherapy, targeted small molecule therapy, or radiation therapy ≤2 weeks prior to registration or who has not recovered to ≤ Grade 1 or baseline from adverse events due to the previously administered agent.

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

3.29a Received major surgery ≤2 weeks prior to registration, subject must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3.29b Known additional malignancy that is progressing or requires active treatment or that may interfere with interpretation of response evaluation, in the judgment of the investigator.

3.29c Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging ≤4 weeks prior to registration and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids ≤7 days prior to registration. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

3.29d Active autoimmune disease (including but not limited to: patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g. Wegener's Granulomatosis]); CNS or motor neuropathy considered of autoimmune origin (e.g., Guillain-Barre Syndrome and Myasthenia Gravis, multiple sclerosis)) 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.

3.29e Known history of or any evidence of active, non-infectious pneumonitis.

3.29f Active infection requiring systemic therapy.

3.29g History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

3.29h Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.29i Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

3.29j Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or other immune checkpoint inhibitor (e.g. anti-CTLA4).

3.29k History of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

3.29l Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

3.29m Received a live vaccine within 30 days of planned start of study therapy.
Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.

4.0 Test Schedule

Tests and procedures	Active Monitoring Phase			
	≤28 days prior to registration	Day 1 Cycle 1	Day 1 Cycles 2 -8 and beyond (+/-3 days)	End of treatment (PD, withdrawal, or removal[9]) (+7days)
History and exam, wt, ECOG PS	X	X[6,8]	X[6]	X
Height	X			
Adverse event assessment	X	X[8]	X	X
Concomitant medication review	X	X[8]	X	
Hematology: CBC/ differential	X	X	X	X
Chemistry: SGOT (AST), ALT, alk phos, T. bili, creatinine, calcium,, Na, K, glucose, LDH, bicarbonate, uric acid, Mg, Phosphorus, total protein, blood urea nitrogen, albumin	X	X	X	
PT/INR and aPTT	X			
Urinalysis[3]	X			
T3, FT4 and TSH	X	X	X	
Tumor measurement (should include at least a CT of the abdomen/pelvis, and appropriate imaging of any other target site lesions) [1, 10]	X		X[5]	X
CEA	X		X[7]	X
Pregnancy test	X[2]			
Mandatory blood sample (see Section 14.0) [K]	X	X	X[4]	X
Mandatory tissue sample (see Section 17.0)	X			

1. Use same imaging throughout the study.
2. For women of childbearing potential only. Must be done ≤7 days prior to registration.
3. Urine blood, glucose, protein, specific gravity. Microscopic exam if abnormalities on urinalysis results.
4. Collected cycles 2, 3, 4, 8 (see Section 14.0). Kits are required for this collection.
5. Every 4 cycles beginning with end of cycle 4, and at end of treatment.
6. Directed physical exam only.
7. Every even-numbered cycle, beginning with cycle 2, and at end of treatment.
8. ≤24 hours prior to treatment.
9. Continued study treatment beyond initial radiographic disease progression may be allowed; see Section 13.4 for details. These

patients would continue follow-up per test schedule until confirmed progression.
10. To be submitted <60 days after registration
R Research funded (see Section 19.0). Mandatory research blood draws should be collected and submitted *after* the patient is registered onto the study, but before beginning study treatment.

5.0 Grouping Factor

None

6.0 Registration Procedures

6.1 To register a patient, access the ACCRU web page at [redacted] go to the Application section and click on "Registration" and enter the registration/randomization application. The registration application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Instructions for the registration/randomization application are available on the above web page under the Study Resources section, "Application Training."

Prior to initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted]. If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Application Training" at [redacted]; click on "Registration, Installation & Entry Instructions."

6.2 Correlative Research

A mandatory correlative research component is part of this study; the patient will be automatically registered onto this component (see Sections 3.17, 14.0 and 17.0).

6.3 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with ACCRU. Approvals should be uploaded using the online [redacted]. If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals is required until the study has been closed through your IRB.

6.4 Prior to accepting the registration, the registration/randomization, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility

- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.5 At the time of registration, the following will be recorded:
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her sample(s) to outside researchers.

6.6 Treatment cannot begin prior to registration and must begin ≤10 days after registration.

6.7 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.8 All required baseline symptoms (see Section 10.5) must be documented and graded.

6.9a Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.

6.9b Study drug is available on site.

6.9c Blood draw kit is available on site.

7.0 Protocol Treatment

7.1 Treatment Schedule

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg (flat dosing)	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

Note: Trial treatment should begin ≤10 days after registration and as close as possible to the date on which treatment is allocated/assigned.
Note: Details on preparation and administration of pembrolizumab (MK-3475) are provided in section 15.0.

7.2 For this protocol, the patient must return to the consenting ACCRU institution for evaluation at least every 21 days (+/- 3 days) during treatment.

7.3 Dosing interruptions, not due to adverse effects.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record.

7.4 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

7.5 Dose Administration

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).

7.6 Treatment Continuation

To permit continued study treatment beyond initial radiographic disease progression the following will be required:

a) The patient's performance status must be stable
b) Clinical symptoms and signs of disease progression must be absent
c) A repeat scan to assess for true disease progression must be performed in approximately 4 weeks
d) Any patient with pending organ compromise must be discontinued from study treatment

Note: See section 13.4 for patients that have initial progression

7.7 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.

7.71 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject'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.

7.72 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy, biological therapy, immunotherapy, not specified in this protocol

- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

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

There are no prohibited therapies during event monitoring.

7.8 Diet/Activity/Other Considerations

7.81 Diet

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

7.82 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods, or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

7.83 Use in Pregnancy

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

The 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 the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy recorded on the CRF.

7.84 Use in Nursing Women

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

8.0 Dosage Modification Based on Adverse Events

8.1 Dose Levels

No dose level adjustments are recommended for any adverse reaction, but the dosing interval may be increased by 1 week if required.

8.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per **the table below**.

Dose Modification Guidelines for Drug-Related Adverse Events. Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03

CTCAE System/Organ/ Class (SOC)	Adverse Event/ Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Gastrointestinal disorders	Diarrhea/Colitis (8.4)	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
		4	Permanently discontinue	Permanently discontinue
Investigations	Increased AST ALT, or Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
		3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Metabolism and nutrition disorders	Hyperglycemia (8.5)	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
		4	Permanently discontinue	Permanently discontinue
Endocrine disorders	Hyperthyroidism/ Hypothyroidism (8.7)	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
		4	Permanently discontinue	Permanently discontinue
	Other: Hypophysitis (8.6)	2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
		3-4	Withhold or permanently discontinue	
General disorders and administration site conditions	Infusion Reaction (8.9)	3-4	Permanently discontinue	Permanently discontinue

CTCAE System/Organ/ Class (SOC)	Adverse Event/ Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Respiratory, thoracic and mediastinal disorders	Pneumonitis (8.3)	2-4	Permanently discontinue	Permanently discontinue
Renal and urinary disorders	Renal Failure or Nephritis (8.9a)	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
		3-4	Permanently discontinue	Permanently discontinue
Cardiac disorders	Myocarditis	1-2	Withhold	Based on severity of the AE administer corticosteroids. Ensure adequate evaluation to confirm etiology and/or exclude other causes
		3-4	Permanently discontinue	Permanently discontinue
	All other immune-related AEs	2	Withhold	Based on type and severity of AE administer corticosteroids Ensure adequate evaluation to confirm etiology and/or exclude other causes
		3	Withhold or discontinue based on the type of event; Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis	
			Recurrent grade 3	Permanently discontinue
		4	Permanently discontinue	Permanently discontinue
	All Other Drug-Related Toxicity[2]	3 (Severe)	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.

CTCAE System/Organ/ Class (SOC)	Adverse Event/ Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
		4	Permanently discontinue	Permanently discontinue
	Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event. [1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline therapy should be held up to 3 weeks. If this does not resolve to grade 2, therapy should be discontinued. Steroids can be used to treat elevated AST/ ALT (see section 8.7). Resolution to grade 2 with steroid treatment will be allowed continuation on therapy. [2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.			

8.3 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.

8.4 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** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, 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.

8.5 Type 1 diabetes mellitus (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.

8.6 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.

8.7 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 liothyronine, is indicated per standard of care. Treatment with pembrolizumab may be continued.

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.

8.8 Hepatitis or Hepatic function decline

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.

8.9a 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.

8.9b Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. The table below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

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 subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs.	**Stop Infusion and monitor symptoms.** 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 subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one 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 subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg P.O. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg P.O. (or equivalent dose of antipyretic).
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) **Grade 4:** Life-threatening; pressor or ventilator support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

9.0 Ancillary Treatment/Supportive Care

9.1 Supportive Care Guidelines

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 and in greater detail in section 8.0. 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.

All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

Note: if after the evaluation the event is determined not to be related, the site investigator is instructed to follow the reporting guidance but does not need to follow the treatment guidance. Refer to the table in section 8.1 for dose modification.

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

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol. Refer to the adverse event and serious adverse event sections of the protocol for detailed information..

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.

- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website.(

a. Adverse event monitoring and reporting is a routine part of every clinical trial.

b. Identify the grade and severity of the event using the CTCAE version 4.03.

c. Determine whether the event is expected or unexpected (see Section 10.2).

d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

f. Determine if other reporting is required (see Section 10.5).
g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 **EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting**

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.5). *

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not require expedited reporting.
Endocrine disorders	Hypothyroidism	1,2,3
	Other, specify:	1,2,3
Gastrointestinal disorders	Enterocolitis	1, 2
	Intra-abdominal hemorrhage	1,2
	Other, specify:	1,2
Respiratory, thoracic and mediastinal disorders	Pneumonitis	1,2
	Dyspnea	1,2
	Cough	1,2
	Respiratory failure	1,2
	Other, specify	1,2
Renal and urinary disorders	Nephritis	1, 2
	Hematuria	1,2
	Proteinuria	1,2
Investigations	Increased AST/ALT	1,2,3
	Increased bilirubin	1,2,3
	Creatinine increased	1,2
Infections and infestations	Hepatitis viral	1,2,3

These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol or to administer protocol directed treatment (i.e. 131I therapy)
- Hospitalization planned before informed consent (where the condition requiring hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

* Report any clinically important increase in the **rate** of a serious suspected adverse reaction (at your study) site over that which is listed in the protocol or investigator brochure as an expedited event.

* Report an expected event that is greater in severity or specificity than expected as an expedited event

* An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

A list of known/expected AEs is reported in the investigator brochure, package insert or the literature, including AEs resulting from a drug overdose.

10.331 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**

  - Death attributable to a CTCAE term.

  - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

  - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

  - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

  - Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.332 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:

  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])

  - Myelodysplastic syndrome (MDS)

  - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.333 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.334 Pregnancy

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected. *In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.*

NOTE: When submitting ACCRU Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

10.335 Study drug overdose ≥1000mg is the accidental or intentional use of the drug in the amount higher than the starting dose being studied.

10.3351 Any study drug overdose during the study should be noted on the CRF (AE Log found in the Forms Packet).

10.3352 All AEs associated with an overdose should both be entered on the Adverse Event CRF and reported using the procedures

detailed in Reporting of SAEs, even if the events do not meet serious criteria. If the AE associated with an overdose does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as non-serious on the SAE form and the Adverse Event CRF.

10.4 Expedited Adverse Event Reporting Requirements for IND Agents

10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting via the **ACCRU Adverse Event Expedited Report Form** for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death

2) A life-threatening adverse event

3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours

4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

5) A congenital anomaly/birth defect.

6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour / 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour / 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- 7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Special Instructions:

- Follow site-specific reporting guidelines.
- Submit the ACCRU Adverse Event Expedited Report Form to the ACCRU SAE Coordinator via fax [redacted] or email [redacted]. The ACCRU SAE Coordinator will provide copies to Merck Global Safety by fax ([redacted] within 2 working days of SAE occurring or being noted.
- Other relevant safety information, drug overdoses, and Non-Serious Events of Clinical Interest should be handled in the same manner as SAEs. A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices Agency (PMDA), or other local regulators. Investigators will cross-reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX [redacted]) at the time of submission to the FDA.
- The ACCRU SAE Coordinator will forward to [redacted] as appropriate. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously

reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.
If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Baseline and Adverse Events Evaluations

Pre-treatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation per the CTCAE v4.03 grading unless otherwise stated in the table below:

System Organ Class (SOC)	CTC Adverse Event Term (CTCAE v.4.03)	Baseline	At each evaluation
Investigations	Aspartate aminotransferase (AST) increased	X	X
	Alanine aminotransferase (ALT) increased	X	X
	Blood bilirubin increased	X	X
	Alkaline phosphatase increased	X	X
Endocrine Disorders	Hyperthyroidism	X	X
	Hypothyroidism	X	X
	Other: Specify hypophysitis	X	X

10.53 **Case Report Forms** - Academic and Community Cancer Research United (ACCRU)

Submit the following AEs not specified in Section 10.5 (paper or electronic, as applicable)

10.531 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.532 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.533 Grade 5 AEs (Deaths)

10.5331 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5332 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.54 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1)[1] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline. Evaluations will be performed by the investigator at the times of treatment.

11.1 Schedule of Evaluations: For the purposes of this study, patients should be reevaluated every 12 weeks (i.e. 4 cycles),

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Note: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the

attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

iii If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained <u>at least four</u> weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see Section 11.44).

- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. <u>These lesions can be non-nodal or nodal (as defined in 11.21)</u>, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- Minimum sum of the dimensions (MSD): The minimum of the BSD and the PBSD.

- Sum of Perpendicular Diameters: The sum of the products of the two largest perpendicular diameters of a lesion will be calculated and reported. The SPD will be used to calculate the total measurable tumor burden per irRC assessment.

- Total Measurable Tumor Burden: per the irRC, all index and measurable new lesions are taken into account. The SPD of the two largest index lesions (five lesions per organ, up to 10 visceral lesions) is calculated at baseline and at each subsequent reassessment. The SPD of new, measurable lesions (>5 x 5 mm; up to five new lesions per organ, 10 total visceral lesions) are added together for the total tumor burden.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

Target lesions will be assessed using RECIST criteria for all primary endpoints (see **table below**).

Response Criteria per RECIST 1.1

	RECIST 1.1*
Complete Response (CR)	Disappearance of all target lesions AND each target lymph node must have short-axis reduction to <1.0 cm
Partial Response (PR)	At least 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking the BSD as reference (see Section 11.41).
Progression (PD)	At least one of the following must be true: a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD. c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

*Primary endpoint.
**Secondary endpoint. Tumor burden includes index, non-index, and emerging lesions while on therapy.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all non-target lesions.

  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following table:

Overall Responses by RECIST 1.1

Target Lesions & Target Lymph Nodes	**Non-Target Lesions & Non-Target Lymph Nodes**	**New Sites of Disease**	**Overall Objective Status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the ACCRU protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

***NOTE: For those patients who have initial PD, a confirmation scan will be required around 4 weeks later to confirm PD, assuming the patient is eligible to remain on treatment after initial PD (see 13.4 for further details). If progression is confirmed then the date of disease progression will be the first date the patient met the criteria for progression based on standard RECIST 1.1 criteria.

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

12.1 Type of Prior chemotherapy

All prior lines of chemotherapy (adjuvant vs. palliative, or both) and identities of prior drug regimens administered (FOLFOX vs. XELOX, etc.) should be noted for each patient. Of note, no prior immunotherapies may have been given.

12.2 Number of lines of prior chemotherapy

0 vs. 1 vs. 2 vs. 3 vs. 4 or more prior treatment courses.

12.3 Site of primary tumor:

Duodenal vs. jejunal vs. ileal

12.4 Prior Radiation Therapy:

Yes vs. no, including specific notation whether prior radiation therapy had been previously administered to the abdomen/pelvis.

12.5 MSI status

MSS vs MSI-L vs MSI-H, vs. unknown

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.2 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated such that evaluating for primary end point is in question. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.3 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material will be required per Section 18.0 of the protocol and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.4 Patients will continue on treatment until disease progression, intolerable toxicity, or patient refusal. To permit continued study treatment beyond initial radiographic disease

progression the following will be required:

a) The patient's performance status must be stable
b) Clinical symptoms and signs of disease progression must be absent
c) A repeat scan to assess for true disease progression must be performed in approximately 4 weeks
d) Any patient with pending organ compromise must be discontinued from study treatment

After discontinuation of treatment or once a patient has confirmed disease progression, patients will continue in event monitoring only follow-up as outlined in section18.

13.5 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. .

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.
- Confirmed radiographic disease progression (but remain on trial for long term survival)
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment. To permit continued study treatment beyond initial radiographic disease progression, see section 7.6 Treatment Continuation.

Administrative reasons

Subjects who discontinue trial treatment for any reason will move into the event-monitoring phase and should be assessed every 3 months until progression and every 6 months after progression for a maximum follow-up time of 5 years from study entry.

13.6 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course

Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation.

13.7 Subject Replacement Strategy

A subject that discontinues from the trial will not be replaced.

13.8 Clinical Criteria for Early Trial Termination
Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete;
2. Poor adherence to protocol and regulatory requirements;
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects;
4. Plans to modify or discontinue the development of the study drug.

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

13.9 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
  - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
    - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
    - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

  Or

  - Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.

- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

Visit requirements are outlined in Section 4.0.

14.0 Body Fluid Biospecimens

14.1Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Specimen mandatory or optional?	Collection Tube	Volume to collect per tube (number of tubes to be collected)	Blood product being processed and submitted	Baseline	Cycles 1-4 and 8	End of Treatment	Additional processing required at site after draw?	Storage/ shipping conditions[1]	Analysis Plan
Mandatory	Sodium heparin	10 mL (6)	Whole blood	X	X	X	No	Room (ambient) temperature – DO NOT FREEZE	Immunological analyses, germline DNA, and optional banking
Mandatory	Streck cell free DNA BCT	10 mL (2)	plasma	X	X	X	Yes	Room (ambient) temperature – DO NOT FREEZE	Cell free DNA analysis

*Note: Blood draws should not be collected and submitted until after the patient is registered/randomized to the study.

After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.27 for detailed shipping instructions).

14.2 **Kits *will* be used for this study** and will contain supplies for collecting and shipping specimens.

14.21 Participating institutions may obtain kits by e-mailing [redacted] at [redacted] E-mail requests should include the site address and phone number, contact information and number of kits being requested.

14.22 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. Please allow 1-2 weeks to receive the kits.

14.23 Specimens may be collected Monday through Thursday. If a Friday collection is needed please make arrangements with [redacted] ahead of time to make arrangements (1-2 weeks prior, if possible).

14.24 Label specimen tubes with protocol number, ACCRU patient ID number, and time and date blood drawn.

14.25 Collect all blood/blood products according to specific kit instructions.

14.26 Any questions concerning sample collection and shipments can be directed to [redacted] at the Research Base by phone [redacted] or e-mail [redacted]

14.27 Shipping

14.271 Verify ALL sections of the ACCRU Blood Specimen Submission Form, and specimen collection labels are completed and filled in correctly. Enter information from the ACCRU Blood Specimen Submission Form into the remote data entry system ≤7 days after specimen collection (see Forms Packet).

14.272 Send heparin tubes and Streck cell free DNA ambient or at room temperature to:

[redacted]

14.273 Notify Michael Thompson at the Research Base by phone [redacted] or e-mail [redacted] that blood has been shipped.

14.3Study Methodology and Storage Information

14.31 Blood/blood product samples will be collected for the following research

14.311 Nucleic acid extraction and storage of DNA and/or RNA for future pharmacogenetic assays will be performed by [redacted] laboratory, [redacted] will store DNA will be stored frozen at -70ºC, according to patient consent information (see Section 6.5) until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of ACCRU studies.)

14.312 A portion of the serum/plasma will initially be analyzed for the presence of immunologic markers and cell free DNA in [redacted] laboratory using standard laboratory protocols. According to patient consent information (see Sections 6.2 and 6.5), remaining serum/plasma will be stored frozen at -70ºC by BAP, until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of ACCRU studies.)

14.4 Return of Genetic Testing Research Results

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

15.1 **Pembrolizumab (Keytruda®) -** IND #130955

Investigator Brochure available on the ACCRU web site.

15.11 **Background**: Pembrolizumab is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1 receptor thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has a high affinity and potent receptor blocking activity for PD-1.

15.12 **Formulation**: Pembrolizumab is available as a liquid, 25mg/ml (4ml), 100 mg/vial. Pembrolizumab is available as for subcutaneous injection as 165 mg/mL and 130 mg/mL liquid sterile solutions.

15.13 **Preparation and storage**: Vials should be stored in the refrigerator at temperatures between 2°C to 8°C. Drug concentrate is further diluted with normal saline (or 5% dextrose) in the concentration range of 1 to 10. mg/mL The infusion solution in the IV bag should be immediately administered. Diluted pembrolizumab should be stored at room temperature for a cumulative period of up to 6 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags can be stored at 2°C to 8°C for a cumulative time of 24 hours. This 24-hour total hold time from reconstitution may include up to 6 hours at room temperature. IV bags must be allowed to come to room temperature before use.

15.14 **Administration:** Pembrolizumab is administered by intravenous infusion over 30 minutes through a 0.22 micron in-line filter. The final infusion volume must be between 1 and 10 mg/mL. Maximum rate of infusion should not exceed 6.7 mL/minute through a peripheral or indwelling catheter. Flush the line with 0.9% NaCL following the completion of the infusion.

15.15 **Pharmacokinetic information**:

Absorption – Because Pembrolizumab is administered intravenously, it is immediately and completely bioavailable. Steady-state concentrations of Pembrolizumab are reached by 16 weeks of repeated dosing with a Q3 regimen and the systemic accumulation is 2.1-fold. The peak concentration, trough concentration, and area under the plasma concentration versus time curve at steady state of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg Q3W.

Distribution – Pembrolizumab has a limited volume of distribution.

Excretion – The terminal elimination half-life (t½) is estimated to be 22 days at steady state.

Metabolism – Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its CL.

15.16 **Potential Drug Interactions**: There are no known significant drug interactions.

15.17 **Known potential toxicities**:

Very common known potential toxicities, ≥10%:
Gastrointestinal disorders; diarrhea, nausea, abdominal pain
Skin and subcutaneous tissue disorders; rash, pruritis
General disorders and administration site conditions: fatigue

Common known potential toxicities, ≥1%≤10%:

Blood and lymphatic system disorders; anemia
Immune system disorders: infusion related reaction
Endocrine disorders: hyperthyroidism, hypothyroidism
Metabolism and nutrition disorders: decreased appetite
Nervous system disorders: headache, dizziness, dysgeusia
Respiratory, thoracic, and mediastinal disorders: pneumonitis, dyspnea, cough
Gastrointestinal disorders: colitis, vomiting, constipation, dry mouth
Skin and subcutaneous tissue disorders: severe skin reactions, vitiligo, dry skin, erythema
Musculoskeletal and connective tissue disorders: arthralgia, myositis, musculoskeletal pain, pain in extremity
General disorders and administration site conditions: asthenia, edema, pyrexia, influenza like illness, chills
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased

Uncommon known potential toxicities, ≥0.1% - 1%:

Infusion related reactions:
Blood and lymphatic system disorders: neutropenia, thrombocytopenia, leukopenia, lymphopenia, eosinophilia
Endocrine disorders: hypophysitis, adrenal insufficiency, thyroiditis, hypopituitarism
Metabolism and nutrition disorders: type I diabetes mellitus, hyponatremia, hypokalemia, hypocalcemia
Psychiatric disorders: insomnia, confusional state
Nervous system disorders: epilepsy, lethargy, peripheral neuropathy
Eye disorders: uveitis, dry eye
Cardiac disorders: myocarditis, atrial fibrillation
Vascular disorders: hypertension
Gastrointestinal disorders: pancreatitis
Hepatobiliary disorders: hepatitis
Skin and subcutaneous tissue disorders: lichenoid keratosis, psoriasis, alopecia, dermatitis, dermatitis acneiform, eczema, hair color changes, papule

Musculoskeletal and connective tissue disorders: tenosynovitis
Renal and urinary disorders: nephritis, acute kidney injury
Investigations: blood bilirubin increased, amylase increased, hypercalcemia

Rare known potential toxicities, <0.1% (Limited to important or life-threatening):

Blood and lymphatic system disorders: immune thrombocytopenic purpura, hemolytic anemia

Immune system disorders: sarcoidosis
Nervous system disorders: Guillain-Barre syndrome, myasthenic syndrome
Gastrointestinal disorders: small intestinal perforation, exacerbation of myasthenia gravis
Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema nodosum

The risk profile for Pembrolizumab also includes two important potential risks: a) myasthenic syndrome, and b) an increased risk of severe complications (such as early severe graft versus host disease and veno occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors.

Patients with multiple myeloma who were treated with pembrolizumab in combination with either pomalidomide or lenalidomide and dexamethasone, had an increased number of serious side effects and deaths as compared to patients who received only dexamethasone and either pomalidomide or lenalidomide. The benefit-risk profile is unfavorable for the combination of pembrolizumab, pomalidomide, and dexamethasone in relapsed refractory multiple myeloma, and the combination of pembrolizumab, lenalidomide, and dexamethasone in newly diagnosed treatment-naive multiple myeloma.

Post marketing reports identified Vogt-Koyanagi-Harada syndrome and hemophagocytic lymphohistiocytosis.

15.18 **Drug procurement:**
Each participating ACCRU treating location will be responsible for monitoring the supply of pembrolizumab and will use the Drug Order Request Form on the ACCRU web site to order additional supplies as needed. Before registration of first patient fax a drug order request form to procure a starter supply. Fax the completed form to the following:

Clinical Research Services, a division of Rx Crossroads by McKesson
Fax: [redacted]

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.19 Nursing guidelines:

15.191 Pembrolizumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

15.192 Diarrhea can be seen, however, it is less common than that seen with anti-CTLA-4 agents. However it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

15.193 Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Treat per section 9.0 and monitor for effectiveness.

15.194 Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

15.195 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any shortness of breath, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse oximetry checked and consider immediate imaging per the treating physician.

15.196 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well." Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by the treating physician.

15.197 Patients who are started on steroid therapy for any side effects of pembrolizimab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

15.198 Fatigue is common and may or may not be associated with immune related side effects. Assess patient's fatigue level prior to each cycle of therapy and report any changes to the study team.

15.199a Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.

15.199b Patients who have undergone an allogenic bone marrow transplant, have an increased risk of severe complications including early GVHD, and veno-occlusive disease, if they have previously been treated with pembrolizumab.

15.199c Myocarditis has been reported and associated with pembrolizumab. Instruct patients to report chest pain, shortness of breath, or dyspnea to study team immediately and/or seek emergency medical attention.

15.199d Autoimmune hematologic disorders including ITP and hemolytic anemia have been reported. Monitor blood counts closely and report any abnormalities to the study team.

15.199e Rare neurologic disorders including Guillain-Barre syndrome and myasthenia gravis have been reported. Instruct patients to report any neurologic symptoms including weakness, parathesias or numbness, tingling to the study team immediately.

16.0 Statistical Considerations and Methodology

16.1 Study Overview

This study will assess the confirmed response rate associated with Pembrolizumab (MK-3475) in small bowel adenocarcinoma. Additional endpoints consist of progression-free survival (PFS), overall survival (OS), and adverse events. Translational endpoints will be assessed as well using an exploratory analysis, given the small sample size.

16.2 Primary Endpoint

This study will assess the confirmed response rate associated with MK-3475/Pembrolizumab in small bowel adenocarcinoma. Confirmed response rate will be defined as meeting RECIST 1.1 criteria on two consecutive evaluations at least 4 weeks apart. Confirmed response will be evaluated using the first year of treatment (first 18 cycles of treatment). All patients meeting the eligibility criteria who have a signed consent form and have begun treatment will be evaluable for response.

16.3 Study Design for Primary Endpoint

16.31 Ho vs. Ha Hypothesis for the Primary Endpoint

To evaluate the confirmed response rate we will be using a 1-stage design to test the hypothesis of the treatment being ineffective (Ho: $p < 10\%$) vs. the hypothesis of the treatment being clinically effective (Ha: $p > 30\%$).

16. 32 Final Analysis Decision Rule

Enter a total of 35 evaluable patients. If 6 or fewer of these 35 patients have a confirmed response, we will conclude that this treatment is insufficiently active in this population. If 7 or more of these 35 patients have a confirmed response (20%), this will be considered adequate evidence of efficacy of this treatment and may be recommended for further testing in subsequent studies.

16.33 Sample Size and Power

We anticipate accruing an additional 5 patients to account for ineligibilities, cancellations, major violations, or other reasons. Therefore, maximum accrual is 41 patients. This design has a significance level of 0.06 when the confirmed response rate is 10%, and 94% power to detect a confirmed response rate of 30%.

16.4 Total Sample Size

35 evaluable patients will be enrolled, if the study reaches full accrual. We anticipate accruing an additional 5 patients to account for ineligibility's, cancellations, major violations, or other reasons. Therefore, maximum accrual is 41 patients.

16.5 Accrual time and Study Duration

The anticipated accrual rate is approximately 3 patients per month. Therefore, the accrual period for this phase II study is expected to be approximately 14 months, if the study goes to full accrual. The final analysis can begin approximately 30 months after the trial begins, i.e. as soon as the last patient has been monitored for 12 months plus data clean-up and analysis.

16.6 Secondary endpoints

These endpoints include progression-free survival (PFS), overall survival (OS), and adverse events.

- Progression-free survival (PFS) is defined as the time from study entry to the first of either disease progression or death from any cause, where disease progression will be determined based on RECIST 1.1 criteria. PFS will be estimated using the Kaplan-Meier method.
- Overall survival (OS) is defined as the time from study entry to death from any cause. OS will be estimated using the Kaplan-Meier method.
- Adverse events: The maximum grade for each type of adverse event will be summarized using CTCAE version 4.03. The frequency and percentage of grade 3+ adverse events will be summarized.

16.7 Translational studies

All translational research will be exploratory and hypothesis generating due to the small sample size. We will correlate clinical data (i.e. response, OS, PFS, adverse events) with translational marker data (i.e. MMR/MSI, PDL1 expression, Cell free DNA, genetic sequencing data, blood markers, Bim levels, T cell markers, sPD-L1, total mutational burden, etc.). These correlations will be done using the Chi-square or Fisher's exact test for categorical data and Kaplan-Meier methods (including the log-rank test) for the survival endpoints. Univariate Cox regression models will also be done to assess for marker effects on survival endpoints. Descriptive statistics and graphical methods will be used to summarize the data as well. All these analyses will be done overall and by MMR/MSI status.

Genetic/genomic testing performed for clinical purposes will be requested for patients from the local sites, and will be deidentified for inclusion in analyses.

16.8 Data & Safety Monitoring

The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The trial is monitored continually by the study team who are notified of every grade 4 and 5 event in real time. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.9a AE Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event

of either (1) the study re-opening to accrual after any temporary suspension or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may also choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.
Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy any of the following criteria across both cohorts combined.

- If at any time, 4 of the initial 10 treated patients or 40% or more of all patients (i.e. when accrual is greater than 10 patients) have experienced a grade 4 non-hematologic adverse event.
- If at any time, 2 patients have experienced a grade 5 adverse event (non -progressive disease).
- In addition, each grade 5 event will be reviewed on a case by case basis in a real time fashion to determine whether study accrual should be suspended. We may suspend accrual after just 1 grade 5 AE, if needed.

16.9b Accrual Monitoring Stopping Rule

Given the expected accrual rate is around 3 patients per month, it is expected that the study will take around 14 months to fully accrue. We plan to monitor the accrual continually and if we only end up accruing 5 patients or less in the first year (after study activation), we will consider stopping the trial for slow accrual.

16.9c Primary Endpoint Completion Time Estimation (For clinicaltrails.gov reporting)

The primary endpoint is the confirmed response rate, evaluated over the first year of treatment. The final analysis is expected to take place around 30 months after the study begins, so we expect that the primary endpoint completion time to be around 30 months after study activation.

16.9d Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Based on prior studies involving similar disease sites, we expect about 10% of patients will be classified as minorities by race and about 30% of patients to be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	0	0
Not Hispanic or Latino	13	28	41
Ethnic Category: Total of all subjects	13	28	41
Racial Category			

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
American Indian or Alaskan Native	1	0	1
Asian	0	1	1
Black or African American	0	1	1
Native Hawaiian or other Pacific Islander	0	1	1
White	11	25	36
Racial Category: Total of all subjects	13	28	41

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission

17.11 Summary Table of Tissue Biospecimens for This Protocol

Type of tissue biospecimen to submit	Mandatory or optional	When to submit	Reason for submission (background/methodology section)	Where to find specific details for biospecimen submission
Formalin-fixed paraffin-embedded (FFPE) tissue blocks with corresponding H&E OR 30 5- or 10-micron unstained slides with corresponding H&E) *Can be archival tissue	Mandatory	≤60 days after registration	Correlative studies (Section 17.3)	Section 17.2

If an institution is not able to provide the tissue, it does not cause the patient to be ineligible; however, the collection of these tissues is **strongly recommended**.

17.2 Paraffin Embedded Tissue Blocks/Slides (mandatory for research tissue)

17.21 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block from the primary or recurrent/metastatic Small Bowel Adenocarcinoma. A corresponding H&E slide from the submitted block must be provided to permit quality assessment (QA) of tissue block.

17.22 The FFPE tissue block is preferred; however, if an institution is unable to provide a tissue block, cut 20 five-micron unstained slides and mount on charged glass slides and 10 ten-micron unstained slides mounted on uncharged slides. **Label the slides with the ACCRU patient ID number, accession number, and order of sections (i.e., 1-11). H&E stain the first cut slide (i.e., slide labeled 1). Please do not re-label over the original label.** For samples containing less than 7square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. **Do not bake or place cover slips on the slides.**

17.23 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- Paraffin embedded tissue blocks with corresponding H&E (or 30 slides) per instructions in section 17.22
- Research Tissue Specimen Submission Form
- Surgical Pathology Report
- Operative Report-Optional

17.24 Ship all block/slide tissue specimens and accompanying materials to the following:

[redacted]

17.3 Study Methodology and Storage Information

17.31 Tissue microarray testing. FFPE tumor tissue blocks/slides will be collected in order to assess correlation of responses to treatment with PDL1 staining by immunohistochemistry (IHC). For tissue blocks received, tissue microarrays (TMAs) may be constructed and analyzed. For TMA constructions, the donor block remains intact except for 6 small (0.6mm) holes where the cores were taken. This process has minimal impact on the utility of the block for future clinical diagnostic needs. TMA construction and IHC stains will be performed in the Pathology Research Core Lab, Mayo Clinic Rochester. FISH analyses will be performed in the laboratory of [redacted].

17.32 Immunohistochemical analyses. The following protein biomarkers will be assessed by immunohistochemistry (IHC) on tumor samples obtained at baseline:

- MMR (MLH1, MSH2, MSH6, PMS2)
- PDL1 staining
- Lymphocyte-specific markers *(CD4, CD8, Bim, etc.)*

PD-L1 staining will be performed. All other IHC testing will be performed in the laboratory of [redacted] Analysis of all IHC slides, pathologic assessment will be performed by [redacted]

17.33 Nucleic acid analyses. PCR analysis for DNA mismatch repair deficiency/microsatellite insufficiency will be performed retroactively at the central lab on all tissue samples using the Promega MSI Analysis assay.

Genomic analyses (whole exome, RNA-Seq, etc.) may be performed at a future date for further characterization of total mutational burden, biomarkers, etc. DNA and/or RNA will be extracted and stored as stated in 17.54.

17.34 At the completion of the study, any unused/remaining material will be stored in the ACCRU Central Operations Office (Attn: Pathology Coordinator) for future research according to the patient consent permission (see Section 6.0). Potential future research may include immunohistochemistry (IHC) analyses, DNA extraction, and/or tissue microarray (TMA) construction to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. For TMAs, the donor block remains intact except for 6 small (0.6mm) holes where the cores were taken. This process has minimal impact on the utility of the block for future clinical diagnostic needs. When a protocol is developed, it will be presented for IRB review and approval.

17.35 Banking of tumor tissue, according to the patient consent permission is for future research. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for Mayo Clinic Cancer Center studies.)

17.36 The institutional pathologist will be notified by the ACCRU Operations Office (Pathology Coordinator) if the block may be depleted.

17.37 Blocks requested to accommodate individual patient management will be returned promptly upon request.

17.4 Return of Genetic Testing Research

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sough regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

18.0 Records and Data Collection Procedures

All data must be entered by Remote Data Entry (RDE) and completed by qualified and authorized personnel. Access the RAVE RDE system through the iMedidata portal at [redacted]. All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions [redacted]. NOTE: All reports must be de-identified and labeled with the study number, ACCRU patient ID number and initials.

18.1 Submission Timetables

Initial Material(s) -

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study	≤2 weeks after registration
Adverse Event Baseline	
Research Blood Submission - Baseline (see Section 14.0)	
Research Tissue Submission - Baseline (see Section 17.0)	
Concomitant Medication - Baseline	
Path Reporting (see Section 17.0)[1]	
RECIST Measurement – Baseline	
End of Active Treatment/Cancel Notification	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Attach a copy of OP and path reports in RAVE using the Supporting Documentation Form for documentation of disease. This is in addition to the pathology material requirements for tissue submission (Section 17.0)

Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Evaluation/Treatment	X[2]	X
Adverse Event Form	X	X
RECIST Measurement	X[1]	X[1]
Research Blood Submission	X (see Section 14.0)	
Pathology Submission		
Concomitant Medication	X	X
End of Active Treatment/Cancel Notification Form		X
Deviation Form[3]	X	
ADR/AER	At each occurrence (see Section 10.0)	

1. Attach a copy in RAVE for documentation of response or progression on the Supporting Documentation Form.
2. Complete at each evaluation during Active Treatment (see Section 4.0).
3. Submit only if applicable.

Follow-up Materia(s)

CRF	Event Monitoring Phase[1]				
	q. 3 months until PD	At PD	After PD q. 6 mos.	Death	New Primary
Event Monitoring Form	X[2]	X[2]	X	X	At each occurrence

1. If a patient is still alive 5_years after registration, no further follow-up is required.
2. Attach a copy in RAVE for documentation of progression on the Supporting Documentation Form.

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded:

19.21 Mandatory blood samples done for research.

19.22 Mandatory blood samples done for future research.

19.3 Other budget concerns: The study agent, pembrolizumab will be provided by Merck at no charge.

20.0 References

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