Abbreviated Title: CAPOX Pembrolizumab in BTC

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Title: A Phase 2 Study of Pembrolizumab, a Monoclonal Antibody Against PD-1, in Combination with Capecitabine and Oxaliplatin (CAPOX) in Subjects with Advanced Biliary Tract Carcinoma (BTC)

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Investigational Agents:

None

Commercial Agents:

Pembrolizumab (Keytruda)

Capecitabine

Oxaliplatin

PRÉCIS

Background:

- The most compelling argument in favor of testing immune-based strategies (and anti-PD1 therapy) in biliary tract cancers (BTC) is that chronic inflammation appears to be the most common etiologic factor in the development of biliary tract cancer.
- Single-agent activity has been shown for PD1-directed therapy in BTC. Given the potential for oxaliplatin-induced immunogenic cell death we would like to evaluate the combination of CAPOX chemotherapy with pembrolizumab.

Objective:

- To determine the 5-month PFS of Pembrolizumab in combination with CAPOX in patients with advanced biliary tract carcinoma.

Eligibility:

- Histologically confirmed diagnosis biliary tract carcinoma OR histopathological confirmation of carcinoma in the setting of clinical and radiological characteristics which, together with the pathology, are highly suggestive of a diagnosis of biliary tract carcinoma.
- Patients must have at least one prior chemotherapeutic regimen.
- Patients must have disease that is not amenable to potentially curative resection.
- No prior treatment with oxaliplatin.

Design:

- The proposed study is a phase II study of Pembrolizumab in combination with CAPOX in patients with advanced biliary tract carcinoma.

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1. INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective:

- To determine the 5-month PFS of Pembrolizumab in combination with capecitabine and oxaliplatin chemotherapy (CAPOX) in patients with advanced biliary tract carcinoma.

1.1.2 Secondary Objectives:

- To determine the safety, tolerability and feasibility of Pembrolizumab in combination with capecitabine and oxaliplatin chemotherapy (CAPOX) in patients with advanced biliary tract carcinoma.
- To evaluate the response rate and overall survival in patients with advanced biliary tract cancer during and following treatment with Pembrolizumab in combination with capecitabine and oxaliplatin chemotherapy (CAPOX) in patients with advanced biliary tract carcinoma.

1.1.3 Exploratory Objectives:

- To measure changes in PDL1 expression in the tumors of patients with advanced biliary tract cancer following treatment with capecitabine and oxaliplatin chemotherapy (CAPOX) in patients with advanced biliary tract carcinoma.
- To measure changes in immune parameters in the peripheral blood and tumors in patients with advanced biliary tract cancer following treatment with Pembrolizumab in combination with capecitabine and oxaliplatin chemotherapy (CAPOX) in patients with advanced biliary tract carcinoma.

1.2 BACKGROUND AND RATIONALE

1.2.1 Biliary tract cancer/Cholangiocarcinoma: current standard of care.

The term biliary tract carcinoma (BTC) refers primarily to cancers which develop in the gallbladder and intra- and extra-hepatic biliary ductal system, although periampullary tumors are often considered part of this group as well. BTC is a relatively uncommon diagnosis, and randomized studies are few and far between. Among the new cases of BTC that are diagnosed every year in the United States, there are approximately 6500 cases of gallbladder carcinoma, 3000 cases of extrahepatic cholangiocarcinoma, and 3000 cases of intrahepatic cholangiocarcinoma[1].

As is the case for most solid tumors, surgical resection is the only curative approach for patients with BTC, although recurrence rates are high and the majority of patients who initially present with the disease are not resectable. Patients with periampullary tumors or extrahepatic cholangiocarcinomas commonly present with localized disease – primarily because of the early development of jaundice – and are more likely to be operable. In contrast, complete surgical resection of intrahepatic cholangiocarcinomas is rarely feasible with clear margins. Gallbladder carcinoma is frequently identified incidentally at the time of cholecystectomy for presumed cholelithiasis, in which case re-exploration and further extended resection is usually advised[2]. For metastatic or unresectable disease the modest standard of care for BTC comprises gemcitabine in combination with cisplatin chemotherapy, based on the ABC-02 trial in which a

total of 410 patients with unresectable locally advanced or metastatic disease were randomly assigned to receive gemcitabine with or without cisplatin[3]. Median progression-free and overall survival were superior in the combination arm (8.0 versus 5.0 months and 11.7 versus 8.1 months, respectively; P<0.001), with the benefit seen consistently across the BTC subtypes. For patients who progress following first-line therapy there is no outright standard second-line option and therapy is usually an extrapolation from agents used in pancreatic or other gastrointestinal cancers[4]. Clearly, there is an unmet need here to improve the treatment options at every stage for patients diagnosed with this relatively uncommon cancer type.

1.2.2 Immune-based approaches in gastrointestinal malignancies

The past number of years have seen much progress for immune-based approaches in solid tumor malignancies, with FDA approvals for various strategies, including dendritic cell vaccination (prostate cancer) as well as so-called immune checkpoint inhibition, targeting CTLA4 or the PD1/PDL1axis (melanoma, lung, kidney cancer)[5-7]. These latter therapies in particular have generated enormous excitement across the entire field of oncology, providing real and major benefit to a significant minority of patients, as well as teaching us a great deal about the immune system in our efforts to predict who will benefit from treatment. Appreciation of the role of immune-evasion in developing tumors was evidenced by its inclusion as one of the (updated) hallmarks of cancer[8]. The next steps seem to be clear, at least in outline, with current attempts in the clinic focusing on identifying those patients who will or will not respond to treatment while at the same time expanding the proportion of patients in each cancer type who can experience the real and dramatic benefits seen with immune-based approaches. The next frontier is for these treatments to prove themselves, even in principle, in diseases which have thus far proved relatively refractory. So far, with some notable exceptions, this has unfortunately included cancers of the gastrointestinal tract, including BTC. One of the first studies evaluating and showing impressive results of PD1/PDL1-directed therapy was disappointing from a GI cancer viewpoint[9]. There were no responses in any of cohorts containing patients with colorectal (N=18), pancreatic (N=14) and gastric (N=7) cancer. Similarly, negative results for GI cancers were seen both in other studies of anti-PD1 therapy and also CTLA4 inhibition[10-12]. The notable exceptions to this disappointing, preliminary experience, have been in mismatch repair-deficient colorectal cancer – where exceptional responses to PD-1 inhibition have been seen – and also hepatocellular carcinoma[13, 14]. The former situation results in a marked increase in the non-synonymous mutagenic burden within tumors, thereby – presumably – increasing the likelihood that a tumor-specific neoantigen is generated which is recognized by the immune system[15]. This of course is relevant for any tumor type which happens to have a high mutagenic burden, either because of inherited or acquired mismatch repair deficiency - resulting in a degree of microsatellite instability (MSI-hi) – or other factors. In the study by Le et al. MSI-hi non-colorectal cancers also responded excellently well and in melanoma and non-small cell lung cancer mutagenic burden has been associated with benefit to immune checkpoint inhibition[16, 17]. The findings of activity of anti-PD1 therapy in HCC are particularly apt for cholangiocarcinoma however, given their overlapping etiology and the common basis of both tumor types in inflammation. In BTC itself, emerging data suggests clinical activity with immune checkpoint inhibition in the clinic and, though very preliminary, is encouraging, particularly in the context of the underlying rationale for why this should be the case[18, 19].

1.2.3 Inflammation and predisposition to biliary tract carcinoma.

The causative link and similarity between inflammation and cancer development stretches back to the 19th century observations of Rudolph Virchow and, indeed, even two millennia earlier than that to the time of the first physicians[20]. Chronic inflammation can greatly facilitate cancer development and progression through a number of means, culminating in the development of an immunosuppressed microenvironment, whereby host anti-tumor immunity is evaded or inhibited[21]. This broad and sometimes paradoxical relationship between cancer and inflammation is particularly relevant in BTC, a cancer – like HCC, the other, more prevalent primary liver cancer – whose main associated predisposing conditions have chronic inflammation as their common underlying pathological denominator. Although the majority of patients with BTC will have no identifiable cause on an individual basis, strong associations exist between BTC and various disparate inflammatory conditions[22]. The dominant known risk factor for gallbladder carcinoma is cholelithiasis-induced chronic inflammation[23], whereas – worldwide – infestation of the biliary ducts by parasites or persistent hepatolithiasis are important predisposing factors for intrahepatic cholangiocarcinoma[24]. In the US and Europe primary biliary cirrhosis and sclerosing cholangitis are all established risk factors for BTC, as are causes of intrahepatic inflammation – hepatitis, diabetes, obesity for example – whose importance in the etiology of intrahepatic cholangiocarcinoma is being increasingly appreciated[25]. Recent studies have linked liver disease associated with the increasing incidence of chronic hepatitis C virus infection with intrahepatic cholangiocarcinoma[26], which may explain in part the increasing occurrence of this subtype (intrahepatic type) of biliary tract cancer[27]. For established cancer the Glasgow prognostic score (GPS), an inflammation-based prognostic score, has been shown to predict for postoperative outcome for BTC[28].

The finding of an immune role in the etiology of BTC is important because it raises the possibility of an immune-based remedy in at least a proportion of patients. This is not only relevant for established cancer but also in the long antecedent period of inflammation and pre-malignancy where the opportunity for prevention exists. It has been shown that cholangiocytes have the ability to present antigens and can activate a subset of lymphocytes called Natural Killer T (NKT) cells[29]. Primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) are characterized by a marked hepatic mononuclear infiltration, but this is also a feature of other chronic liver diseases, including environmentally-driven conditions such as alcoholic cirrhosis[30]. As stated above, all of these conditions increase the risk of developing BTC[31]. In PSC, a marked CD4+ and CD8+ T-cell infiltration in portal tracts and around bile ducts is seen[32]. Interestingly, it seems that the pattern of antigen-driven clonal expansion of T cells may vary according to the underlying predisposing condition, with distinct T-cell receptor (TCR) signatures reflective of different antigenic repertoires[30]. This was suggested by Liaskou et al. who performed high-throughput sequencing of the TCR beta chain complementarity-determining region 3 of liver-infiltrating T cells in samples derived from patients with primary sclerosing cholangitis, primary biliary cirrhosis and alcoholic cirrhosis[30]. These analyses revealed the presence of distinct disease-associated clonotypes which differed by degree. For example, in alcohol-related disease, a pronounced oligoclonal nature of liver infiltrating T cells was observed, in contrast to a higher diversity amongst T-cells infiltrating PSC.

1.2.4 Immunogenicity of biliary tract carcinoma.

The success of immune checkpoint inhibition is dependent first and foremost upon the presence of an already existing endogenous anti-tumor immune response, which can then be amplified or

disinhibited. In the absence of initial immune recognition this class of agents won't be effective, as – by definition – there will be no adaptive resistance or suppression to overcome. Spontaneous immune responses do occur in established BTC. This was illustrated in dramatic fashion by Rosenberg and colleagues who performed whole-exome-sequencing on the resected tumor of a patient with metastatic chemo-refractory cholangiocarcinoma in order to identify mutations which could serve as neo-antigens[33]. By generating tandem minigene (TMG) constructs of each of the mutations and co-culturing with expanded populations of the isolated tumor infiltrating lymphocytes (TIL), they were able to identify a clonal population of CD4+ T helper 1 (T(H)1) cells which were reactive to a mutation in erbb2 interacting protein (ERBB2IP) in the tumor. Via adoptive transfer of enriched populations of these cells, cultured ex-vivo, the investigators could produce persistent tumor regression. This case confirms that tumor-associated antigen (TAA)-provoked immune responses do occur in cholangiocarcinoma as well as illustrating that, in principle, the exact nature of this response can be isolated by currently available technologies, quantitatively enhanced, enriched, and then administered back to the patient with therapeutic effect[33]. Beyond the proof of concept however, the wider relevance of this case to cholangiocarcinoma is uncertain. It was notable in this patient that only 26 nonsynonymous mutations were identified in the tumor, a relatively low number in comparison to, for example, UV-associated melanoma or cigarette-induced lung cancer, where a much greater mutagenic burden appears to increase the chances of generating an epitope or epitopes capable of inciting a strongly reactive immune response. Cholangiocarcinoma in general is not a highly mutated cancer. For example, in 239 cases of BTC in whom whole-exome sequencing was performed the median numbers of non-silent somatic mutations across the ICC (N=137 cases), ECC (N=74 cases) and gallbladder cancer (N=28 cases) subtypes were 39, 35 and 64, respectively[34]. Interestingly, in that analysis, a small proportion (5.9%) of cases were identified as having a very high number of mutations (median no. = 641), 5 of whom had defects in the mismatch-repair apparatus. We have seen already that this population of MSI-hi tumors respond excellently well to anti-PD1 therapy[35]. Also, of special interest in this analysis was that via unsupervised clustering of global gene expression levels, determined by transcriptome sequencing, four molecular subgroups of BTC were elucidated which could be divided into prognostic categories. The group which had the poorest prognosis demonstrated enrichment for genes involved in the immune system and cytokine activity. The hypermutated tumors were part of this cluster and expression of immune checkpoint molecules, including PD-L1, was significantly higher in this poor outcome group. This suggests that in addition to the pro-tumorigenic effects of inflammation, escape from immunity is achieved by the tumor – at least in a significant proportion of cases – via the upregulation of targetable (and now FDA-approved) strategies.

Perhaps the best indicator of an already existing, but possibly suppressed, antitumor immunity is the presence of immune cells which have already migrated to the tumor. Tumor infiltrating lymphocytes (TIL) have been shown in a variety of non-GI cancers to be prognostic as well as predictive of efficacy in immune and non-immune therapeutic approaches[36-39]. In melanoma, the presence of T-cell-infiltration, particularly those with high CD8 T-cell content, are more likely to be associated with PD-L1 expression in tumor cells – making them more susceptible to anti-PD1/PDL1 treatment – and an improved prognosis[39]. The presence of TIL has likewise been shown to be a favorable prognostic factor in a variety of GI cancers such as colorectal cancer and pancreatic cancer[40-42]. Recent evidence has highlighted the link between overall mutagenic burden, immune reactivity and – in the case of UV-associated melanoma, cigarette-

induced lung and MMR-deficient colon cancer especially – dramatic responses to immune checkpoint inhibition. However, Tran and colleagues have recently suggested that the relationship is more nuanced than that, with the finding – through the same TMG approach mentioned above – of immunoreactive TIL even in the setting of low burden mutational burden[43]. These investigators found that in patients with gastrointestinal cancers whose tumors had, as expected, a low mutation burden (range 10-155) T-cell responses against at least one somatic mutation were still present and identifiable in nine out of ten cases.

In BTC, the prevalence and prognostic relevance of infiltrating T-lymphocytes has also been documented. Sabbatino et al. evaluated lymphocyte infiltration (as well as HLA and PDL1 expression in 27 cases of ICC[44]. All tumor specimens had TIL, and this correlated – as one would expect – with HLA expression. Nakakubo et al. investigated the significance of tumor-infiltrating immune cells in 110 surgically resected biliary tract cancer (gallbladder) specimens[45]. They found high levels of CD4+ T cell (51.1%), CD8+ T cell (37.8%), NK cell (33.3%), and dendritic cell (48.9%) infiltration. CD4+ and CD8+ T cell infiltration correlated with decreasing tumor invasion, and high numbers of infiltrating DCs correlated with decreasing lymph-node tumor metastasis. Furthermore, increased infiltration of CD4+ and CD8+ T cells and DCs exhibited a significant correlation with prolonged survival. In a similar analysis, Goeppert et al. evaluated immune cell infiltration in 375 cases of biliary tract cancer obtained following surgical resection[46]. Approximately half the patients had some degree of intraepithelial CD8 T cell tumor infiltration and this – in addition to other inflammatory infiltrate – decreased with increasing stage of disease. The presence of intraepithelial tumor-infiltrating CD4+ T lymphocytes as well as CD8+ T lymphocytes correlated significantly with a longer overall survival in BTC patients. Interestingly, patients who had higher total regulatory T lymphocyte counts had a better survival outcome. The prognostic value of Tregs in other GI tumor types, especially colorectal cancer, has been variable in terms of whether it was a favorable or adverse factor[47]. In cholangiocarcinoma cell lines it has been shown that down-regulation of FOXP3 inhibits tumor cell invasion by reducing the quantity of MMP-9 and MMP-2 as well as immunosuppressive cytokines (IL-10 and TGF-b1) produced by the tumor cells leading to better T-cell survival, suggesting that FOXP3 plays an important role in the evolution of the malignant phenotype[48].

It was also of note in the large sample analyzed by Goeppert et al that differences were observed in the composition of inflammatory infiltrate by anatomical subtype with comparatively less CD8+ infiltration in intrahepatic disease relative to extrahepatic disease and gallbladder cancer. Indeed, the prognostic significance of the presence of intraepithelial T and B lymphocytes pertained only to these subtypes and not to intrahepatic cholangiocarcinoma. The potential difference in inflammatory infiltrate according to anatomical subtype noted by Goeppert et al. is intriguing, but perhaps not surprising given the differences in molecular derangement or gene expression, different cell of origin as well as in incidence, risk factors and indeed outcome[49, 50]. Although clinically the anatomical subtypes are treated the same (surgical resection if technically feasible, gemcitabine-based chemotherapy, radiation) this paradigm has evolved more through expediency and clinical trial design or enrollment issues rather than being driven by biological considerations. As we move into the immunotherapeutic era we will need to pay more attention to this, perhaps by stratification measures to ensure that enough patients in each subtype are treated.

Given that antigen-specific adaptive responses are brokered by MHC class 1-presentation of tumor peptide to T cells, it has been reported by many investigators across many disease types that one method of immune evasion is achieved by virtue of changes in expression or downregulation of MHC I[51-53]. Indeed, downregulation of MHC I expression is more frequently observed in advanced disease stages and tumors which are poorly differentiated[54, 55].

Goeppert et al. analyzed the impact of the expression of MHC I on patient survival in BTC as well as the quantitative and qualitative relationship of this factor to tumor-infiltrating immune cell types[56]. They evaluated a large cohort of patients (N=334), including extrahepatic (n=129) and intrahepatic cholangiocarcinomas (n=146), as well as adenocarcinomas of the gallbladder (n=59). In addition, 71 high-grade biliary intraepithelial lesions (BilIN 3) were included. MHC I expression was assessed semi-quantitatively and broadly divided into two groups of high and low expression patterns, roughly half in half (47.6% Vs 52.4%).There was a trend for higher MHC I expression in lower Union for International Cancer Control (UICC) stages (P=0.074) and in particular biliary intraepithelial neoplasia (BilIN) 3, where significantly higher MHC I expression levels were seen compared to invasive tumors (P=0.004) in addition to a significant association between high MHC I expression and low tumor grade. There was also an association between MHC I expression and the number of tumor-infiltrating immune cells. Interestingly, the investigators found that the associations differed by anatomical subtype. The association between inflammatory infiltrate and MHC I expression for the whole cohort pertained to ECC, whereas in ICC, MHC I expression was correlated significantly only with the number of tumor-infiltrating CD8+ T cells. In GBAC, the smallest cohort, a significant correlation of MHC I expression was only seen for CD68+ macrophages. Higher MHC I expression on tumor cells was also significantly associated with longer overall survival with patients exhibiting strong MHC I expression having an improved median overall survival of 28 months (versus 20 months for low expression; P=0.006). Looking at the subtypes the investigators found in their analysis that the prognostic significance of MHC I expression on tumor cells, although not reaching statistical significance, was by trend stronger in ECC and GBAC compared with ICC, again suggesting that mechanisms of immune escape may vary with anatomical subtype.

PD-L1 expression in tumors, induced by interferon-gamma, has been shown to predict for response to PD1-inhibtion[57]. The relationship is not absolute and additional factors exist in the tumor microenvironment which contribute to the immunosuppression and dictate the manner of response. Nevertheless, PDL1 expression is likely to be the first companion diagnostic to make it into clinical practice as a predictive test of benefit to checkpoint inhibition. In BTC Ye et al. evaluated the expression of B7-H1 (PD-L1) and its ligand PD-1 in N=31 surgically resected cases in addition to the corresponding cancer adjacent tissues[58]. Expression of PD-L1 and PD-1 was found to be up-regulated in cholangiocarcinoma tissues compared with the cancer adjacent tissues. Tumor-related PD-L1 expression was significantly correlated with both tumor differentiation and pTNM stage and was inversely correlated with CD8+ tumor-infiltrating lymphocytes. In the analysis by Sabbatino et al. 8 of 27 ICC cases expressed PD-L1[44].

1.2.5 Translational immune-based efforts in BTC

There is a paucity of randomized clinical trials for BTC, no doubt because of the relative rarity of this tumor type. In addition, the cholangiocarcinoma-specific phase 2 studies which are available to patients tend towards the evaluation of chemotherapeutic combinations (e.g. FOLFIRINOX or gemcitabine + nab-Paclitaxel) which have already shown efficacy in other indications, and the

usefulness of which investigators are attempting to assert in BTC. As a result of this, progress in BTC has seemed to lag behind that of other, more common solid tumors, with a dearth of studies evaluating new and innovative drugs. Traditionally, BTC patients could for the most part only access clinical trials in the phase 1 setting. With the advent of immune-based approaches, this paradigm shows signs of change, with less emphasis on the initial dose-escalation phase of drug development - important mainly for dose limiting toxicity (DLT) determination in the evaluation of cytotoxic agents - in favor of large, basket studies allowing multi-histology cohorts, such as the initial anti-PD1 studies[59, 60], in which pure DLT-determination in the first 28days is less crucial. Table 2 shows the currently open and accruing studies employing an immune-based approach currently available on clinicaltrials.gov and which are specific to BTC or have BTC explicitly stated as an eligible histology.

In terms of published or presented clinical data for immune approaches in BTC the experience in the literature is dominated by peptide vaccines, most commonly directed against mucin protein 1 (MUC1) or Wilm's Tumor protein 1 (WT1)[61]. These small studies have been well tolerated without showing a strong clinical signal of efficacy[62, 63]. For example, Aruga and colleagues conducted a small phase I clinical trial evaluating multiple-peptide vaccination for patients with advanced BTC[64]. The vaccine selected comprised three cancer-testis antigens that were identified using cDNA microarray technology coupled with laser microdissection and which were found to be overexpressed in nearly 100% of BTC. Patients were vaccinated on a continuous basis even if their disease had progressed. Peptide-specific T cell immune responses were observed in all patients and stable disease, prolonged in a couple of cases and associated with increased CXCR3+CCR4- T cells, was observed in 5 of 9 patients. The median PFS and OS of 3.4 and 9.7 months respectively. The same investigators had earlier tested a different four-peptide vaccine, similarly well tolerated observing peptide-specific T-cell immune responses in seven of nine patients and clinical responses – including two instances of minor response not reaching PR criteria - observed in six of nine patients[65]. Dendritic-cell based vaccines have also been evaluated, most commonly in combination with standard modalities, such as surgical resection and/or chemoradiation, and which complicates assessment of efficacy[66, 67].

The published or presented experience with immune checkpoint inhibitors is very preliminary. Documented response to anti-CTLA4 therapy (with tremelimumab) has been seen, interestingly manifesting as a delayed response after initial progression of disease[18]. The early data for anti-PD1 inhibition (pembrolizumab) has been recently presented, showing encouraging evidence of efficacy (17% partial response rate) in BTC, and which seems broadly in line with use of this agent in other solid tumor studies where no pre-selection based on PD-L1 expression or MSI status was performed[19].

One of the great advantages and promises of immune-based approaches is the potential role for their combination with standard therapies, either cytotoxic agents which have immune-modulatory effects or strategies such as radiation or interventional radiologic procedures, in whom participation of the immune system has been shown to be a determinant in how they work[68]. Certain chemotherapeutics can activate rather than suppress the immune system and that a robust immune response is a necessary component determining tumor response[69]. Gemcitabine is a nucleoside analogue that is part of the standard treatment, and probably the most common chemotherapeutic agent used in BTC[3, 70]. The immune effects of gemcitabine have been studied perhaps more than for any other drug used in GI cancer. Its effects on the immune system are diverse[68]. With regard to BTC Koido et al. demonstrated that in ICC cells

isolated from a patient with malignant ascites immunogenic modulation of the cells could be induced by gemcitabine with upregulation of MHC class I and II, calreticulin – a modulator or immunogenic cell death – MUC1 and WT1 mRNA[71]. Interestingly, the authors found that gemcitabine also induced up-regulation of immunosuppressive PDL1, suggesting a potential rationale for combination therapy. Ablative therapies are occasionally employed in the management of BTC, although with a much smaller role than in HCC for example. Following RFA, tumor antigens from necrotic tumor are taken up by antigen-presenting cells (mainly DCs), activating tumor-specific immune responses[72, 73]. Ablated tumor tissue promotes DC maturation[74, 75]. A tumor-specific immune response may prevent recurrent disease in addition to treating distant metastases. Several preclinical and clinical studies have documented an increase in peripheral immunity following ablation[74, 76-79]. We are currently conducting a study evaluating subtotal RFA in combination with anti-CTLA4 therapy (NCT01853618) in patients with HCC and BTC. Provisionally, this approach is feasible and safe, with some early evidence of efficacy, which needs to be confirmed with more patient numbers and more mature follow-up[80].

1.2.6 Pembrolizumab

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4)/kappa isotype designed to directly block the interaction between PD-1 and its ligands, programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

On 04-Sep-2014, the United States (U.S.) Food and Drug Administration (FDA) granted accelerated approval to KEYTRUDA® for treatment of subjects with unresectable or metastatic melanoma and disease progression following treatment with ipilimumab (IPI) and, if BRAF V600 mutation positive, a BRAF inhibitor. The recommended dose of KEYTRUDA is 2 mg/kg administered as an intravenous (IV) infusion over 30 minutes every 3 weeks (Q3W) until disease progression or unacceptable toxicity. This indication was approved based on tumor response rate and durability of response (data cutoff date 18-Oct-2013) observed in a total of 411 IPI-refractory plus IPI-naïve melanoma subjects enrolled in P001 and treated with 1 of 3 dose regimens of pembrolizumab (2 mg/kg Q3W, 10 mg/kg Q3W, or 10 mg/kg every 2 weeks [Q2W]). An improvement in survival or disease-related symptoms had not yet been established at the time of the FDA filing.

On October 24, 2016, the U.S. Food and Drug Administration approved pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test.

This was the first FDA approval of a checkpoint inhibitor for first-line treatment of lung cancer. This approval also expanded the indication in second-line treatment of lung cancer to include all patients with PD-L1-expressing NSCLC.

The FDA approval added the following indications for pembrolizumab:

- Patients with metastatic NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS] greater than or equal to 50%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

- Patients with metastatic NSCLC whose tumors express PD-L1 (TPS greater than or equal to 1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.

Approval was based on results of two randomized, controlled trials that demonstrated statistically significant improvements in progression-free survival (PFS) and overall survival (OS) for patients randomized to pembrolizumab compared with chemotherapy.

In a trial of 305 patients who had no prior treatment for metastatic NSCLC and TPS greater than or equal to 50%, those who received pembrolizumab (200 mg every 3 weeks) had a significant improvement in PFS (HR 0.50 [95% CI: 0.37, 0.68]; p<0.001) with a median PFS of 10.3 months versus 6.0 months for those receiving platinum-based chemotherapy. A pre-specified interim analysis demonstrated a statistically significant improvement in OS for patients randomized to pembrolizumab as compared with chemotherapy (HR 0.60 [95% CI: 0.41, 0.89]; p<0.005).

In a three-arm trial of 1033 patients who were previously treated for metastatic NSCLC with a TPS greater than or equal to 1%, those randomized to pembrolizumab 2 mg/kg every 3 weeks (HR 0.71 (95% CI: 0.58, 0.88]; p<0.001) or pembrolizumab 10 mg/kg every 3 weeks (HR 0.61 [95% CI: 0.49, 0.75]; p<0.001) had an improved OS compared with patients receiving docetaxel. The median survival was 10.4 months in the pembrolizumab 2 mg/kg arm, 12.7 months in the pembrolizumab 10 mg/kg arm, and 8.5 months in the docetaxel arm.

The recommended dose and schedule of pembrolizumab for NSCLC is 200 mg intravenously every three weeks.

1.2.6.1 Nonclinical Pharmacology

Pembrolizumab binds to human and Cynomolgus monkey PD-1 with comparable affinity and blocks the binding of human and Cynomolgus monkey PD-1 to PD-L1 and PD-L2 with comparable potency. Pembrolizumab does not cross-react with dog, rat, or mouse PD-1.

Pembrolizumab does not bind immunoglobulin superfamily members cluster of differentiation 28 (CD28), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), or inducible T-cell co-stimulator (ICOS).

Pembrolizumab strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer subjects, and nonhuman primates. In T-cell activation assays using human donor blood cells, the half-maximal effective concentration (EC_{50}) has been approximately 0.1 to 0.3 nM. In addition to interleukin-2 (IL-2), tumor necrosis factor alpha (TNF α), interferon gamma (IFNɣ), and levels of other cytokines were found to be modulated by pembrolizumab. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells. In the in vitro peripheral blood mononuclear cell (PBMC) and whole blood cytokine release assays, the cytokine levels induced by pembrolizumab were low and comparable to those induced by trastuzumab. Pembrolizumab does not induce antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).

Using anti–murine PD-1 surrogate antibodies, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these experiments in mice, anti–PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU), and combination therapy results in increased complete tumor regression rates in vivo. Studies also revealed that immunosuppressive doses of dexamethasone included in combination with agents used in standard-of-care treatment for NSCLC do not reduce the anti-tumor efficacy of an anti–murine PD-1 surrogate antibody.

1.2.7 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent pembrolizumab. 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 pembrolizumab 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 was identified. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life. 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 was performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, was within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab 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 pembrolizumab 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 wastage.

1.2.8 CAPOX in biliary tract carcinomas

For metastatic or unresectable disease the modest standard of care for BTC comprises gemcitabine in combination with cisplatin chemotherapy, based on the ABC-02 trial in which a total of 410 patients with unresectable locally advanced or metastatic disease were randomly assigned to receive gemcitabine with or without cisplatin[3]. Median progression-free and overall survival were superior in the combination arm (8.0 versus 5.0 months and 11.7 versus 8.1 months, respectively; P<0.001), with the benefit seen consistently across the BTC subtypes. For patients who progress following first-line therapy there is no outright standard second-line option and therapy is usually an extrapolation from agents used in pancreatic or other gastrointestinal cancers[4]. The choice in this study of CAPOX as an acceptable chemotherapy component is an extrapolation of the wide use of oxaliplatin/5FU-based combinations in all GI cancers. The use of capecitabine (as opposed to infusional 5-FU) has the added convenience of not requiring continuous IV infusion.

2 ELIGBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histopathological confirmation of biliary tract carcinoma (BTC) by the Laboratory of Pathology of the NCI prior to entering this study OR histopathological confirmation of carcinoma in the setting of clinical and radiological characteristics which, together with the pathology, are highly suggestive of a diagnosis of biliary tract carcinoma. The term BTC includes intra- or extrahepatic cholangiocarcinoma, gallbladder cancer or ampullary cancer.

2.1.1.2 Patients must have disease that is not amenable to potentially curative resection. Patients must have received, been intolerant of or refused at least one line of chemotherapy.

2.1.1.3 Patients must have at least one focus of measurable metastatic disease per RECIST 1.1. (Section **6.3**).

2.1.1.4 Patients must have at least one focus of metastatic disease that is amenable to pre- and on-treatment biopsies. Ideally the biopsied lesion should not be one of the target measurable lesions, although this can be up to the discretion of the investigators.

2.1.1.5 Age ≥18 years

2.1.1.6 ECOG performance status 0-1 (see **Appendix A**)

2.1.1.7 Patients must have normal organ and marrow function as defined below:

leukocytes	≥3,000/mcL
absolute neutrophil count	≥ 1,000/mcL
platelets	≥ 100,000/mcL
total bilirubin	≤ 2 xULN
Serum albumin	≥ 2.5g/dl
Patients are eligible with ALT or AST up to 5 x ULN.	
creatinine	<1.5X institution upper limit of normal OR
creatinine clearance	≥45 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

2.1.1.8 Patients must have recovered from any acute toxicity related to prior therapy, including surgery. Toxicity should be ≤ grade 1 or returned to baseline.

2.1.1.9 Patients must not have other invasive malignancies within the past 5 years (with the exception of non-melanoma skin cancers, non-invasive bladder cancer or localized prostate cancer for whom systemic therapy is not required).

2.1.1.10 Patient must be able to understand and willing to sign a written informed consent document.

2.1.1.11 The effects of Pembrolizumab in combination with Capecitabine and Oxaliplatin on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation and up to 120 days after the last dose of the drug. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

2.1.2 Exclusion Criteria

2.1.2.1 Patients who have had standard of care chemotherapy, large field radiotherapy, or major surgery must wait 2 weeks prior to entering the study.

2.1.2.2 Previous treatment with immune checkpoint inhibitors.

2.1.2.3 Patients who have undergone prior liver transplantation are ineligible.

2.1.2.4 Patients with known brain metastases will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

2.1.2.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active systemic infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia (excluding insignificant sinus bradycardia and sinus tachycardia) or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.2.6 History of (non-infectious) pneumonitis that required steroids, evidence of interstitial lung disease or active, non-infectious pneumonitis.

2.1.2.7 History of chronic autoimmune disease (e.g., Addison's disease, multiple sclerosis, Graves' disease, Hashimoto's thyroiditis, rheumatoid arthritis, hypophysitis, etc.) with symptomatic disease within the 3 years before randomization. Note: Active vitiligo or a history of vitiligo will not be a basis for exclusion.

2.1.2.8 Dementia or significantly altered mental status that would prohibit the understanding or rendering of Information and Consent and compliance with the requirements of the protocol

2.1.2.9 Active or history of inflammatory bowel disease (colitis, Crohn's), irritable bowel disease, celiac disease, or other serious, chronic, gastrointestinal conditions associated with diarrhea. Active or history of systemic lupus erythematosus or Wegener's granulomatosis.

2.1.2.10 Currently receiving immunosuppressive doses of steroids or other immunosuppressive medications (inhaled and topical steroids are permitted)

2.1.2.11 History of sarcoidosis syndrome.

2.1.2.12 Known history of active tuberculosis.

2.1.2.13 Patients should not be vaccinated with live attenuated vaccines within 1 month of starting pembrolizumab treatment.

2.1.2.14 Active hepatitis B or C infection.

2.1.2.15 HIV-positive patients receiving anti-retroviral therapy are excluded from this study due to the possibility of pharmacokinetic interactions between antiretroviral medications and pembrolizumab. HIV positive patients not receiving antiretroviral therapy are excluded due to the possibility that pembrolizumab may worsen their condition and the likelihood that the underlying condition may obscure the attribution of adverse events.

2.1.2.16 History of hypersensitivity reaction to human or mouse antibody products.

2.1.2.17 Female patients who are pregnant or breastfeeding. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Pembrolizumab in combination with Capecitabine and Oxaliplatin, breastfeeding should be discontinued.

2.1.2.18 Patients with unhealed surgical wounds for more than 30 days.

2.1.2.19 Prior therapy with oxaliplatin

2.1.3 Recruitment Strategies

The study may be abstracted into a plain language announcement posted on NIH websites, including www.clinicaltrials.gov and the CCR website, and on NIH social media platforms. Outside providers and colleagues may directly refer patients for screening into this study.

2.2 SCREENING EVALUATION

Studies should be done within 28 days prior to enrollment unless otherwise noted below.

Note: Screening evaluation testing/procedures are conducted under the separate screening protocol, 01-C-0129 (Eligibility Screening and Tissue Procurement for the NIH Intramural Research Program Clinical Protocols).

- Complete medical history (including prior hormone use) and physical examination (including height, weight, vital signs, EKG, and ECOG performance status).
- Laboratory Evaluation
    - Hematological profile: CBC with differential and platelet count.
    - Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, total and direct bilirubin, calcium, phosphorus, albumin, magnesium,
    - Serum or urine pregnancy test for female participants of childbearing age (in the absence of prior hysterectomy).
    - HIV, Hepatitis B and C serology and/or viral load
    - TB testing (if clinically indicated)
- CT or PET of chest, abdomen and pelvis (or MRI abdomen)
- Histologic confirmation (at any time point prior to enrollment). A block or unstained slides of primary or metastatic tumor tissue will be required from each participant to confirm diagnosis with analysis being performed by the Laboratory of Pathology, NIH. If there is no available tumor sample, biopsy will be performed to confirm the diagnosis.

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.3.1 Treatment Assignment Procedures (For registration purposes only):

Cohorts

Number	Name	Description
1	1	Subjects with advanced biliary tract carcinoma

Arms

Number	Name	Description
1	1	Pembrolizumab + Oxaliplatin + Capecitabine

Arm assignment

Subjects in Cohort 1 will be directly assigned to Arm 1.

2.4 BASELINE EVALUATION

Tests done at screening do not need to be repeated on baseline if performed in designated time frame.

Within 28 days prior to first dose:

- CT or PET of chest, abdomen and pelvis (or MRI abdomen)
- Electrocardiogram
- HLA phenotype (any time prior to first dose)
- Optional tumor biopsy for research

Within 7 days prior to first dose:

- History and physical exam with vital signs

Within 72 hours prior to first dose:

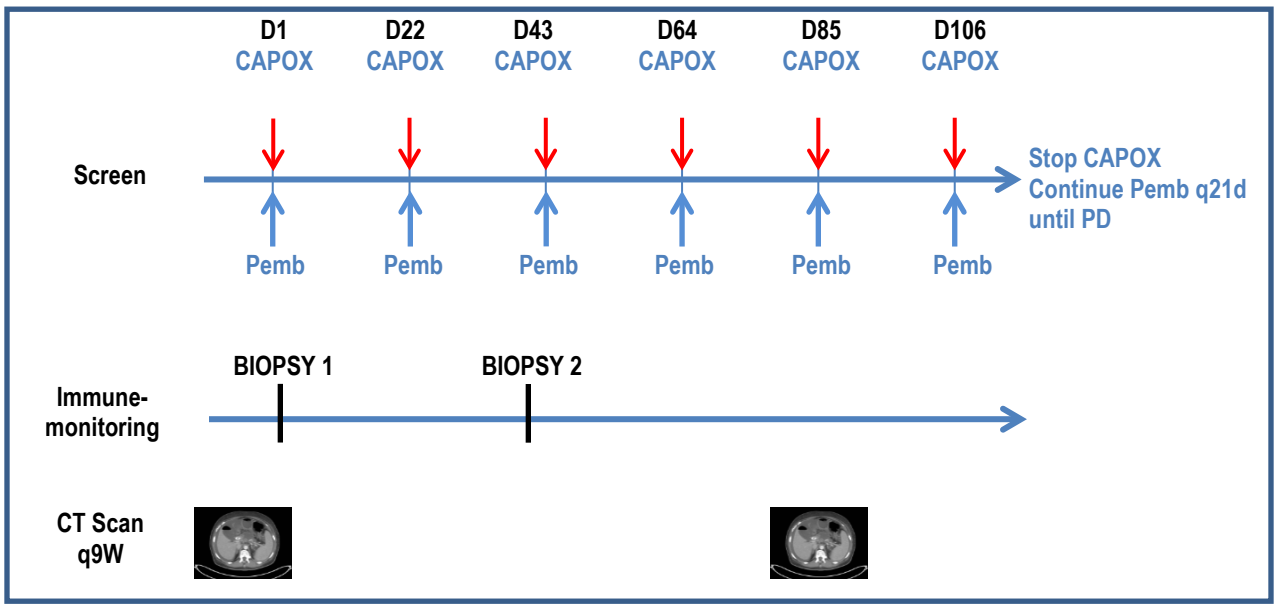
- Serum or urine pregnancy test for female participants of childbearing age (in the absence of prior hysterectomy).

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

The proposed study is a phase II study of Pembrolizumab in combination with CAPOX in patients with advanced biliary tract carcinoma.

Group	N	PEMBROLIZUMAB	CapOx
Previously treated BTC	19	Day 1: Pembrolizumab 200mg IV, 30 minutes. q-3-weekly until PD	Day 1: Oxaliplatin 130mg/m^2 IV over 2 hours Days 1–14: Capecitabine 750 mg/m^2 twice daily PO. q-3-weekly for 18 weeks



3.2 SCHEDULE

Pembrolizumab and Oxaliplatin should be administered on Day 1 of cycles 1-6. Pembrolizumab should be infused first and Oxaliplatin should be given at least 30 minutes after Pembrolizumab.

Capecitabine should be administered orally with first dose the evening of Day 1 of cycles 1-6 and last dose the morning of day 14 of cycles 1-6, given as intermittent treatment.

Cycle length is 3 weeks (consisting of 2 weeks of capecitabine treatment followed by 1 week without capecitabine treatment).

Starting in cycle 7, Pembrolizumab should be administered alone on Day 1, continuing once every 3 weeks until disease progression.

Each cycle may start up to 3 days before or after the scheduled Day 1 due to administrative reasons.

3.3 DRUG ADMINISTRATION

3.3.1 Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion on Day 1 of each cycle. Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 25 – 40 mins). Please see section **11.1.2** for preparation instructions.

3.3.2 CAPOX

Capecitabine should be administered at a dose of 750 mg/m2 PO every 12 hours (+/- 4 hours window is allowed) (equivalent to a total daily dose of 1500 mg/m2). Doses will be rounded downward to the nearest 150 mg. Patients will begin Capecitabine dosing on the first day of cycles 1-6 and will continue to receive Capecitabine for 14 days. Patients will be instructed to take Capecitabine with food. No morning dose should be taken on day 1 of the cycle and no

evening dose should be taken on day 14 of the cycle. Patents will complete and return Patient's Diary (**Appendix C**).

Oxaliplatin should be administered on D1 of cycles 1-6 at a dose of 130mg/m² IV Infusion in 500mls Glucose 5% over 2 hours. Please see section **11.2.3** for preparation instructions. Premedication with ondansetron 8mg and dexamethasone 8mg will be given 15-30 mins prior to infusion.

3.4 DOSING DELAYS AND MODIFICATIONS

3.4.1 General guidance

If, in the opinion of the investigator, a toxicity is considered to be due solely to one drug (e.g. hand-foot syndrome secondary to capecitabine, neurotoxicity due to oxaliplatin), the dose of the other drug does not require modification.

When, at the beginning of a treatment cycle, treatment delay related to either oxaliplatin or capecitabine treatment alone is indicated, both oxaliplatin and capecitabine treatment should be delayed (except in the case of oxaliplatin-related neurological adverse events). Treatment should only be restarted when the requirements for restarting both oxaliplatin and capecitabine are met, or when oxaliplatin has to be discontinued but the requirements for restarting capecitabine alone are met.

Dose modifications for isolated abnormal hematologic lab values will be based on hematological parameters at start of a treatment cycle. There is no scheduled sampling during a treatment cycle and thus, no scheduled collection of nadir values.

If capecitabine must be discontinued permanently due to toxicity, the patient may continue on oxaliplatin alone. If the patient has SD or better on study, and both capecitabine and oxaliplatin are stopped prematurely for toxicity, the PI may consider continuing pembrolizumab.

3.4.2 Dose Modifications for Hematologic Toxicity

Capecitabine is not expected to worsen or unduly prolong episodes of neutropenia/granulocytopenia. The next treatment cycle can only start if hematologic toxicity has recovered to grade ≤ 1. No dose reductions or interruptions will be required for anemia (non-hemolytic) as it can be satisfactorily managed by transfusions.

3.4.3 Dose Modifications for Neutropenia for Capecitabine and Oxaliplatin

	Grade 2 1.0 ≤ ANC < 1.5 x 109/L Platelets > 50 - < 75 x 109/L	Grade 3 0.5 ≤ ANC < 1.0 x 109/L Platelets > 10 - < 50 x 109/L	Grade 4 ANC < 0.5 x 109/L Platelets < 10 x 109/L
1st occurrence	No dose adjustment	Capecitabine 75% of original dose + oxaliplatin 100 mg/m2	Capecitabine 50% of original dose + oxaliplatin 85 mg/m2
2nd occurrence	No dose adjustment	Capecitabine 75% of original dose + oxaliplatin 85 mg/m2	Stop treatment permanently
3rd occurrence	No dose adjustment	Stop treatment permanently unless it is in the best interest of the patient to treat with	Not applicable

	Grade 2 1.0 ≤ ANC < 1.5 x 109/L Platelets > 50 - < 75 x 109/L	Grade 3 0.5 ≤ ANC < 1.0 x 109/L Platelets > 10 - < 50 x 109/L	Grade 4 ANC < 0.5 x 109/L Platelets < 10 x 109/L
		capecitabine monotherapy at 75% of original dose	

3.4.4 Capecitabine

Given that capecitabine is an FDA-approved agent, dose adjustments and management will be as per standard of care, as outlined in the package insert. Capecitabine will be withheld in cases of Grade 2 or greater hand-foot syndrome or mucositis that do not respond to medical management. Capecitabine will be restarted after the symptoms improved to Grade 1. The dose of Capecitabine may be adjusted in the event of recurrent Grade 2 or greater hand-foot syndrome, neutropenia, or other Capecitabine toxicities that have not been attributed to other study agents.

Summary of management of common Capecitabine toxicities	
Toxicity	**Capecitabine dose modification**
Grade 2 hand foot syndrome	Interrupt until ≤ grade 1. May then restart capecitabine at full dose. For second occurrence, hold capecitabine until ≤ grade 1, then restart capecitabine one dose level lower (75% of starting dose first occurrence, 50% of the starting dose the second occurrence, discontinue the third occurrence).
Grade 3 hand foot syndrome	Interrupt until ≤ grade 1. Then restart capecitabine one dose level lower (75% of starting dose first occurrence, 50% of the starting dose the second occurrence, discontinue the third occurrence).
*Dose reductions for capecitabine 1. Starting dose 2. 75% of the starting dose 3. 50% of the starting dose	

3.4.5 Oxaliplatin

3.4.5.1 Peripheral neuropathy

Oxaliplatin is consistently associated with two types of peripheral neuropathy, which includes paresthesia and dysesthesias of the hands, feet, and peri-oral region. Patients treated with oxaliplatin in this study will be counseled to avoid cold drinks and exposure to cold water or air, especially for 3 to 5 days following oxaliplatin administration.

3.4.5.1.1 Neurologic Toxicity Scale for Oxaliplatin Dose Adjustments

Description	Grade	1st occurrence	2nd occurrence	3rd occurrence
Paresthesia/dysesthesias that do not interfere with function	1	no dose reduction	no dose reduction	no dose reduction
Paresthesia/dysesthesias, interfering with function, but not activities of daily living (ADL)	2	no dose reduction	no dose reduction	100 mg/m2

Description	Grade	1st occurrence	2nd occurrence	3rd occurrence
Paresthesia/dysesthesias b with pain or with functional impairment that also interfere with ADL	3	no dose reduction	100 mg/m2	Stop treatment permanently
Persistent paresthesia/dysesthesias that are disabling or life-threatening	4	Stop treatment permanently	Stop treatment permanently	Stop treatment permanently
ACUTE: (during or after the 2-hour infusion) laryngopharyngeal dysesthesias		increase duration of next infusion to 6 hours	N/A	N/A

3.4.5.2 Laryngopharyngeal dysesthesias

An unusual laryngopharyngeal dysesthesia, a loss of sensation of breathing (acute respiratory distress) without any objective evidence of respiratory distress (hypoxia, laryngospasm, or bronchospasm), also has been observed. This neurotoxicity may be induced or exacerbated upon exposure to cold.

If a patient develops laryngopharyngeal dysesthesia, the patient's oxygen saturation should be evaluated via a pulse oximeter and, if normal, reassurance, a benzodiazepine or other anxiolytic agent should be considered and the patient should be observed in the clinic until the episode has resolved. The oxaliplatin infusion may then be continued at 1/3 the rate. Because this syndrome may be associated with the rapidity of oxaliplatin infusion, subsequent doses of oxaliplatin should be administered as 6-hour infusions (instead of the normal 2-hour infusion).

Patients on oxaliplatin should not receive cold drinks or ice chips on Day 1 of each cycle as this may exacerbate oral or throat dysesthesias, as well as laryngopharyngeal dysesthesia.

3.4.5.3 Allergic reactions

For Grade 1 or 2 acute hypersensitivity reactions, no dose modification of oxaliplatin is required if, in the investigator's opinion, it is in the patient's best interest to continue. Pre-medication with dexamethasone 20 mg IV, diphenhydramine 50 mg IV, and one of the following: cimetidine 300 mg IV, ranitidine 50 mg IV, or famotidine 20 mg IV 30 minutes prior to study drug administration is suggested. If an allergic reaction persists into the next cycle, administer 50 mg dexamethasone PO 12 hours and 6 hours prior to administration of oxaliplatin.

For Grade 3 or 4 acute hypersensitivity reactions, treatment with oxaliplatin should be discontinued.

3.4.6 Pembrolizumab

The following broad guidelines for dose delivery schedule delays and alternations apply to pembrolizumab and are dependent on the clinical and laboratory assessment on the day of dosing. Pembrolizumab can be delivered within 72 hours of planned interval to accommodate scheduling issues/logistics.

Based on the mechanism of action of pembrolizumab leading to T-cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this study.

Potential irAEs may be similar to those seen with the use of ipilimumab, BMS-936558 (anti-PD-1 mAb), and BMS-936559 (anti-PD-L1 mAb) and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), and endocrinopathies[6, 59, 60]. These AEs are inflammatory in nature and can affect any organ.

Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy. In addition to the dose modifications shown in **Table 1**, it is recommended that management of irAEs follow the guidelines outlined for ipilimumab[81]. These guidelines recommend the following:

1. Subjects should be evaluated to identify any alternative etiology
2. In the absence of clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related
3. Symptomatic and topical therapy should be considered for low grade events (all Grade 1 events, dermatologic and pruritus Grade 2 events).
4. Systemic corticosteroids should be considered for a persistent low-grade event or for a more severe event
5. More potent immunosuppressives should be considered for events not responding to systemic steroids (e.g., infliximab, mycophenolate, etc.).

Dose modifications will not be required for AEs that are clearly not attributed to pembrolizumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant, or which are ascribable to CAPOX. Dose reductions of pembrolizumab are not permitted.

General guidelines regarding dose modification are provided in **Table 1**. All toxicities will be graded according to NCI CTCAE v4.0.

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.

Table 1: Dose Modification Guidelines for Drug-Related Adverse Events, version 10-22-2017

General instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Increased bilirubin	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	stable
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

3.5 STUDY CALENDAR

	Screening	Baseline	Cycles 1-6[5]	Cycle 7- to PD[5]	EOT[9]	Follow Up[10]
Pembrolizumab [1]			X	X		
Oxaliplatin[2]			X			
Capecitabine[3]			X			
Informed consent	X					
Medical history [4]	X	X				
Concomitant meds			X	X		
Adverse event evaluation			X	X	X	
Physical exam [4]	X	X	X	X	X	
Vital signs[4]	X	X	X	X	X	
Height	X					
Weight[4]	X		X	X		
Performance Status[4]	X		X	X	X	
CBC w/differential, Platelets [4]	X		X[13]	X[13]	X	
PT, INR, PTT, Fibrinogen			X[13]	X[13]	X	
Serum chemistry [4, 12]	X		X[13]	X[13]	X	
HIV, Hepatitis B and C serology and/or viral load	X					
HLA		X				
Thyroid Panel			X[13]	X[13]	X	
TB testing (if clinically indicated)	X					
Serum or urine pregnancy test[4]	X	X				

	Screening	Baseline	Cycles 1-6[5]	Cycle 7- to PD[5]	EOT[9]	Follow Up[10]
Tumor markers: aFP, CEA or Ca 19.9[4]			X[13]	X[13]		
EKG[4]	X	X				
Confirmation of dx by NCI LP	X					
Restaging radiologic Evaluation[4]	X	X	X[6]	X[6]		
Optional Tumor biopsy		X	X[7]			
Immune monitoring [11]			X	X		
Blood for TCR beta sequencing[14]			X	X		
Advance Directive[8]		X				
Annual telephone contact						X

[1] 200 mg of Pembrolizumab will be administered as a 30-minute IV infusion Day 1 of each cycle.

[2] Oxaliplatin will be administered on D1 of each cycle at a dose of 130mg/m² IV

[3] Capecitabine will be administered at a dose of 750 mg/m^2 PO every 12 hours. Doses will be rounded downward to the nearest 150 mg. Patients will begin Capecitabine dosing on the Day 1 of each cycle and will continue to receive Capecitabine for 14 days.

[4] Tests performed at screening do not need to be repeated on baseline or Cycle 1 Day 1 if performed in designated time frame

[5] Each cycle is 21 days. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

[6] CT/PET/MRI of chest abdomen and pelvis. Restaging scans every 9 weeks +/- 7 days.

[7] Performed on cycle 3 Day 1 only +/- 7 days

[8] As indicated in section **10.3**, all subjects will be offered the opportunity to complete an NIH Advance Directive form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended but is not required.

[9] The off-treatment visits/labs will occur if patient is agreeable to coming back and physically able to return for the visit. This visit may should occur around day 30 post the last dose of study drug. If toxicities cause discontinuation of therapy, patients will be followed until resolution of toxicity to at least Grade 1. If the patient cannot return to the Clinical Center for this visit, a request will be made to collect required clinical labs from a local physician or laboratory. If this is not possible, patients may be assessed by telephone for symptoms.

[10] Follow-up will be annual telephone contact to assess survival status. Every attempt will be made to contact patient/subject including: contacting referring physician, contacting emergency contact patient identified on admission, checking SSDI (Social Security Death Index)

[11] Immune monitoring on Day 1 of cycles 1-4, then every 12 weeks until PD, +/-48 hours' time window applies

[12] Electrolytes, BUN, creatinine, AST, ALT, total and direct bilirubin, calcium, phosphorus, albumin, magnesium, uric acid, amylase. Uric acid and amylase do not need to be done on screening

[13] Within 48 hours prior to study drug

[14] D1 of each cycle until PD, +/-48 hours' time window applies

3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy

3.6.1 Criteria for Removal from Protocol Therapy

Treatment may continue until one of the following criteria applies:

- Disease progression (per immune-related response criteria).
- Intercurrent illness that prevents further administration of treatment
- Unacceptable toxicity as defined in section **3.4**
- Participant requests to be withdrawn from active therapy
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Delayed recovery from toxicity that prevents re-treatment in ≤ 28 days of scheduled therapy
- Investigator discretion
- Positive pregnancy test

3.6.2 Off-Study Criteria

- Participant requests to be withdrawn from study
- Investigator discretion
- Death
- PI decision to end the study

3.6.3 Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

All routine and appropriate supportive care (including blood products) will be provided during this study, as clinically indicated, and in accordance with the standard of care practices. Clinical judgment should be utilized in the treatment of any AE experienced by the patient.

Information on all concomitant medications, administered blood products, as well as interventions occurring during the study must be recorded on the patient's eCRF.

4.1 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. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

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

4.1.1 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.

4.1.2 Diarrhea/Colitis

- Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should

be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

- For Grade 2 diarrhea/colitis, administer oral corticosteroids.
- For Grade 3 or 4 diarrhea/colitis, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

4.1.3 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.

4.1.4 Hypophysitis

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

4.1.4.1 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.

4.1.5 Hepatic

- For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).

Treat with IV or oral corticosteroids

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

4.1.6 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.

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.

Table 2 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 2: Treatment guidelines for those who experience infusion reaction associated with pembrolizumab.

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	Subject may be pre-medicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	(e.g., from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the subject should be pre-medicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	
<u>Grades 3 or 4</u> 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 ventilatory 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 is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH

The correlative studies which we wish to perform are outlined below and summarized in the table. A description of each test including a brief statement of rationale and processing information is made below.

Test/assay	Volume blood (approx.)	Type of tube	Collection point (+/- 48hrs)	Location of specimen analysis[2]
Immune- monitoring	120mls (for PBMC)	EDTA	See Study Calendar **3.5**	Greten Lab
	5-10mls (for serum)	EDTA		
Immune cell infiltration (e.g. CD3+ CD4/8 cells etc.) as well as other surface markers such as PD-L1.	Optional tumor biopsy	NA	Baseline and Cycle 3 Day 1 +/- 7 days	Greten Lab
RNA Nanostring analysis (nCounterPan Cancer Immunology Profile)	Optional tumor biopsy		Cycle 3 Day 1 +/- 7 days	Greten Lab
TCR beta sequencing.	Optional tumor biopsy		Cycle 3 Day 1 +/- 7 days	Adaptive Biotechnologies[1].
TCR beta sequencing.	PBMC	EDTA, 5 ml	See Study Calendar **3.5**	Adaptive Biotechnologies[1]

[1] Lara Gruye, Adaptive Biotechnologies, 1551 Eastlake Ave E #200, Seattle, WA 98102 (855) 466-8667. Coded linked samples without key will be sent to Adaptive Biotechnologies.

[2] Blood samples will initially be sent to the Figg laboratory for barcoding and storage.

5.2 NCI CORRELATIVE STUDIES

5.2.1 Immune monitoring

- We will analyze PBMC for quantitative and functional changes of effector cells as well as analyze sera for cytokines and chemokines. The effect on (i) CD4 T cell number and activity, (ii) CD8 T cell number and activity, (iii) NK cell number and activity, (iv) Treg number, (vi) MDSC: frequency + functional assay, (vii) selected cytokines in serum, and (viii) the detection of tumor-associated antigens using tetramer assay.
- Patients will undergo blood sampling (c.120mls blood) on the time points outlined in the Study Calendar **3.5**. 12 purple EDTA tubes will be used. Blood will initially be sent to the Figg laboratory for barcoding and processing. On certain occasions, the blood may also be brought to the Greten lab for processing and analysis.
- Specimens will be labeled with the study identifier only and will be shipped to the address above, either on dry ice or at ambient temperatures as required by the type of sample to be analyzed.

5.2.2 Tumor Biopsy

An optional tumor biopsy will be performed at baseline for analysis of PD-L1 expression as well as other factors such as immune infiltration. We will also attempt an optional CT guided biopsy at a subsequent timepoint (after 6 weeks) if the patient is willing and the procedure can be performed safely. Tumor Tissue will be processed by the Department of Pathology, NCI, NIH (Dr. David Kleiner). Two core biopsies will be the attempted. For each specimen obtained the core will be divided in two parts for Surgical Pathology and frozen preservation. If for some reason only one core is able to be obtained, the core will be divided, with half submitted to Surgical Pathology and half used for PD studies.

1) Formalin-fixed.
    i. The half fixed in 10% formalin will be submitted to Surgical Pathology, CCR/NCI (Bldg. 10, 2N212).
    ii. The specimens will have routine H&E stains made as well as 5 additional unstained sections.
2) Frozen-preservation
    i. Two 1.5 ml cryogenic vials (obtained from Greten lab) will be labeled with the patient's name, accession number (HP#) and date using a waterproof sharpie.
    ii. The isotherm flask (Greten lab) will be filled with liquid nitrogen on the morning of the procedure and will be available together with the cryogenic vials when radiology page the contact person to collect the specimens.
    iii. Once the biopsy is ready, the half-core to be cryopreserved will be transferred into an empty 1.5-mL cryogenic vial with the use of sterile, pre-chilled (in dry ice) disposable tweezers.
    iv. The vial with specimen will be immediately dropped into liquid nitrogen contained in an isotherm flask.
    v. The frozen half will be transferred in the isotherm flask to the protocol-specified location for that particular analysis.

5.2.3 Tumor tissue analysis

Tumor samples from biopsies will be send to the pathology for cancer evaluation, only leftover samples will be used for research.

(i) IHC will be performed on tumor tissue for assessment of immune cell infiltration (e.g. CD3+ CD4/8 cells etc.) as well as other surface markers such as PD-L1.

(ii) Tumor samples will also be used for Nanostring analysis (nCounterPan Cancer Immunology Profile) and TCR beta sequencing. For TCR (cell receptor) gene usage may be quantitated in samples using conventional sequencing techniques of the T cell receptor variable region of the beta chain as is specified in Material Transfer Agreement between NCI and Adaptive Biotechnologies. Fewer than 100 genes will be analyzed. For TCR Beta Sequencing the NCI Thoracic and GI Oncology Branch will release coded tumor and PBMC samples collected in association with this protocol to: Lara Gruye, Adaptive Biotechnologies, 1551 Eastlake Ave E #200, Seattle, WA 98102 (855) 466-8667.

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS Screens and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. All samples will be sent to Blood Processing Core (BPC) for processing and storage until they are distributed to Dr. Greten's lab sample analysis as described in the protocol. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

5.3.1 Samples Managed by Dr. Figg's Blood Processing Core (BPC)

5.3.1.1 BPC contact information

Please e-mail at NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

5.3.1.2 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the LABrador (aka LabSamples) utilized by the BPC. This is a secure program, with access to LABrador limited to defined Figg lab personnel, who are issued individual user accounts. Installation of LABrador is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

LABrador creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without LABrador access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Sample bar-codes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the LABrador. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables

5.3.1.3 Sample Storage

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in LABrador. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused

samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with NIH Intramural IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following NIH Intramural IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested).

The PI will record any loss or unanticipated destruction of samples as a deviation. Reports will be made per the requirements of section **7.2.**

5.3.2 Procedures for Storage of Tissue Specimens in the Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissues are stored for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. In some cases, this approval has been obtained via the original protocol on which the patient was enrolled.

5.3.3 Procedures for storage of specimens in the Laboratory of Dr. Greten

Patient samples, collected for the purpose of research under IRB approved protocols where Dr Greten is Principal Investigator, may be archived in the Dr Greten laboratory. All data associated with archived clinical research samples is entered into the web-based NCI Labmatrix database, centralized system with access controlled via centralized login. Access to this database is limited to Dr Greten research staff, requiring individual login and password. All staff in the Dr Greten laboratory have received annually updated NIH/CIT training and maintain standards of computer security.

The data recorded for each sample may include the patient ID, trial name/protocol number, date drawn/collected, treatment cycle/post-transplant time point, cell source (e.g. peripheral blood, marrow, tissue) as well as box and freezer location. All received samples will receive a unique bar code number, which will be added to the sample NCI Labmatrix database.

Samples are stored in freezers at -80°C (sera, plasma, tissue samples) or under liquid nitrogen (cells), according to stability requirements. These freezers are located onsite at the Dr Greten laboratory. Access to samples from a protocol for research purposes will be by permission of the Principal Investigator.

Contact information:

Sophie Wang

Building 10 Rm 3B44

Phone: 240-858-3218

E-mail: sophie.wang@nih.gov

5.3.4 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described in sections above. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reports will be made per the requirements of section **7.2**.

5.4 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

TCR (cell receptor) gene usage may be quantitated in samples using conventional sequencing techniques of the T cell receptor variable region of the beta chain. Fewer than 100 genes will be analyzed. For TCR Beta Sequencing the NCI Thoracic and GI Oncology Branch will release coded tumor and PBMC samples to Adaptive Biotechnologies.

5.4.1 Privacy and Confidentiality of medical information/biological specimens

Fresh tumor and blood samples will be stored in a minus 80-degree freezer. Initially the samples of each patient will be sent to Dr. Figg's lab (**5.3.1**). At no time will patient's names be used on the blood and tissue samples. The molecular studies will be performed at the Adaptive Biotechnologies, 1551 Eastlake Ave E #200, Seattle, WA 98102 (855) 466-8667. Subject's genetic data will be deposited in a database such as dbGaP. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the subject. This is discussed in the consent.

5.4.2 Management of Results

There are not going to be incidental findings in this study and the results of molecular studies will not be communicated to the patient.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and Labmatrix ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Study Day 1 of Cycle 1 through 30 days after the subject received the last study drug administration. Beyond 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

Grade 1 adverse events will not be recorded.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

I will share coded, linked human data generated in this research for future research

- in a NIH-funded or approved public repository clinicaltrials.gov, dbGaP
- in BTRIS
- with approved outside collaborators under appropriate agreements
- in publication and/or public presentations

at the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 9 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4-8 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[82] and Modified Immune-related response criteria (irRC) **Appendix B.** Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.3.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with pembrolizumab.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.3.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'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.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

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. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. 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.

Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. 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: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, 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. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published[83-85]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer[86].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). 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: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). 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, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.3.4 Response Criteria

6.3.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

6.3.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump

target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.3.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

<table>
<tr><th>Target Lesions</th><th>Non-Target Lesions</th><th>New Lesions</th><th>Overall Response</th><th>Best Overall Response when Confirmation is Required*</th></tr>
<tr><td>CR</td><td>CR</td><td>No</td><td>CR</td><td>≥4 wks. Confirmation**</td></tr>
<tr><td>CR</td><td>Non-CR/Non-PD</td><td>No</td><td>PR</td><td rowspan="3">≥4 wks. Confirmation**</td></tr>
<tr><td>CR</td><td>Not evaluated</td><td>No</td><td>PR</td></tr>
<tr><td>PR</td><td>Non-CR/Non-PD/not evaluated</td><td>No</td><td>PR</td></tr>
<tr><td>SD</td><td>Non-CR/Non-PD/not evaluated</td><td>No</td><td>SD</td><td>Documented at least once ≥4 wks. from baseline**</td></tr>
<tr><td>PD</td><td>Any</td><td>Yes or No</td><td>PD</td><td rowspan="3">no prior SD, PR or CR</td></tr>
<tr><td>Any</td><td>PD***</td><td>Yes or No</td><td>PD</td></tr>
<tr><td>Any</td><td>Any</td><td>Yes</td><td>PD</td></tr>
<tr><td colspan="5">* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</td></tr>
</table>

Note:	Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

6.3.5 Duration of Response

6.3.5.1 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

6.3.5.2 Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.4 MODIFIED IMMUNE-RELATED RESPONSE CRITERIA (IRRC)

Modified immune-related response criteria (irRC) will also be employed in this study. This new classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. The irRC were created using bi-dimensional measurements (as previously widely used in the World Health Organization criteria). For this trial, the concepts of the irRC are combined with RECIST 1.1 to come up with the modified irRC. Please refer to **Appendix B**, for further details.

6.5 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI

Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.5 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATOR (MERCK)

7.5.1 Auditing and Monitoring.

With reasonable advance notice and at reasonable times, during and after the completion of the Protocol, NCI will permit Collaborator or its designee(s) to access the NIH Clinical Center to audit the conduct of the research, as well as to audit source documents containing Raw Data, to

the extent necessary to verify compliance with FDA Good Clinical Practice (International Conference on Harmonization (ICH) E6: "Good Clinical Practice: Consolidated Guidance; 62 Federal Register 25, 691 (1997)) and the Protocol(s)".

7.5.2 Safety Reports.

The Principal Investigator will report to Merck all SAEs which involve death or a life-threatening event which are deemed to be possibly, probably, or definitely related to Pembrolizumab within two (2) calendar days of receipt of these events by the Principal Investigator.

The Principal Investigator will use its best efforts to report other SAEs whether or not related to Pembrolizumab to the Collaborator within six (6) calendar days of receipt of these events by the Principal Investigator. Adverse Event reports of cancer will be provided to Merck when the Principal Investigator receives them. The Collaborator Global Safety department will receive Adverse Experience Reports, from the Principal Investigator via fax (215-993-1220) or secure email (aer_mailbox@merck.com). Data exchange of individual adverse event reports exchanged will be confirmed within one (1) business day. If confirmation is not received, then the Principal Investigator will contact Collaborator to determine if the original report needs to be re-sent.

8 STATISTICAL CONSIDERATIONS

The primary objective of this study is to determine in a preliminary, limited size trial whether Pembrolizumab in combination with CAPOX is associated with a 5-month progression free probability, which exceeds 25% when used to treat patients with biliary tract cancer.

Based on our analysis of data from previous trials of patients with similar eligibility requirements the median progression free survival in biliary tract carcinoma is 2.5 months. This translates to 25% without progressive disease at 5 months following an exponential failure model. Based on these results, it would be useful to demonstrate whether Pembrolizumab in combination with CAPOX is able to be associated with a median PFS of 5 months, which would correspond to 50% of patients having stable disease at 5 months. The trial will be conducted using a two-stage optimal design (Simon R, Controlled Clinical Trials, 10:1-10, 1989). In order to attempt to determine if the agent offers any improvement, using alpha=0.10 and beta =0.10 as acceptable error probabilities, the trial will target 50% as the desirable proportion of patients who are still without progression at the five-month evaluation (p1=0.50), and will be considered inadequate if only a fraction consistent with 20% are without progression by the same evaluation time (p0=0.20).

Initially, 10 patients will be enrolled and evaluated for progression. Enrollment will be temporarily halted after the 10th patient has been accrued, unless we know that 3 patients have passed the 5-month point without progression. If 3 or more of the first 10 patients enrolled have not progressed at the 5-month evaluation, then accrual will continue until a total of 17 patients have been entered. If, among the first 10 patients accrued, 0 to 2 are able to be progression-free at the 5-month evaluation, then no further patients will be enrolled after such a determination has been made. If 6 or more of the total cohort of 17 patients have been found to be progression-free at 5 months, then this will indicate an adequate progression free probability to justify further consideration of Pembrolizumab in combination with CAPOX in this population of patients. On the other hand, if 3 to 5 of 17 are progression-free at 5 months, this will be considered

insufficient. Under the null hypothesis (20% progression free at 5 months), the probability of being able to stop accrual after 10 patients have been evaluated at 5 months is 68%.

In addition to evaluation of the proportion of patients that are progression-free at 5 months, the progression-free survival for patients will also be analyzed via a Kaplan-Meier curve. This curve will be compared informally to other published results in similar patients. As well, the overall response rate will be reported, and the overall survival will be reported using a Kaplan-Meier curve. It is anticipated that up to 10 patients per year will be able to enroll onto this protocol. Thus, it is expected that accrual of up to 17 total patients can be completed in approximately 2 years. In order to allow for a small number of unevaluable patients, the accrual ceiling will be set at 19 patients.

To evaluate the response rate, proportion of patients obtaining CR and PR per RECIST 1.1 criteria of all evaluable patients will be analyzed.

To address safety, tolerability and feasibility of Pembrolizumab in combination with CAPOX chemotherapy, adverse events will be tabulated by grade according to CTCAE and analyzed and reported descriptively.

9 COLLABORATIVE AGREEMENTS

9.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

A CRADA (03145) is in place with Merck for the supply of the commercial agent pembrolizumab.

9.2 MATERIAL TRANSFER AGREEMENT

MTA (40860-16) is in place with Adaptive Biotechnologies

10 HUMAN SUBJECTS PROTECTIONS

10.1 RATIONALE FOR SUBJECT SELECTION

Subjects treated on this study, will be individuals with advanced biliary tract carcinoma, which has recurred (or persisted) after appropriate standard treatment. Individuals of any race or ethnic group will be eligible for this study. Eligibility assessment will be based solely on the patient's medical status. Recruitment of patients onto this study will be through standard CCR mechanisms. No special recruitment efforts will be conducted.

10.2 PARTICIPATION OF CHILDREN

Individuals under the age of 18 will not be eligible to participate in this study because they are unlikely to have biliary tract carcinoma, and because of unknown toxicities in pediatric patients.

10.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisional impaired. For this reason and because there is a prospect of direct benefit from research participation (section **10.4**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH

Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisional impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

10.4 Evaluation of Benefits and Risks/Discomforts for all participants

10.4.1 Risk of Optional Biopsy

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent.

10.4.2 Risks of exposure to ionizing radiation

This research study involves two CT guided biopsies collected for research purposes only. Subjects undergoing two optional biopsy collections will be exposed to 1.5 rem. This amount of radiation is below the guideline of 5 rem per year allowed for adult research subjects by the NIH Radiation Safety Committee.

10.4.3 Research Blood Collection Risks

Risks of blood draws include pain and bruising in the area where the needle is placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

10.4.4 Other Risks

Potential risks include the possible occurrence of any of a range of side effects which are listed in section **11** and in the Consent Document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described.

10.4.5 Benefits

The potential benefit to a patient that goes onto study is a reduction in the bulk of their tumor which may or may not have favorable impact on symptoms and/or survival.

10.5 Consent Process and Documentation

The procedures and tests involved in this study and the associated risks, discomforts and benefits of these processes, will be carefully explained to the patient and a signed informed consent document will be obtained prior to entry onto the study.

For the optional biopsies for research in the protocol, the patient will consent at the time of the procedure with the original form going to Medical Records and a copy placed in the research record. If the patient refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

10.5.1 Re-Consent via Telephone

Consent via telephone may only be used when re-consent is required, and the patient is not scheduled to come for a clinic visit in a timely fashion.

Telephone consent will be obtained and documented per OHSRP/IRBO and CCR policies and procedures.

11 PHARMACEUTICAL INFORMATION

Pembrolizumab (Keytruda) is approved for the treatment of patients with metastatic melanoma, NSCLC and HNSCC.

Oxaliplatin is approved for the treatment of patients with advanced colon and colorectal cancer.

Capecitabine is approved for the treatment of patients with adjuvant colon, metastatic colorectal and metastatic breast cancer.

None of these drugs are approved for the treatment of patients with advanced biliary tract carcinoma, the use in the current protocol. The investigation is not intended to support a new indication for use or any other significant changes to labeling or advertising in any of the commercial agents used on the study. The investigation does not involve a route of administration or dosage level in use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug products.

11.1 PEMBROLIZUMAB

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

Clinical Supplies will be provided by Merck as summarized in **Table 3**.

Table 3: Product Descriptions

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

11.1.1 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

11.2.1 Drug Product

Pembrolizumab (MK-3475) Solution for Infusion, 100 mg/ 4 mL vial

Pembrolizumab (MK-3475) Solution for Infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab (MK-3475). The product is preservative-free solution which is essentially free of extraneous particulates.

Cap color of MK-3475 (Pembrolizumab) 100 mg vials:

Both red and salmon color caps may be used. Though the cap color may be different, the product inside the vial is the same MK-3475 drug product.

11.1.2 Stability and Handling of Drug Product

Pembrolizumab (MK-3475) Solution for Infusion, 100 mg/ 4 mL vial: pembrolizumab (MK-3475) Solution for Infusion vials should be stored at refrigerated conditions (2 – 8 °C) and protected from light.

Note: vials should be stored in the original box to ensure the drug product is protected from light.

Pembrolizumab (MK-3475) infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) or regional equivalent or 5% Dextrose Injection, USP (5% dextrose) or regional equivalent and the final concentration of pembrolizumab (MK-3475) in the infusion solutions should be between 1 mg/mL and 10 mg/mL.

Please note, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.

Local guidelines should be followed for collection of diluent information such as manufacturer, lot and expiry. When the diluent is provided by Merck, the drug accountability log should be used for collection of diluent information.

Pembrolizumab (MK-3475) SHOULD **NOT** BE MIXED WITH OTHER DILUENTS.

Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion

In addition, IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) for up to 20 hours. If refrigerated, allow the IV bags to come to room temperature prior to use.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed.

Sites should follow their SOPs for drug transport and delivery, with all possible effort to minimize agitation of the drug product between the pharmacy and the clinic

- Do not use PEMBROLIZUMAB (MK-3475) if discoloration is observed.
- DO NOT SHAKE OR FREEZE THE VIAL(S).
- DO NOT ADMINISTER THE PRODUCT AS AN (INTRAVENOUS (IV) PUSH OR BOLUS).
- DO NOT COMBINE, DILUTE OR ADMINISTER IT AS AN INFUSION WITH OTHER MEDICINAL PRODUCTS.
- Any departure from the guidance listed in this manual, must be discussed with sponsor

11.1.3 Clinical Supplies Disclosure

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

11.1.4 Storage and Handling Requirements

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

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

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

11.1.5 Returns and Reconciliation

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

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

11.2 OXALIPLATIN

Oxaliplatin will be supplied by the local pharmacy using supply purchased from commercial sources.

11.2.1 Toxicity

The most common side effects of oxaliplatin include:

- neutropenia, anemia, thrombocytopenia, hypertension, diarrhea, nausea, vomiting, constipation, oral mucositis, abdominal pain, anorexia, fatigue, injection site reactions, alopecia and dehydration
- Potentially serious toxicities include:
- Grade 3/4 hypersensitivity, including anaphylactic/anaphylactoid reactions, to oxaliplatin has been observed in 2-3% of colon cancer patients. These reactions are usually managed with standard epinephrine, corticosteroid, antihistamine therapy, and require discontinuation of therapy or desensitization protocol for continuation of therapy.
- Peripheral sensory neuropathy (acute ≤ 14 days and persistent > 14 days) was reported in adjuvant patients treated with ELOXATIN as part of FOLFOX with a frequency of 92% (all grades) and 13% (grade 3). At the 28-day follow-up after the last treatment cycle, 60% of all patients had any grade (Grade 1=40%, Grade 2=16%, Grade 3=5%) peripheral sensory neuropathy decreasing to 39% at 6-month follow-up (Grade 1=31%, Grade 2=7%, Grade 3=1%) and 21% at 18 months of follow-up (Grade 1=17%, Grade 2=3%, Grade 3=1%).
- Overall, neuropathy was reported in patients previously untreated for advanced colorectal cancer in 82% (all grades) and 19% (grade 3/4), and in the previously treated patients in 74% (all grades) and 7% (grade 3/4) events. Information regarding reversibility of neuropathy was not available from the trial for patients who had not been previously treated for colorectal cancer.

- Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES, Posterior Reversible Encephalopathy Syndrome) has been observed in clinical trials (< 0.1%) and postmarketing experience. Signs and symptoms of RPLS could be headache, altered mental functioning, seizures, abnormal vision from blurriness to blindness, associated or not with hypertension. Diagnosis of RPLS is based upon confirmation by brain imaging.
- Pulmonary Toxicity. oxaliplatin has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal. The combined incidence of cough and dyspnea was 7.4% (any grade) and < 1% (grade 3) with no grade 4 events in the oxaliplatin plus infusional 5-fluorouracil/leucovorin arm compared to 4.5% (any grade) and no grade 3 and 0.1% grade 4 events in the infusional 5- fluorouracil/leucovorin alone arm in adjuvant colon cancer patients. In this study, one patient died from eosinophilic pneumonia in the oxaliplatin combination arm. The combined incidence of cough, dyspnea and hypoxia was 43% (any grade) and 7% (grade 3 and 4) in the oxaliplatin plus 5-fluorouracil/leucovorin arm compared to 32% (any grade) and 5% (grade 3 and 4) in the irinotecan plus 5-fluorouracil/leucovorin arm of unknown duration for patients with previously untreated colorectal cancer. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, ELOXATIN should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.
- Hepatotoxicity as evidenced in the adjuvant study, by increase in transaminases (57% vs. 34%) and alkaline phosphatase (42% vs. 20%) was observed more commonly in the oxaliplatin combination arm than in the control arm. The incidence of increased bilirubin was similar on both arms. Changes noted on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal alterations, perisinusoidal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be considered, and if appropriate, should be investigated in case of abnormal liver function test results or portal hypertension, which cannot be explained by liver metastases

11.2.2 Formulation

11.2.2.1 Powder

ELOXATIN is supplied in single-use vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution. Lactose monohydrate is also present as an inactive ingredient.

11.2.2.2 Solution

ELOXATIN is supplied in single-use vials containing 50 mg, 100 mg or 200 mg of oxaliplatin as a sterile, preservative-free, aqueous solution at a concentration of 5 mg/ml. Water for Injection, USP is present as an inactive ingredient.

11.2.3 Preparation

11.2.3.1 Powder

Reconstitution or final dilution must never be performed with a sodium chloride solution or other chloride containing solutions.

The lyophilized powder is reconstituted by adding 10 mL (for the 50 mg vial) or 20 mL (for the 100 mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP. Do not administer the reconstituted solution without further dilution. The reconstituted solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP.

After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration [2-8°C (36-46°F)]. After final dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)].

ELOXATIN is not light sensitive.

11.2.3.2 Solution

Do not freeze and protect from light the concentrated solution.

A final dilution must never be performed with a sodium chloride solution or other chloride containing solutions.

The solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP.

After dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)].

After final dilution, protection from light is not required.

ELOXATIN is incompatible in solution with alkaline medications or media (such as basic solutions of 5-fluorouracil) and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with 5% Dextrose Injection, USP prior to administration of any concomitant medication.

11.2.4 General

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and discarded if present.

Needles or intravenous administration sets containing aluminum parts that may come in contact with oxaliplatin should not be used for the preparation or mixing of the drug. Aluminum has been reported to cause degradation of platinum compounds.

11.2.5 Stability and Storage

Powder for solution for infusion:

Store under normal lighting conditions at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Concentrate for solution for infusion:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Do not freeze and protect from light (keep in original outer carton).

11.2.6 Administration procedures

Please see section **3.3.2.2**.

11.2.7 Incompatibilities

No specific cytochrome P-450-based drug interaction studies have been conducted. No pharmacokinetic interaction between 85 mg/m2 oxaliplatin and 5-fluorouracil/leucovorin has been observed in patients treated every 2 weeks. Increases of 5-fluorouracil plasma concentrations by approximately 20% have been observed with doses of 130 mg/m2 oxaliplatin dosed every 3 weeks. Because platinum-containing species are eliminated primarily through the kidney, clearance of these products may be decreased by co-administration of potentially nephrotoxic compounds; although, this has not been specifically studied.

11.3 CAPECITABINE

Chemical Name: 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine

Other Names: xeloda

Classification: Fluoropyrimidine carbamate

M.W.: 359.35

11.3.1 Source

Capecitabine will be supplied by the local pharmacy using supply purchased from commercial sources.

11.3.2 Toxicity

Most common adverse reactions (≥30%) were diarrhea, hand-and-foot syndrome, nausea, vomiting, abdominal pain, fatigue/weakness, and hyperbilirubinemia. Other adverse reactions, including serious adverse reactions, have been reported.

Pooled Phase 3 Colorectal Trials: Percent Incidence of Adverse Reactions in ≥5% of Patients

Adverse Event	**Capecitabine (n=596)**		
	Total %	**Grade 3 %**	**Grade 4 %**
Number of Patients With > One Adverse Event	96	52	9
Body System/Adverse Event			
GI			
Diarrhea	55	13	2
Nausea	43	4	–
Vomiting	27	4	<1
Stomatitis	25	2	<1
Abdominal Pain	35	9	<1
Gastrointestinal Motility Disorder	10	<1	–
Constipation	14	1	<1
Oral Discomfort	10	–	–
Upper GI Inflammatory Disorders	8	<1	–
Gastrointestinal Hemorrhage	6	1	<1

Adverse Event	Capecitabine (n=596)		
	Total %	Grade 3 %	Grade 4 %
Number of Patients With > One Adverse Event	96	52	9
Body System/Adverse Event			
Ileus	6	4	1
Skin and Subcutaneous			
Hand-and-Foot Syndrome	54	17	NA
Dermatitis	27	1	–
Skin Discoloration	7	<1	–
Alopecia	6	–	–
General			
Fatigue/Weakness	42	4	–
Pyrexia	18	1	–
Edema	15	1	–
Pain	12	1	–
Chest Pain	6	1	–
Neurological			
Peripheral Sensory Neuropathy	10	–	–
Headache	10	1	–
Dizziness*	8	<1	–
Insomnia	7	–	–
Taste Disturbance	6	1	–
Metabolism			
Appetite Decreased	26	3	<1
Dehydration	7	2	<1
Eye			
Eye Irritation	13	–	–
Vision Abnormal	5	–	–
Respiratory			
Dyspnea	14	1	–
Cough	7	<1	1
Pharyngeal Disorder	5	–	–
Epistaxis	3	<1	–
Sore Throat	2	–	–
Musculoskeletal			
Back Pain	10	2	–
Arthralgia	8	1	–

Adverse Event	Capecitabine (n=596)		
	Total %	Grade 3 %	Grade 4 %
Number of Patients With > One Adverse Event	96	52	9
Body System/Adverse Event			
Vascular			
Venous Thrombosis	8	3	<1
Psychiatric			
Mood Alteration	5	–	–
Depression	5	–	–
Infections			
Viral	5	<1	–
Blood and Lymphatic			
Anemia	80	2	<1
Neutropenia	13	1	2
Hepatobiliary			
Hyperbilirubinemia	48	18	5

– Not observed
* Excluding vertigo

NA = Not Applicable

11.3.3 Formulation and preparation

Tablets: 150 mg and 500 mg

XELODA is supplied as biconvex, oblong film-coated tablets for oral administration. Each light peach-colored tablet contains 150 mg capecitabine and each peach-colored tablet contains 500 mg capecitabine. The inactive ingredients in XELODA include: anhydrous lactose, croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate and purified water. The peach or light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides.

11.3.4 Stability and Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). KEEP TIGHTLY CLOSED.

Care should be exercised in the handling of XELODA. XELODA tablets should not be cut or crushed. Procedures for the proper handling and disposal of anticancer drugs should be considered. Any unused product should be disposed of in accordance with local requirements, or drug take back programs. Several guidelines on the subject have been published.

11.3.5 Administration procedures

Please see section **3.3.2.1**

11.3.6 Incompatibilities

- Anticoagulants: Monitor anticoagulant response (INR or prothrombin time) frequently in order to adjust the anticoagulant dose as needed.
- Phenytoin: Monitor phenytoin levels in patients taking XELODA concomitantly with phenytoin. The phenytoin dose may need to be reduced.
- Leucovorin: The concentration of 5-fluorouracil is increased and its toxicity may be enhanced by leucovorin.
- CYP2C9 substrates: Care should be exercised when XELODA is co-administered with CYP2C9 substrates.
- Food reduced both the rate and extent of absorption of capecitabine.

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13 APPENDICES

13.1 APPENDIX A-PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

13.2 APPENDIX B- MODIFIED IMMUNE-RELATED RESPONSE CRITERIA (IRRC)

This new classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. The irRC were created using bi-dimensional measurements (as previously widely used in the World Health Organization criteria). For this trial, the concepts of the irRC are combined with RECIST 1.1 to come up with the modified irRC.

For modified irRC, only target and measurable lesions are taken into account. In contrast to the RECIST 1.1 criteria, the modified irRC criteria (a) require confirmation of both progression and response by imaging at 6 weeks after initial imaging and (b) do not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm per lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥ 20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline, during the trial, and at the end of trial visit. All measurements should be recorded in metric notation. The modified irRC based on RECIST 1.1 are displayed below.

Modified immune-related response criteria are defined as follows:

New measurable lesions: Incorporated into tumor burden.

New non-measurable lesions: Do not define progression but precludes (irCR).

Overall irCR:	Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to 10 mm.
Overall irPR:	Sum of the longest diameters of target and new measurable lesions decreases ≥ 30%.
Overall irSD:	Sum of the longest diameters of target and new measurable lesions neither irCR, irPR, (compared to baseline) or irPD (compared to nadir).
Overall irPD:	Sum of the longest diameters of target and new measurable lesions increases ≥ 20% (compared to nadir), confirmed by a repeat, consecutive observations at least 4 weeks (normally it should be done at 6 weeks) from the date first documented.

Overall Responses Derived from Changes in Index, Non-Index, and New Lesions

Measurable Response	Non-Measurable Response		Overall Response Using Modified irRC
Index and New, Measurable Lesions (Tumor Burden)[1]	Non-Index Lesions	New, Non-Measurable Lesions	
Decrease 100%	Absent	Absent	irCR[2]
Decrease 100%	Stable	Any	irPR[2]
Decrease 100%	Unequivocal progression	Any	irPR[2]
Decrease ≥ 30%	Absent / Stable	Any	irPR[2]
Decrease ≥ 30%	Unequivocal progression	Any	irPR[2]
Decrease < 30% to increase < 20%	Absent / Stable	Any	irSD
Decrease < 30% to increase < 20%	Unequivocal progression	Any	irSD
Increase ≥ 20%	Any	Any	irPD

[1] Decreases assessed relative to baseline
[2] Assuming that the response (irCR and irPR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart (normally it should be done 6 weeks apart).

13.3 APPENDIX C PATIENT'S MEDICATION DIARY _____

Cycle_____

Patient's ID _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment
2. You will take capecitabine _____mg twice a day. You should take the tablets with food at approximately the same time each day.
3. Dose: _____150 mg _____ 500 mg
4. Record the date, the number of tablets that you took, and when you took them.
5. If you have any comments or notice any side effects, please record them in the comments column.
6. Please bring this form and your bottles of capecitabine when you come for your clinic visits.

Day	**Date**	**Time of AM Dose**	**# of Tablets Taken 150 mg**	**500mg**	**Time of PM Dose**	**# of Tablets Taken 150 mg**	**500mg**	**Comments**
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								

Patient's signature: _____