Supplementary material

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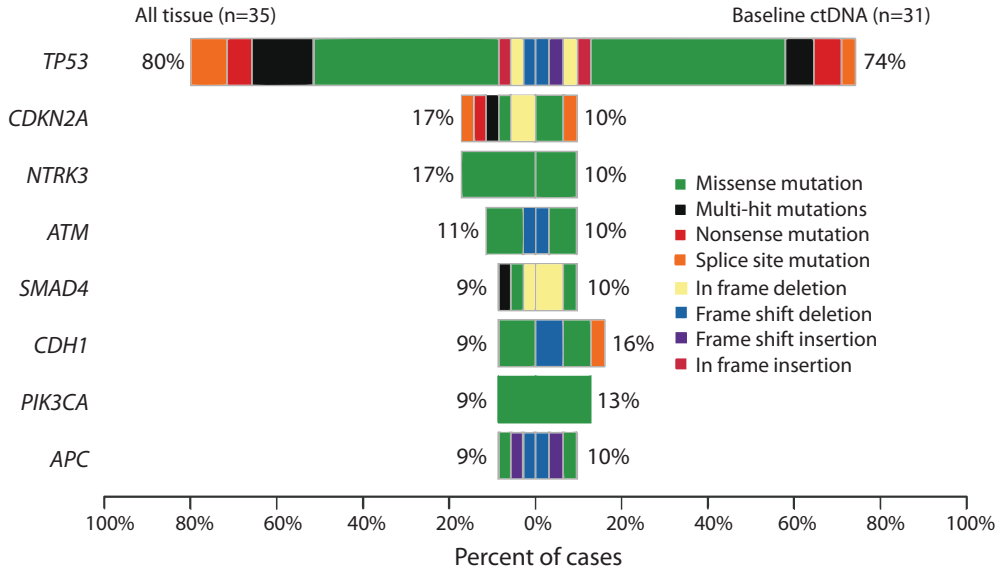
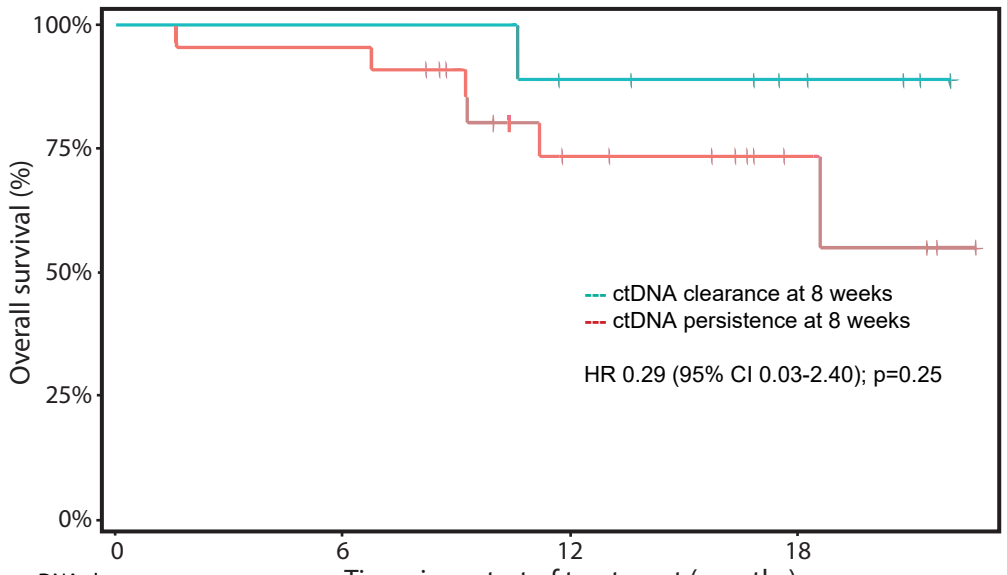
Supplementary Figure 1: Circulating tumor DNA analysis and response to treatment
(A) Plasma-based ctDNA analysis (right side) identified a comparable mutational profile compared to tissue-based next generation sequencing (left side). (B) Overall survival in patients with ctDNA clearance at 8 weeks compared to those with persistent ctDNA at 8 weeks. ctDNA=circulating tumor DNA. PD-L1=programmed death-ligand 1. CPS=combined positive score. Rego=regorafenib. Nivo=nivolumab. PFS=progression-free survival. VAF=variant allele frequencies. HR=hazard ratio. CI=confidence interval.

(A)



(B)



ctDNA clearance				
At Risk	9	9	7	4
Events	0	0	1	1
ctDNA persistence				
At Risk	22	21	10	4
Events	0	1	5	5

Supplementary Table 1: : Baseline demographic and clinical characteristics of induction and non-induction cohorts

ECOG=Eastern Cooperative Oncology Group. MMR=mismatch repair. MSI=microsatellite instability. PD-L1=programmed death-ligand 1. CPS=combined positive score.

	Induction cohort (n=11)	**Non-induction cohort (n=24)**
Median age, years (interquartile range)	65 (57, 69)	56 (52, 63)
Sex		
Men	9 (82%)	17 (71%)
Women	2 (18%)	7 (29%)
Race		
White	9 (82%)	19 (79%)
Asian	2 (18%)	5 (21%)
Primary tumor location		
Esophageal	6 (55%)	5 (21%)
Gastroesophageal junction	2 (18%)	6 (25%)
Gastric	3 (27%)	13 (54%)
ECOG performance status		
0	11 (100%)	13 (54%)
1	0 (0%)	11 (46%)
Disease stage		
Metastatic	9 (82%)	20 (83%)
Recurrent disease	2 (18%)	4 (17%)
Locally advanced, unresectable	0 (0%)	0 (0%)
Organs with metastases		
1	2 (18%)	3 (13%)
≥2	9 (82%)	21 (88%)
Sites of metastases		
Lymph nodes	10 (91%)	20 (83%)
Liver	5 (45%)	7 (29%)
Peritoneum	2 (18%)	9 (38%)
Lungs	5 (45%)	6 (25%)
Bones	0 (0%)	6 (25%)
Pleura	0 (0%)	3 (13%)
Soft tissue	1 (9%)	2 (8%)
Adrenal glands	1 (9%)	1 (4%)
Ovaries	0 (0%)	2 (8%)

Kidneys	1 (9%)	1 (4%)
Bladder	1 (9%)	0 (0%)
Signet ring carcinoma		
Yes	6 (55%)	10 (42%)
No	5 (45%)	14 (58%)
MMR or MSI status		
MMRp/MSS	10 (91%)	24 (100%)
MMRd/MSI-H	0 (0%)	0 (0%)
Unknown	1 (9%)	0 (0%)
Measurable disease	10 (91%)	19 (79%)
Non-measurable, evaluable disease	1 (9%)	5 (21%)
Pretreatment PD-L1 status		
CPS <1 (negative)	6 (55%)	14 (58%)
CPS ≥1 (positive)	5 (44%)	10 (42%)
CPS ≥5 (high)	3 (27%)	6 (25%)

Supplementary Appendix 1: Study protocol and statistical analysis plan

MSK PROTOCOL COVER SHEET

A Phase II Study of Nivolumab in Combination with FOLFOX and Regorafenib in Patients with HER2-Negative Metastatic Esophagogastric Cancer

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

“A phase II study of nivolumab in combination with FOLFOX and regorafenib in patients with HER2-negative metastatic esophagogastric cancer” (CA209-69U) is a single-arm, open-label, nonrandomized, single-institution, phase II study of nivolumab in combination with FOLFOX (5-fluorouracil [5-FU], leucovorin, and oxaliplatin) and regorafenib as first-line therapy in patients with HER2-negative metastatic esophagogastric adenocarcinoma. The primary objective of this study is to determine the efficacy of the drug combination as measured by 6-month progression-free survival (PFS). Secondary objectives include determining the safety, response rate, and efficacy of this treatment approach. Correlative studies will be performed to explore genomic alterations and potential biomarkers associated with treatment response and to generate relevant patient-derived organoid models. The central hypothesis of this trial is that regorafenib and chemotherapy can modulate antitumor immunity and the tumor microenvironment, synergizing with anti–programmed death-1 (PD-1) therapy to enhance the therapeutic activity of the combination. We plan to enroll 35 end-point evaluable patients, and we anticipate it will take 18 months to enroll the study population. The study will continue until all treated patients experience disease progression or intolerable toxicity or are otherwise withdrawn.

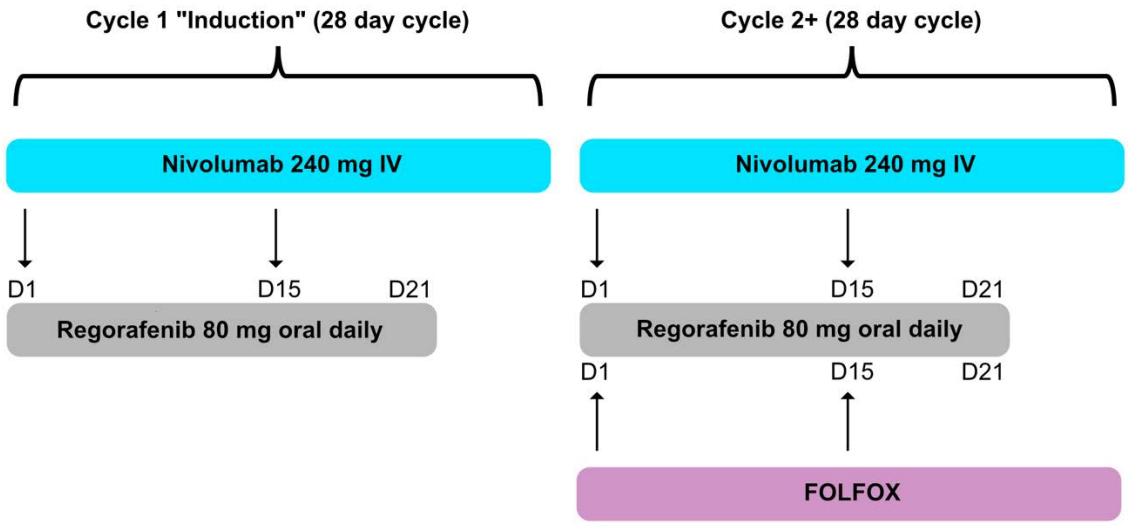

Figure 1. Schematic of trial with induction regorafenib/nivolumab followed by addition of chemotherapy

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objective:

- Determine the efficacy of nivolumab in combination with FOLFOX and regorafenib in patients with previously untreated metastatic esophagogastric cancer, as measured by 6-month PFS.

2.2 Secondary Objectives:

- Establish the safety of nivolumab in combination with FOLFOX and regorafenib in patients with metastatic esophagogastric cancer.
- Determine the overall response rate (ORR; defined as complete response [CR] + partial response [PR]) and the clinical benefit (defined as stable disease [SD] + CR + PR).
- Observe other measures of efficacy, including median PFS and overall survival (OS) (median, 1-year).

2.3 Exploratory Objectives:

- Collect archival tumor samples for correlative analysis, including but not limited to immunohistochemical (IHC) analysis and targeted next-generation sequencing (NGS; MSK-IMPACT) to identify genomic alterations and tumor mutational burden (TMB).
- Explore PD-L1 expression as measured by combined positive score (CPS) as a predictive biomarker.
- Use circulating tumor DNA (ctDNA) and peripheral blood mononuclear cells (PBMCs) collected during the course of the study to explore the mechanisms of primary and acquired resistance to FOLFOX, nivolumab, and regorafenib and the relationship of these mechanisms to response, PFS, and OS.
- Bank tumor and blood material at screening and post progression for future correlative analysis, including but not limited to whole-exome analysis to determine the mutation load and specific neoantigen landscape.
- Explore the activity of induction regorafenib and nivolumab in patients with metastatic esophagogastric cancer.
- Use patient biopsy specimens to generate patient-derived organoids (PDOs). Organoids will be cocultured with pretreatment and on-treatment PBMCs to assess antitumor immunity and its modulation by treatment.
- Estimate median PFS and OS in patients who received induction regorafenib and nivolumab

3.0 BACKGROUND AND RATIONALE

3.1 Introduction

Esophagogastric cancer is the fifth most common cancer worldwide, with 1 million new diagnoses annually, and is the third leading cause of cancer death.[1] Approximately 28,000 new cases of gastric cancer and 18,000 new cases of esophageal cancer are diagnosed in the United States each year. Treatment for locally advanced disease often involves multiple modalities, including surgery, radiation, and perioperative and/or preoperative chemotherapy. Even when the most-aggressive regimens are used, however, patients with locally advanced esophagogastric cancer have a high risk of recurrence.

Approximately half of patients present with metastatic disease at diagnosis. Systemic therapy is the mainstay of treatment for metastatic esophagogastric cancer, with chemotherapy as the

standard first-line treatment. Therapy is largely palliative and rarely results in complete or durable responses; median OS remains <1 year. Immunotherapy with checkpoint inhibitors that block PD-1 signaling and targeted therapy with tyrosine kinase inhibitors, such as regorafenib, have shown clinical activity in later lines of therapy, but the role of these agents in first-line treatment in combination with chemotherapy remains undefined. Following the establishment of preclinical and clinical data suggesting regorafenib and PD-1 inhibitors have potential additive and/or synergistic activity with chemotherapy, we propose a phase II clinical trial combining regorafenib, nivolumab, and FOLFOX chemotherapy for first-line treatment of patients with metastatic esophagogastric adenocarcinoma.

3.2 FOLFOX in Esophagogastric Cancer

Chemotherapy has long been the foundation of first-line treatment of advanced esophagogastric cancer. As a single agent, 5-FU is associated with response rates of 20%-30%,[2] and combining 5-FU with other cytotoxic drugs significantly improves efficacy.[3] Previous trials have shown that FOLFOX is well-tolerated and has similar activity to other reference regimens in advanced esophagogastric cancer.[4–9] The substitution of oxaliplatin for cisplatin has been shown to be noninferior with regard to OS, with significantly lower rates of grade 3 and 4 neutropenia, nephrotoxicity, nausea, renal toxicity, thromboembolism, and alopecia.[8,10] Compared with 5-FU and cisplatin, 5-FU and oxaliplatin was associated (albeit not statistically significantly) with improved median PFS (5.8 vs. 3.9 months; p=0.077) and OS (10.7 vs. 8.8 months).[8] The addition of a third cytotoxic agent, such as docetaxel, to 5-FU and platinum-containing regimens may increase therapeutic activity but at the expense of significantly more toxicity, including grade 3 and 4 neutropenia, diarrhea, and neuropathy.[11,12] Although epirubicin has historically been used to treat esophagogastric cancer, studies have demonstrated no benefit from the addition of epirubicin to contemporary chemotherapy regimens.[13] FOLFOX has thus emerged as a standard regimen for first-line treatment of advanced esophagogastric adenocarcinoma, balancing strong efficacy with acceptable toxicity.

Reflecting its overall favorable tolerability, FOLFOX has been safely combined with other biologic agents, including immunotherapy and targeted therapy. In our phase II study combining FOLFOX with regorafenib in metastatic esophagogastric adenocarcinoma, the regimen was well-tolerated with no unexpected toxicities.[14] Collectively, these clinical data establish FOLFOX as an accepted first-line treatment for advanced esophagogastric cancer and a favorable backbone for novel combination regimens.

3.3 Role of Regorafenib in Esophagogastric Cancer

Preclinical and clinical data suggest that pathologic angiogenesis and extracellular matrix remodeling through tumor vascular endothelial growth factor receptor 2 (VEGFR2) signaling promote esophagogastric cancer growth and metastasis.[15–17] Other tyrosine kinase–regulated pathways, including the platelet-derived growth factor receptor and fibroblast growth factor receptor pathways, can also promote esophagogastric cancer progression.[18,19] In the second-

line setting, the anti-VEGFR2 antibody ramucirumab is approved either as monotherapy or in combination with paclitaxel.[20,21] However, several studies have failed to demonstrate clinical benefit for the addition of antiangiogenic agents to first-line therapy.[22–24]

Regorafenib is a small-molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. In preclinical models, regorafenib demonstrated robust antitumor activity against several cancer types *in vivo*, including xenografts derived from patients with gastric cancer.[25,26] These promising data have led to multiple clinical studies evaluating the efficacy of regorafenib, including three global phase III trials leading to FDA approval. Among these was the CORRECT trial, an international, randomized, double-blind, placebo-controlled study that enrolled 760 patients with metastatic colorectal cancer refractory to standard therapies.[27] Patients were randomized to regorafenib plus best supportive care or placebo plus best supportive care. Regorafenib was provided at a dose of 160 mg daily on a 3-weeks-on/1-week-off schedule. This study showed an improved median OS of 6.4 months (regorafenib) vs. 5.0 months (placebo) (HR, 0.77; 95% CI, 0.64-0.94; p=0.0052), leading to FDA approval in 2012. The most frequent grade ≥3 adverse events (AEs) with regorafenib included hand-foot skin reaction (HFSR; 17%), fatigue (15%), diarrhea (8%), hyperbilirubinemia (8%), and hypertension (7%). Regorafenib has also shown clinical activity in gastrointestinal stromal tumors, as demonstrated by the phase III GRID trial, which randomized 199 patients with metastatic and/or unresectable gastrointestinal stromal tumor refractory to imatinib and sunitinib to receive either regorafenib (160 mg once daily on a 3-weeks-on/1-week-off cycle) or placebo.[28] Regorafenib treatment was associated with a 3.9-month improvement in median PFS (4.8 vs. 0.9 months; HR, 0.27; p<0.0001). In the randomized, double-blind, placebo-controlled, phase III RESORCE trial, regorafenib also showed a survival benefit in patients with hepatocellular carcinoma and prior progression on sorafenib.[29] In this study, 573 patients were randomized 2:1 to regorafenib (160 mg daily on a 3-weeks-on/1-week-off cycle) or placebo. Median OS was longer with regorafenib than with placebo (10.6 vs. 7.8 months; HR, 0.63; 95% CI, 0.50-0.79; p<0.0001). Regorafenib was well-tolerated, with grade ≥3 AEs including hypertension (15%), HFSR (13%), fatigue (9%), and diarrhea (3%).

Additional studies have shown that regorafenib is active in the treatment of esophagogastric cancer. INTEGRATE was a multinational, randomized, phase II trial of regorafenib (160 mg daily on a 3-weeks-on/1-week-off cycle) in patients with chemotherapy-refractory advanced gastric adenocarcinoma. Regorafenib treatment demonstrated a statistically significant improvement in median PFS compared with placebo (2.6 vs. 0.9 months; HR, 0.40; 95% CI, 0.28-0.59; p<0.001).[30] Toxicities were comparable to those in previously reported studies with regorafenib, and a global phase III trial of regorafenib in refractory advanced esophagogastric cancer (INTEGRATE II) is ongoing.

Regorafenib has also been studied in combination with chemotherapy in first-line therapy for colorectal and esophagogastric cancers. In a single-arm, multicenter, phase II study of

FOLFOX chemotherapy plus regorafenib (160 mg daily on days 4-10 of each 14-day cycle) for metastatic colorectal cancer, the combination demonstrated a manageable safety profile, although the ORR (43.9%) was not improved compared with historical controls.[31] We recently reported a single-center, phase II trial of FOLFOX plus regorafenib (160 mg daily on days 4-10) in patients with untreated metastatic or unresectable esophagogastric adenocarcinoma.[14] The combination was well-tolerated, with the most common grade 3-4 AEs neutropenia (36%), leukopenia (11%), and hypertension (8%). The 6-month PFS was 53% (95% CI, 38%-71%), and the ORR was 54% (95% CI, 37%-70%). Chemotherapy with 5-FU and irinotecan (FOLFIRI) has also been combined with regorafenib 120 mg daily given on a 3 weeks on/1 week off schedule in patients with metastatic colorectal cancer receiving third-line or fourth-line therapy.[32] Toxicities in this trial were acceptable with the most common grade 3-4 AE being HFSR (31.7%) and neutropenia (18.2%). These data demonstrate that regorafenib plus chemotherapy is safe and may serve as a backbone for improved combination regimens.

3.4 Clinical Activity of Anti-PD1 Therapy in Esophagogastric Cancer

PD-1 is a surface molecule on T cells that binds its ligand programmed death-ligand 1 (PD-L1) and suppresses antitumor immunity. Pembrolizumab is a humanized monoclonal antibody that inhibits PD-1 and has been shown to have activity in several malignancies, including esophagogastric cancer. In the phase II KEYNOTE-059 study, patients with metastatic esophagogastric cancer who had previously received ≥2 lines of systemic therapy were given pembrolizumab monotherapy.[33] This trial demonstrated an ORR of 12% regardless of PD-L1 status, which improved to 16% in patients with PD-L1–positive disease. On the basis of these results, pembrolizumab was approved for patients with metastatic chemotherapy-refractory disease with a CPS ≥1. The KEYNOTE-061 study randomized patients with PD-L1–positive esophagogastric cancer with prior progression on first-line platinum plus fluoropyrimidine to receive either pembrolizumab or paclitaxel.[34] Although there was no significant difference in OS in the total population, patients with tumors with high PD-L1 expression (CPS ≥10) had superior median OS with pembrolizumab than with chemotherapy (17.4 vs. 10.8 months; HR, 0.69).

Similar to the experience with pembrolizumab, nivolumab has shown clinical efficacy in advanced esophagogastric cancer. Nivolumab is a fully humanized immunoglobulin G4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2. In the double-blind, placebo-controlled, phase III ATTRACTION-2 trial, which randomized 493 Asian patients with chemotherapy-refractory advanced esophagogastric cancer to nivolumab (3 mg/kg every 2 weeks) or placebo, nivolumab was associated with a significant improvement in OS (5.26 vs. 4.14 months; HR, 0.63).[35] Survival at 12 months was 26.2% with nivolumab and 10.9% with placebo. Treatment-related AEs were similar to those with PD-1 inhibitors in other diseases, with no new safety signals and with the most common events pruritus (15.3%) and rash (13.6%).

3.5 Rationale for Combining Nivolumab with FOLFOX Chemotherapy and Regorafenib

Although immunotherapy has demonstrated activity in patients with advanced esophagogastric cancers refractory to chemotherapy, only a limited proportion of patients benefit. For patients who respond to anti–PD-1 therapy, responses can be durable. Therefore, rational combinations of PD-1 inhibitors with other therapeutic agents have been proposed to potentially enhance clinical efficacy, including in front-line combination therapy.

Recent data indicate that combinations of PD-1 inhibitors and tyrosine kinase inhibitors have clinical efficacy; approved regimens include axitinib plus pembrolizumab for renal cell cancer and lenvatinib plus pembrolizumab for endometrial cancer.[36,37] It has been suggested that regorafenib modulates antitumor immunity, such as through reducing infiltration of tumor-associated macrophages, which can mediate resistance to checkpoint inhibitors.[38] Recently, the phase Ib REGONIVO trial of regorafenib plus nivolumab in patients with heavily pretreated advanced colorectal and gastric cancer demonstrated antitumor activity with the combination.[39] Regorafenib was given on a 3-weeks-on/1-week-off schedule with nivolumab (3 mg/kg every 2 weeks). Of the 25 patients with gastric cancer, 11 responded to treatment (ORR, 44%), and there was 1 CR. Of note, 3 of 7 patients with gastric cancer previously treated with PD-1 or PD-L1 inhibitors had an objective response. Dose-limiting toxicities were seen with regorafenib 160 mg daily in the dose-escalation phase. The regorafenib dose was reduced from 120 mg to 80 mg daily because of frequent maculopapular rash; thus, regorafenib 80 mg (3 weeks on/1 week off) plus nivolumab was identified as the ideal dose for further investigation. Exploratory biomarker analysis suggested stronger activity in PD-L1–positive gastric cancer, with a median PFS of 10.9 months in patients with tumors with CPS ≥1 and 2.9 months in patients with tumors with CPS <1.

PD-1 inhibitors have been safely combined with chemotherapy. It has been suggested that chemotherapy enhances the activity of immunotherapy through multiple mechanisms, such as activating the release of tumor antigens and depleting immunosuppressive cell types, such as regulatory T cells, to modulate the tumor microenvironment. In metastatic non-small cell lung cancer lacking targetable mutations, pembrolizumab plus pemetrexed and platinum therapy is now the standard of care for front-line treatment on the basis of the phase III KEYNOTE-189 trial.[40] KEYNOTE-062 enrolled 763 patients with untreated advanced gastric or gastroesophageal junction cancers and randomized them to chemotherapy, pembrolizumab, or pembrolizumab plus chemotherapy. OS and PFS were unchanged between the chemotherapy and combination chemotherapy plus pembrolizumab arms, but, of note, this study used cisplatin plus fluoropyrimidine as the chemotherapy backbone. Multiple studies have demonstrated that oxaliplatin induces immunologic cell death, in which dying tumor cells stimulate dendritic cells, enhancing antigen processing and presentation to facilitate the priming of CD8+ T cells.[41] In contrast, cisplatin does not activate immunologic cell death on its own, despite a similar mechanism of action.[42] It is therefore possible that oxaliplatin may be a better chemotherapy backbone than cisplatin for combination chemoimmunotherapy regimens

in esophagogastric cancers. Meanwhile, the international phase III CheckMate 649 trial, which is randomizing patients with metastatic esophagogastric cancer to first-line fluoropyrimidine and oxaliplatin ± nivolumab, has completed accrual, and results are pending. Of importance, the combination of FOLFOX and nivolumab has shown no new safety signals in esophagogastric cancer.

Given the potential additive and/or synergistic effects of immunotherapy with regorafenib and chemotherapy, we propose a phase II trial of FOLFOX combined with regorafenib and nivolumab in patients with previously untreated metastatic esophagogastric adenocarcinoma. Triplet combinations with chemotherapy, immunotherapy, and targeted therapy are feasible in esophagogastric cancer, as supported by our recently reported phase II trial of first-line chemotherapy plus trastuzumab and pembrolizumab in patients with HER2-positive metastatic esophagogastric cancer, which showed an ORR of 91%.[43]

3.6 Rationale for Induction Cycle of Regorafenib and Nivolumab

In the proposed trial, patients will receive one cycle of induction regorafenib and nivolumab prior to the addition of FOLFOX chemotherapy in cycle 2. This design is based on our phase II study of first-line chemotherapy plus trastuzumab and pembrolizumab, in which 25 of 37 patients received one cycle of induction trastuzumab and pembrolizumab.[43] Several patients demonstrated tumor responses on imaging after the induction cycle, and 13 of 16 patients (81%) with detectable ctDNA showed a decrease in ctDNA levels after the first dose of pembrolizumab and trastuzumab. In addition, several patients from the phase 1b REGONIVO trial demonstrated partial responses at 6 weeks after initiation of regorafenib and nivolumab, suggesting early activity of the combination.[39] Notably, this study was limited to previously treated Japanese patients, who may have different underlying disease biology compared to non-Asian patients. Thus, the induction phase will provide insight into the activity of regorafenib and nivolumab prior to the initiation of chemotherapy. There are also some emerging data suggesting that previous checkpoint blockade may enhance the activity of later chemotherapy.[44] We will isolate PBMCs and ctDNA from patients before and after exposure to regorafenib/nivolumab and prior to introduction of chemotherapy for translational studies to investigate the interplay between these agents and their effect on antitumor immunity. Lastly, the chemotherapy-free induction phase will allow investigators to assess tolerability of regorafenib/nivolumab dosing prior to adding chemotherapy.

3.7 Rationale for Correlative Studies

Recent efforts using The Cancer Genome Atlas have led to the molecular and genomic characterization of esophageal and gastric cancers, including mutational and copy number status, gene expression, and DNA methylation.[45,46] These analyses have defined four distinct subclasses: (1) tumors with Epstein-Barr virus infection, which frequently harbor *PIK3CA* mutations and profound DNA hypermethylation; (2) microsatellite instability high (MSI-high) tumors with elevated somatic mutation rates and DNA hypermethylation; (3) tumors with

chromosomal instability, which demonstrate marked aneuploidy and recurrent amplifications of receptor tyrosine kinases, such as HER2; and (4) genomically stable tumors with less-distinctive alterations and without aneuploidy and elevated rates of mutation or hypermethylation. At Memorial Sloan Kettering Cancer Center (MSK), NGS and gene copy number analysis are routinely performed on all advanced gastric tumors using the MSK-IMPACT platform, an on-site cancer-associated gene-bait capture NGS assay currently interrogating a panel of 468 genes.[47] Tumors can be assigned to The Cancer Genome Atlas molecular subtypes (excluding Epstein-Barr virus subtype) on the basis of copy number and mutational data. MSI status can be inferred using a clinically validated algorithm to generate an MSI sensor score.[48] Whole-exome sequencing is also routinely performed for identification and validation of biomarkers. Previous clinical studies incorporating NGS with MSK-IMPACT testing on pretreatment and postprogression esophagogastric cancer biopsy specimens have identified genomic alterations that confer resistance to systemic therapies.[49,50] Therefore, we will perform NGS on pretreatment biopsy specimens to identify molecular mechanisms and genomic alterations that are associated with sensitivity and resistance to therapy with FOLFOX, regorafenib, and nivolumab.

Several studies have previously discovered biomarkers that are associated with response to immune checkpoint blockade in certain settings. For example, TMB has been shown to predict survival with immune checkpoint inhibitors across multiple tumor types.[51] Our analysis in esophagogastric cancers demonstrated that high TMB (>9.7 mut/Mb) is associated with improved OS after immunotherapy, although this survival benefit may be driven by patients with MSI-high tumors.[50,52] PD-L1 expression has also been associated with improved responses and a survival benefit in clinical trials, with approximately 40% of patients with metastatic esophagogastric cancers having PD-L1–positive tumors. For example, the KEYNOTE-061 trial, comparing pembrolizumab versus chemotherapy as second-line treatment, found that patients with high PD-L1 expression (CPS ≥10) were more likely to benefit from pembrolizumab, although there was no difference in response to nivolumab on the basis of PD-L1 status in the ATTRACTION-2 study.[34,35] We will assess mutational load through NGS data and IHC analysis for PD-L1 expression to determine whether TMB and PD-L1 expression are correlated with response to combination therapy with FOLFOX, regorafenib, and nivolumab. We will also perform immune profiling using PBMCs to identify changes in the peripheral immune landscape that may be associated with response. To determine whether the combination selects for tumor-specific T cells, we will perform T-cell receptor (TCR) sequencing to assess TCR clonality in the tumor and peripheral blood. Expansion of TCR clones present in the tumor at baseline would suggest that the combination regimen expands tumor-specific T cells. Last, to further probe the tumor immune microenvironment and its correlation with response to the combination of FOLFOX, regorafenib, and nivolumab, we will perform multiplex IHC analysis to quantify changes in the abundance of various immune cells and the expression of immune-stimulatory and immune-suppressive receptors.[53]

To develop patient-derived models that can be interrogated to explore sensitivity and resistance mechanisms, we will collaborate with the Ganesh lab at MSK. The lab has

developed methods to propagate three-dimensional PDOs that can be used to model biology and drug sensitivity.[54] In addition to colon and rectal cancer, the lab has optimized protocols to establish and culture PDOs generated from esophagogastric cancers. Prior studies have demonstrated that PDOs can recapitulate the treatment history of patients with metastatic gastrointestinal cancers.[55] For select patients undergoing endoscopic biopsy, we will generate PDOs from the primary tumor. We will also isolate PBMCs from patients before and during treatment. To analyze the modulation of T-cell function, PDOs will be cultured with PBMCs. Organoids and organoid and PMBC cocultures will be treated with regorafenib, nivolumab, and chemotherapy individually and in combination, and *in vitro* phenotypes (such as tumor organoid cytotoxicity, T-cell activation, and cytokine responses) will be correlated with patient responses.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single-arm, open-label, nonrandomized, single-institution, phase II study of nivolumab in combination with FOLFOX and regorafenib as first-line therapy in patients with metastatic esophagogastric adenocarcinoma. Patients must have evaluable or measurable disease on CT/MRI imaging within 28 days of the start of therapy. The primary objective of this study is to determine 6-month PFS. Secondary objectives include determining the safety, response rate, and efficacy of this treatment approach. Correlative studies will be performed to explore possible genomic alterations and biomarkers associated with response to therapy, and to generate relevant patient-derived organoid models. With a total of 35 patients with esophagogastric adenocarcinoma and using an exact single-stage binomial design, we will have 80% power to detect an improvement in 6-month PFS from a historical control of 53% to 74%, with a type I error rate of 5%.

4.2 Intervention

Each treatment cycle consists of 28 days. Patients will initially receive induction therapy with regorafenib (80 mg on days 1-21 of the 28-day cycle) and nivolumab (240 mg on days 1 and 15 of the 28-day cycle). Starting on cycle 2, day 1, patients will also receive FOLFOX chemotherapy with oxaliplatin (85 mg/m^2 IV), leucovorin (400 mg/m^2 IV), 5-FU (400 mg/m^2 IV bolus), and 5-FU (2400 mg/m^2/day continuous IV infusion over 48 h). If the patient is not a good candidate for induction regorafenib and nivolumab (i.e. symptomatic from a large burden of disease), 5-FU and oxaliplatin can be added during cycle 1 at the treating physician's discretion. The schedule and dosing of regorafenib are supported by the recently reported phase Ib REGONIVO trial, which found that regorafenib 80 mg (3 weeks on/1 week off) is the optimal dose in combination with nivolumab.[39] Patients will continue with this regimen until disease progression, unacceptable toxicity, or development of serious intercurrent illness. Treatment will be performed on the scheduled day (±7-day treatment window). AEs will be monitored and graded in severity in accordance with the guidelines outlined in the National

Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0).

Patients who started with induction regorafenib and nivolumab will undergo a CT or MRI scan at week 4 to assess response to the induction phase prior to starting chemotherapy in cycle 2. All patients will be followed by CT/MRI imaging at week 8 and every 8 weeks thereafter (every 2 cycles), with a scheduling window of 1 to 14 days. Response assessment will be performed using RECIST 1.1. Patients will be monitored for PFS, and they will be followed for OS in the event of disease progression or unacceptable toxicity.

Whole blood will be collected at baseline, at all times of study imaging, and at the end-of-treatment time point for isolation of ctDNA and PBMCs for correlative studies (whole blood will also be collected at cycle 1, day 15 and cycle 2, day 1 for isolation of PBMCs). For generation of organoids, patients may choose to undergo biopsy of tumor at baseline.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

Table 1. Therapeutic agents and starting doses

Drug	Dose	Dose Frequency	Route of Administration
Regorafenib[a]	80 mg	Days 1-21 of each 28-day cycle	Oral
Nivolumab[a,b]	240 mg	Days 1 and 15 of each 28-day cycle	IV infusion
Oxaliplatin[c,d]	85 mg/m^2	Days 1 and 15 of each 28-day cycle	IV infusion
Leucovorin[c,d]	400 mg/m^2	Days 1 and 15 of each 28-day cycle	IV infusion
5-FU[b,c]	400 mg/m^2	Days 1 and 15 of each 28-day cycle	IV infusion
5-FU[b,c]	2400 mg/m^2 over 48 h	Days 1 and 15 of each 28-day cycle	IV infusion

a. Regorafenib and nivolumab are started on cycle 1, day 1. Regorafenib is given as 2 40-mg tablets.
b. Patients for whom FOLFOX has been discontinued may receive nivolumab 480 mg IV every 28 days on Cycle 1, Day 1 instead of 240 mg IV every 14 days at the treating physician's discretion
c. FOLFOX chemotherapy is initiated on cycle 2, day 1.
d. Patients may begin with reduced starting dose of 5-FU IV bolus 300 mg/m^2, leucovorin 300 mg/m^2, infusional 5-FU 2000 mg/m^2 over 48 h and oxaliplatin 70 mg/m^2 if deemed necessary per the treating physician's discretion.

5.1 Nivolumab

Nivolumab will be provided by Bristol Myers Squibb at no charge. Nivolumab is a sterile, preservative-free, nonpyrogenic, clear to opalescent, colorless to pale yellow liquid that may contain light (few) particles.

5.1.1 Nivolumab Dosage and Administration

The planned dosage of nivolumab for this trial is 240 mg IV as a 30-min infusion every 2 weeks. Patients for whom FOLFOX has been discontinued may receive nivolumab 480 mg IV every 28 days on Cycle 1, Day 1 instead of 240 mg IV every 14 days at the treating physician's discretion. Variation in infusion time is permitted per institutional standards. Nivolumab will be administered before chemotherapy. Nivolumab injection for IV use is supplied in single-dose vials, each containing nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and water. The product may contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6. Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein-binding in-line filter at the doses and infusion times specified by the protocol. It is not to be administered as an IV push or bolus injection. Nivolumab can be diluted with 0.9% sodium chloride injection, USP, or 5% dextrose injection, USP, to prepare final concentrations from 1 mg/mL to 10 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, pharmacy reference sheet or investigator's brochure.

5.1.2 Nivolumab Storage and Accountability

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Nivolumab should be stored at 2°C to 8°C (36°F-46°F) and protected from light. The drug should not be frozen or shaken. 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 those stated in the protocol.

5.2 Regorafenib (Bay 73-4506)

Regorafenib will be provided by Bayer at no charge. Regorafenib 40-mg tablets contain regorafenib and the inactive excipients microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, colloidal anhydrous silica, polyvinyl alcohol-part hydrolyzed, talc, titanium dioxide E171 (color index 77891), Macrogol/PEG 33350, lecithin (soy), iron oxide yellow–E172 (color index 77491), and iron oxide red–E172. Regorafenib tablets will be packaged in high-density polyethylene bottles with a white child-resistant closure and induction seal. Each bottle includes 30 tablets and a 3-g desiccant. The bottles will have a label affixed containing study identification, product identification, and quantity of tablets. Once the drug has been received it must be kept in a secure, dry location. Study drug must be stored in its

original bottle at a temperature not above 25°C (77°F). The study drug must be exclusively used for the investigation specified in this protocol, and it will be accessible only to authorized staff.

5.2.1 Regorafenib Dosage and Administration

Regorafenib will be provided by Bayer as 40-mg tablets, which are coated, not divisible, gray-orange-red, oval (length, 16 mm; width, 7 mm; thickness, 4.9-5.6 mm), and 472 mg each in total weight. Tablets are in an immediate-release dosage form with rapid-dissolution characteristics under the *in vitro* test conditions. The regorafenib dose for this study is 80 mg daily orally. Two 40-mg regorafenib tablets should be taken with approximately 8 fluid ounces (240 mL) of water after a low-fat (<30% fat) meal. Some examples of low-fat meals are:

- Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces (240 mL) of skim milk (approximately 319 calories and 8.2 g of fat).
- One cup of cereal with 8 ounces (240 mL) of skim milk, 1 piece of toast with jam (no butter or marmalade), apple juice, and 1 cup of coffee or tea (approximately 520 calories, 2 g fat, 17 g protein, 93 g carbohydrates).

Patients should avoid consuming grapefruit and grapefruit juice or foods and drinks that contain grapefruit or grapefruit juice.

Regorafenib can be taken up to 2 hours before or after (± 2 hours) the regularly scheduled time. Patients who forgot to take a dose within the 2 hour window should skip the dose and take the next scheduled dose at their usual time.

Patients with emesis should not take a replacement dose. A study diary will be completed by patients to ensure compliance with regorafenib.

Patients may take their morning dose before or after their Nivo/FOLFOX infusion – whichever lines up better to their usual schedule.

Dose modifications for toxicity are described in Section 15.2.

5.2.2 Regorafenib Storage and Accountability

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice and Good Manufacturing Practices requirements and the instructions given by the clinical supplies department of MSK and will be inaccessible to unauthorized personnel. The investigator or a responsible party designated by the investigator must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form.

5.2.3 Prior and Concomitant Therapy

All medication that is considered necessary for the subject's welfare and that is not expected to interfere with the evaluation of the study treatment may be given at the discretion of the investigator. All medications (including contrast media) taken within 2 weeks before the start of the study and during the study must be recorded in the subject's source documentation and in the clinical research database (including start/stop dates, dose frequency, route of administration, and indication). Specific caution should be taken when considering or administering a concomitant medication that is metabolized by the cytochrome enzymes CYP2C8, CYP2B6, and CYP2C9. Such concomitant medication should be avoided if possible.

There is no clinical information on the effect of CYP3A4 inhibitors on the pharmacokinetics of regorafenib. Substances that are inhibitors of CYP3A4 activity, such as ketoconazole, are expected to decrease metabolism of regorafenib and thus increase regorafenib plasma concentrations. There are no clinical data evaluating the effect of chronically coadministered CYP3A4 inhibitors on the efficacy of regorafenib. Since there is a possibility of increased regorafenib toxicity upon chronic coadministration of CYP3A4 inhibitors with regorafenib, chronic coadministration of CYP3A4 inhibitors with regorafenib should be avoided if possible.

Permitted concomitant therapy includes:

- Standard therapies for concurrent medical conditions
- Supportive care for any underlying illness
- Palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated
- Granulocyte colony-stimulating factor and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the investigator's discretion. However, they may not be substituted for a required dose reduction
- Treatment with nonconventional therapies (such as acupuncture) and vitamin and mineral supplements are permitted provided they do not interfere with the study endpoints in the opinion of the investigator
- Bisphosphonates

A standard antiemetic regimen for the prophylaxis of acute emesis is recommended on the day of chemotherapy at least 30 min before the administration of chemotherapy. Such a regimen may include a serotonin (5-HT_3) antagonist (e.g., granisetron or ondansetron) with or without a corticosteroid (e.g., dexamethasone).

5.3 Oxaliplatin Dosage and Administration

Investigators should consult the manufacturer's instructions for oxaliplatin for complete prescribing information and follow institutional procedures for the administration of oxaliplatin. Oxaliplatin will first be administered on cycle 2, day 1, and then on day 1 and day 15 of each

28-day cycle. Oxaliplatin will be administered at a dose of 85 mg/m^2 IV per the institutional guidelines.. If deemed necessary per the treating physician's discretion, oxaliplatin can be started at 70 mg/m^2 IV. Oxaliplatin will be administered after the completion of the nivolumab infusion. Oxaliplatin will be continued until progression of disease, intolerable toxicity, or other withdrawal criteria are observed.

5.4 Leucovorin Dosage and Administration

Leucovorin will be prepared and administered per MSK guidelines. Please refer to the FDA-approved package insert for additional information. Leucovorin will first be administered on cycle 2, day 1, and then on day 1 and day 15 of each 28-day cycle. Leucovorin is given concurrently or following oxaliplatin administration at 400 mg/m^2 IV per institutional guidelines. If deemed necessary per the treating physician's discretion, leucovorin can be started at 300 mg/m^2 IV. Leucovorin will be continued until progression of disease, intolerable toxicity, or other withdrawal criteria are observed.

5.5 5-FU Dosage and Administration

Investigators should consult the manufacturer's instructions for 5-FU for complete prescribing information and follow institutional procedures for the administration of 5-FU. 5-FU will first be administered on cycle 2, day 1, and then on day 1 and day 15 of each 28-day cycle. 5-FU will be administered after completion of oxaliplatin and leucovorin infusion. 5-FU 400 mg/m^2 is given as an IV bolus followed by a 2400 mg/m^2 IV infusion over 48 h. If deemed necessary per the treating physician's discretion, 5-FU can be started as 5-FU 300 mg/m^2 given as an IV bolus followed by a 2000 mg/m^2 IV infusion over 48 h. 5-FU will be continued until progression of disease, intolerable toxicity, or other withdrawal criteria are observed.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.1 Participant Inclusion Criteria

- Patients must have histologically or cytologically confirmed metastatic esophageal, gastric, or gastroesophageal junction adenocarcinoma
- Patients must have disease that can be evaluated radiographically within 28 days of the start of study treatment. This may be measurable disease or non-measurable disease per RECIST 1.1.
- Age 18 years or older
- ECOG performance status 0 to 1
- Peripheral neuropathy grade ≤1
- Available archival tissue for correlative analysis (biopsy is required if no archival tissue is available)
- Adequate organ function as defined in Table 2

Table 2. Organ function requirements for eligibility

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1500/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥9 g/dL
Renal	
Serum creatinine	≤1.5X ULN
Hepatic	
Serum total bilirubin	≤1.5X ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5X ULN, except patients with Gilbert's disease (≤3X ULN)
AST and ALT	≤2.5X ULN
Albumin	≥3 mg/dL

ALT, alanine aminotransferase; AST, aminotransferase; ULN, upper limit of normal.

6.2 Participant Exclusion Criteria

- Confirmed HER2-positive disease (IHC 3+ or 2+, fluorescence *in situ* hybridization HER2:CEP17 ratio ≥2)
  - Note: Participants that are IHC 2+ but negative by FSH will be considered HER2-negative and eligible for trial.
- Inability to swallow oral pills
- Prior chemotherapy for metastatic disease. Patients with metastatic disease after treatment for localized esophagogastric cancer may have received prior adjuvant therapy (chemotherapy and/or chemoradiation) if >6 months have elapsed between the end of adjuvant therapy and registration
- Currently participating in a study and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment
- Underwent major surgical procedure within 4 weeks of registration
- Underwent radiation within 2 weeks of registration
- Received prior therapy with regorafenib
- Received prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent
- Diagnosis of immunodeficiency or receipt of systemic steroid therapy or any other form of immunosuppressive therapy within 7 days before the first dose of trial treatment
- A known history of active *Bacillus tuberculosis*
- A known active central nervous system metastases and/or carcinomatous meningitis
- A known history of or any evidence of active, noninfectious pneumonitis
- An active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease, systemic lupus erythematosus, Wegener syndrome [granulomatosis with polyangiitis], myasthenia gravis, Grave's disease, rheumatoid arthritis, hypophysitis, uveitis) within the 3 years before the start of treatment. The following are exceptions to this criterion:
  - Subjects with vitiligo or alopecia
  - Subjects with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment
- A known history of human immunodeficiency virus (HIV 1/2 antibodies)

- Known active hepatitis B (e.g., HBsAg reactive) or hepatitis C (e.g., HCV RNA [qualitative] is detected). Patients with HBsAg reactive on entecavir may be eligible after consultation with hepatologist and study team.
- Received a live vaccine within 30 days of planned start of study therapy
- Active or clinically significant cardiac disease, including congestive heart failure–New York Heart Association class >II, active coronary artery disease, cardiac arrhythmias requiring antiarrhythmic therapy other than beta blockers or digoxin, unstable angina (anginal symptoms at rest), new-onset angina within 3 months before initiation, or myocardial infarction within 6 months before initiation
- Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure >90 mm Hg on repeated measurement) despite optimal medical management
- Evidence or history of bleeding diathesis or coagulopathy
- Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial
- Pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the prescreening or screening visit through 120 days after the last dose of trial treatment
- Unwilling to give written, informed consent, unwilling to participate, or unable to comply with the protocol for the duration of the study

7.0 RECRUITMENT PLAN

We plan to accrue 35 end-point evaluable patients for this study. We anticipate it will take approximately 18 months to complete accrual, which is the time for full accrual for our previous phase II study of first-line FOLFOX plus regorafenib in patients with metastatic esophagogastric cancer. Patients with metastatic esophageal, gastric, or gastroesophageal junction adenocarcinoma who are eligible will be identified for enrollment from MSK clinical practice and clinic lists. All patients with HER2-negative metastatic disease who have not received prior chemotherapy for metastatic disease will be invited to participate in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

Participation in the study is completely voluntary. Patients/LAR will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. Patients will not receive payment for their participation on this study. Patients are free to withdraw from the study without consequence at any time.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at MSKCC. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

Inclusion of women and minorities
The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation with regards to race or gender.

Our institutional demographic information for accrual of patients to esophageal, gastric, or gastroesophageal junction cancer trials reflects the national incidence of this disease: 10%-15% of our patients have been women, and African-American men compose 3%-5% of patients treated on protocol. Given that our protocol accrual closely reflects the national incidence of this disease, no specific strategy will be undertaken to recruit women or persons of color on this trial.

This protocol does not include children because the number of children with esophageal, gastric, or gastroesophageal junction cancer is very small, and because the majority of such patients are already accessed by a nation-wide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in the section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

8.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must *sign* an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.

2. The length of study and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)

4. The name of the investigator(s) responsible for the protocol.

5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

9.0 PRE-TREATMENT/INTERVENTION

Pretreatment evaluation will be performed within 2 weeks of study entry and will include:

- History, concomitant medications, and toxicity assessment
- Physical exam, vital signs, and performance status
- Serum or urine pregnancy test will be performed for women of childbearing potential (WOCBP). All WOCBP should also be instructed to contact the principal investigator (PI) immediately if they suspect they might be pregnant (e.g., late or missed menstrual period) at any time during study participation
- Laboratory evaluation including complete blood count, comprehensive chemistry panel (includes blood urea nitrogen, creatinine, sodium, potassium, chloride, CO_2, calcium, glucose, bilirubin [total], protein [total], albumin, alkaline phosphatase, AST, ALT), thyroid function tests (thyroid-stimulating hormone, T3, T4), and urinalysis
- Research blood tests, including plasma collection for ctDNA analysis and whole-blood collection for PBMCs
- Electrocardiogram

The following must be obtained within 28 days before starting protocol therapy:

- CT/MRI scan of chest, abdomen, and pelvis
- Collection of archival tumor tissue for correlative testing (biopsy is required if no archival tissue is available)

To be completed any time before starting therapy:

- Histological confirmation of cancer diagnosis at MSK before study enrollment

10.0 TREATMENT/INTERVENTION PLAN

Treatment will be administered on an outpatient basis, with each treatment cycle consisting of 28 days. During cycle 1, patients will initiate therapy with nivolumab (240 mg IV) and regorafenib (80 mg daily as 2 40-mg coprecipitate tablets). For each cycle, patients will receive regorafenib 80 mg for day 1-21, and they will be off regorafenib from day 22 to 28 (3 weeks on/1 week off). A CT/MRI scan will be performed week 4 to determine response to the nivolumab and regorafenib induction. Patients will initiate FOLFOX chemotherapy on cycle 2, day 1. If the patient is not a good candidate for induction regorafenib and nivolumab, 5-FU and oxaliplatin can be added during cycle 1 at the treating physician's discretion. If the patient is symptomatic from a large burden of disease and would benefit from chemotherapy to control active cancer-related symptoms at treatment initiation as determined by the treating investigator, 5-FU and oxaliplatin can be added during cycle 1 at the treating physician's discretion. With subsequent cycles, all patients will receive FOLFOX and nivolumab (240 mg IV) on days 1 and 15, and they will receive regorafenib (80 mg daily) on days 1-21 of the 28-day cycle. Treatment will be performed on the scheduled day ±7 days. In the event that one component of the combination regimen is discontinued, patients may continue to receive the other components. For example, in case of discontinuation of oxaliplatin for cumulative toxicity, patients may continue with 5-FU and nivolumab on days 1 and 15 and regorafenib on days 1-21 of each 28-day cycle. If nivolumab is discontinued due to immune-related toxicity, patients may continue to receive regorafenib and FOLFOX (assuming acceptable toxicity). Likewise, if regorafenib is discontinued, patients may continue to receive nivolumab and FOLFOX. If a patient is no longer receiving chemotherapy, nivolumab may be given every 4 weeks at 480 mg IV at the treating physician's discretion.

A CT/MRI scan will be performed at baseline, week 4 (only for patients who have received induction regorafenib and nivolumab), week 8, and every 8 weeks thereafter. CT/MRI scans occurring every 8 weeks will coincide with the 6-month scan. Follow-up will start at the time of disease progression (according to RECIST 1.1) or removal from the study for any reason other than recurrence. Patients who enter the follow-up phase will be followed up for OS.

AEs will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE v5.0. Grade 1 and 2 toxicities will be managed with medical therapy specific to the particular adverse reaction, per Section 15. Patient dose reduction will be allowed depending on the type and severity of toxicity encountered, provided that criteria for patient withdrawal from study treatment have not been met. Evaluation will be made in person when there is concern for a drug-related toxicity, irrespective of grade. Safety will be continuously assessed using the toxicity stopping rules found in Section 14.0 Table 5.

Table 3. Regorafenib + nivolumab + FOLFOX study treatment

Study Drug[a]	Dose	Route of Administration	Day

			1	2	3	4-14	15	16	17	18-21	22-28
Oxaliplatin[b]	85 mg/m^2	IV infusion time per institutional guidelines	X				X				
Leucovorin[b]	400 mg/m^2	IV infusion time per institutional guidelines [c]	X				X				
5-FU[b]	400 mg/m^2	IV bolus injection	X				X				
	2400 mg/m^2	48-h IV infusion	X	X	X		X	X	X		
Nivolumab[d]	240 mg	30-min IV infusion	X				X				
Regorafenib[e,f]	80 mg	Oral tablets	X	X	X	X	X	X	X	X	

[a]Chemotherapy doses may be started at reduced dose per the treating physician's discretion: oxaliplatin 70 mg/m^2 on day 1, followed by or concurrent with leucovorin 300 mg/m^2 IV, followed by 5-FU 300 mg/m^2 IV bolus, followed by 5-FU 2000 mg/m^2 infusion over the course of 48 h.
[b]5-FU, oxaliplatin, and leucovorin will be initiated on cycle 2, day 1.
[c]Leucovorin is given as an IV infusion concurrently with oxaliplatin. Leucovorin may be given as a 30-min infusion if oxaliplatin has been discontinued.
[d]Patients for whom FOLFOX has been discontinued may receive nivolumab 480 mg IV every 28 days on Cycle 1, Day 1 instead of 240 mg IV every 14 days at the treating physician's discretion**.**
[e] Patients should be provided with a prescription for clobetasol 0.05% topical corticosteroid at the time of regorafenib prescription, but should be advised ***not to use this cream unless directed to do so by a medical provider*** (Section 15.2).
[f] Consider dermatology telehealth referral to Dr. Lacouture for pre-treatment counseling prior to D1 of treatment.

10.1 Exploratory Correlative Studies

Details of correlative analysis collections are listed in Appendix 1. Available archival tumor samples will be obtained and stored for future correlative analysis, including but not limited to those listed below. Patients will have the option of consenting to IRB 12-245 and the biospecimen protocol 06-107. For consented patients, any leftover blood or tissue samples will be rebanked for future studies, in accordance with the protocol, upon completion of all exploratory correlative studies.

10.1.1 DNA Sequencing and Immunogenicity Analysis

We will plan to perform next generation sequencing (NGS) on pretreatment tumor tissue from all patients, using the MSK-IMPACT exon-capture platform. DNA extracted from formalin-fixed or frozen primary tumor tissue will be sequenced to identify somatic mutations across all or a subset of the coding regions for >450 genes using the MSK-IMPACT sequencing platform. Tumor sequencing will be performed in the MSK Molecular Genetics Laboratory. We will correlate mutational and copy number status, TMB, and MSI status with response to treatment.

We plan to conduct whole-exome sequencing of DNA from tumors and matched normal blood samples from patients whose disease responds to trial therapy (CR, PR, or prolonged SD) and compare the results to those of analyses of DNA from nonresponders. DNA will be extracted and exon capture will be performed with the use of the SureSelect Human All Exon 50-Mb kit (Agilent Technologies). Enriched exome libraries sequenced on the HiSeq 2000 platform (Illumina) will provide mean exome coverage of >100X (MSK Genomics Core).

MSK investigators have created a bioinformatics tool to translate all mutations in exomes and evaluate binding with major histocompatibility complex class I molecules. The neoantigen signature was generated from the nonamers containing four amino acid strings of peptides that are common to tumors from patients who have experienced long-term benefit from therapy. Candidate neoantigen peptides will be synthesized (GenScript), cultured with autologous PBMCs, and then analyzed by intracellular cytokine staining for interleukin-2, CD107a, macrophage inflammatory protein 1β, tumor necrosis factor–α, and interferon-γ or restimulation of cells with the candidate peptides.

10.1.2 Collection of PBMCs and Immunologic Analyses

Whole blood will be used for isolation of PBMCs. Flow-cytometric analysis will be performed on PBMCs at baseline and during treatment to assess changes in the composition and activation status of lymphocyte subsets, including CD8+ and CD4+ T-cell subsets (activated, effector/memory, regulatory) and populations of those cells as defined by the expression of activation, exhaustion, or signaling markers, such as ICOS, HLA-DR, PD-1, CTLA-4, and/or intracellular IFN-γ. We will also assess monocytes including myeloid-derived suppressor cells (MDSCs)

For subjects who are not participating in organoid collection, approximately 32 mL of whole blood per visit (baseline; cycle 1, day 15; cycle 2, day 1; cycle 3, day 1; every imaging time point; end of treatment) will be collected at ambient temperature into 4 x 8-mL BD sodium heparin cell-preparation tubes for density-gradient centrifugation and isolation of PBMCs and plasma for banking, in accordance with institutional procedures at the MSK Ludwig Center for Cancer Immunotherapy Immune Monitoring Core Facility. After centrifugation, the plasma supernatant will be collected and the PBMC monolayer will be isolated and washed. PBMCs will be resuspended at approximately 6 million to 8 million cells per vial in cell-freezing medium, frozen at -80°C in controlled-rate cooling containers, and then cryopreserved in liquid-nitrogen freezers. Plasma will be frozen in 1.5-mL aliquots and stored at -20°C.

For subjects who are participating in organoid collection, approximately 48 mL of whole blood per visit (baseline; cycle 1, day 15; cycle 2, day 1; cycle 3, day 1; every imaging time point; end of treatment) will be collected at ambient temperature into 6 x 8-mL BD sodium heparin cell-preparation tubes for density-gradient centrifugation and isolation of PBMCs and plasma for banking, in accordance with institutional procedures at the MSK Zuckerman Research Center Room Z1741 in the lab of Dr. Karuna Ganesh. After centrifugation, the plasma

supernatant will be collected and the PBMC monolayer will be isolated and washed. PBMCs will be resuspended at approximately 6 million to 8 million cells per vial in cell-freezing medium, frozen at -80°C in controlled-rate cooling containers, and then cryopreserved in liquid-nitrogen freezers. Plasma will be frozen in 1.5-mL aliquots and stored at -20°C.

10.1.3 ctDNA Blood Collection

Collection of ctDNA will occur at baseline, every 8 weeks to correspond with imaging time points, and the time of treatment discontinuation. Approximately 20 mL of whole blood per visit will be collected at ambient temperature into 2 x 10-mL cell-free DNA blood-collection tubes for plasma isolation.

10.1.4 TCR Sequencing

The presence of tumor-infiltrating lymphocytes and TCR clonality will be assessed by TCR sequencing of tumor and serially collected PBMCs using the ImmunoSEQ assay (Adaptive Biotechnologies) or a similar assay if updated. This assay identifies unique TCRβ chains by sequencing the rearranged CDR3 regions in the β-chain gene locus. The relative abundance of unique TCRβ CDR3 regions across the repertoire and interference of T-cell quantity within each sample are estimated from sequence data. This will allow us to quantify the presence and relative clonality of specific TCR clones in the tumor and peripheral blood.

The number of antigens on tumors that are recognized by the immune system has been defined at the molecular level, including both tumor-associated antigens and tumor-specific antigens. These antigens can be recognized by the adaptive immune system and serve to direct an immunologic response to cancers. Techniques, including intracellular cytokine staining, IFN-y–release assays, and tetramer assays, will be used for quantification and functional characterization of antigen-specific T cells in human peripheral blood and tumor samples. These functional, tumor antigen–specific T cells may be relevant markers of disease response. TCR sequencing will be performed in the Immune Monitoring Core Facility (IMF lab) at MSK.

10.1.5 PD-L1 Testing of Archival Tissue

PD-L1 expression in tumor tissue will be characterized by IHC analysis to explore the relationship between PD-L1 expression (by CPS) and response to therapy. Other exploratory biomarkers, including but not limited to PD-1 expression and markers of T-cell phenotype, may also be evaluated. Testing will be performed at the MSK Pathology lab.

10.1.6 Tumor Microenvironment Analysis

Formalin-fixed paraffin-embedded sections of pretreatment tumors (archival or fresh tissue) will be analyzed using the multiparameter Vectra platform for IHC analysis, focusing on specific

components of the tumor microenvironment (e.g., CD4, CD8, FoxP3 and CD68 as markers of T-cell subsets and tumor-associated macrophages) and immune-inhibitory markers (e.g., PD-L1, indoleamine-2,3-dioxygenase). RNA will be extracted from archival tumors and analyzed for broad expression of genes related to immune function (e.g., type I and type II IFN signatures) using RNAseq, Affymetrix microarray, or targeted multiparameter PCR (i.e., Nanostring). Samples will be analyzed and stored in Dr. Taha Merghoub/ Dr. Jedd Wolchock labs at MSK.

10.1.7 PDO Generation

For patients undergoing endoscopy for disease assessment before starting treatment, we will use biopsy tissue from the primary tumor to generate PDOs in collaboration with the Ganesh lab. Viable organoid models will be cultured alone or with PBMCs to investigate antitumor immunity and responses to chemotherapy, regorafenib, and nivolumab, either alone or in combination. *In vitro* phenotypes (including but not limited to tumor organoid cytotoxicity, T-cell activation, and T-cell cytokine responses) will be correlated with patient responses.

10.1.8 Tumor Biopsies

Pre-treatment tumor biopsies will be used to evaluate biomarker expression, perform next-generation sequencing and TCR sequencing, analyze the tumor microenvironment and generate patient-derived organoids, as described above. In addition, archived tissue from prior tumor biopsies will be analyzed when available. Patients may undergo an optional pre-treatment biopsy of the primary tumor. After obtaining informed consent, a diagnostic biopsy will be performed by endoscopy. The biopsy specimen will be accessioned and sent to pathology for routine analysis (histology, tumor grade, HER2 by IHC, HER2 by FISH, PD-L1 CPS, mismatch repair deficiency testing by IHC and Epstein-Barr virus testing). Where possible, multiple cores will be obtained, with one core biopsy used for PDO generation. When only one core is obtained, half the core will be snap frozen using liquid nitrogen with a selection evaluated for the presence of invasive carcinoma by a participating pathologist and stored for later analysis. The second and larger sample will be formalin fixed and used for IHC and other studies. The number of biopsies taken will be based on the clinical judgement of the endoscopist but ideally will be less than or equal to four.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

Table 4.1. Study flow chart (Induction)

Procedure	Screening [a]	Cycle 1 (28 days)									Cycle 2 (28 days)									Subsequent cycles	EOT [c]	F/U [d]
Days		1	2	3	4 - 14	15	16	17	18 - 21	22 - 28	1	2	3	4 - 14	15	16	17	18 - 21	22 - 28			
Medical hx/ demographics	x	x				x					x				x					x^{g}	x	x
Urine/serum pregnancy test	x										x											
Archival tumor samples[e]	x																					
Optional research biopsy	x^{r}																					
Physical exam[b]	x	x^{f}				x					x				x					x^{g}	x	x
Performance status	x	x				x					x				x					x^{g}	x	x
Toxicities, adverse effect assessment	x	Reported from screening throughout all subsequent cycles																			x	$x^{h,i}$
Hematology[b]	x	x^{f}				x					x				x					x^{g}	x	
Chemistry[b]	x	x^{f}				x					x				x					x^{g}	x	
Magnesium	x	x				x					x				x					x^{g}	x	
TSH, T_3, T_4	x	x									x				x					x^{g}	x	
Tumor Markers[s]	x^{t}	x^{t}								x									x^{l}	X^{s}	x	
INR, APTT	x	Monitored per investigator discretion																				
Urinalysis	x^{j}										x^{j}									x^{j}		
CT/MRI assessment[k]	x									x									$X^{k,l}$	$X^{k,l}$	x	x^{m}
Concomitant medication[n]	x	All medications taken during study will be documented																				
12-lead ECG	x																					
Research test: PBMCs	x					x				x^{p}	x								x^{p}	x^{p}	x	
Research test: ctDNA[q]	x									x^{q}			x				x		x^{q}	x^{q}	x	
FOLFOX[o]											x	x	x		x	x	x			x^{g}		
Nivolumab		x				x					x				x					x^{g}		
Regorafenib		x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x		x^{g}		
Regorafenib dispensing		x									x									x^{g}		
Regorafenib compliance		Compliance will be assessed at every cycle																				

ECG=electrocardiogram; EOT=end of treatment; F/U=follow-up; hx=history; TSH= thyroid-stimulating hormone.

a. Radiological imaging studies and archival tissue within 28 days of start of study treatment, other screening evaluation within 2 weeks before start of study treatment.
b. Physical exam (vital signs [BP, heart rate, temperature], weight, and a review of body systems), chemistry, hematology, and physical exam will be performed on the intended days 1 and 15 of each cycle before chemotherapy or ≤72 h before dosing thereafter. Starting at C7D15, and for all subsequent CXD15, physical exam is optional as per investigator discretion – routine labs should still be performed.
c. Within 28 days of tumor progression or study treatment discontinuation.
d. Assessment by the treating medical oncologist. For those patients no longer followed up by an MSK MD, the clinical trials nurse will make a follow-up phone call every 3 months to assess the patient's vital status.
e. A sample of archival tumor biopsy or other available tumor biopsy sample should be submitted for biomarker analysis during screening. A biopsy is required at screening (baseline) if there is no archival tissue available. Tumor biopsy samples may also be submitted for biomarker analysis at any other time during the course of the clinical study.
f. For physical exam/lab assessments, not required if screening assessments were performed within 72 h of first dose.

g. Cycles ≥3: Procedures will be performed identical to cycle 2, day 1. On day 15 of cycles ≥7, patients will receive treatment and labs only. Radiologic tumor assessment will be at the end of every second cycle (cycles 4, 6, etc.) before the next cycle (cycles 5, 7, etc.).
h. AE monitoring should continue for at least 4 weeks after the last dose of study treatment.
i. Only applies to AEs that occur within 30 days following the last study treatment. Those AEs will be followed up until resolution.
j. Proteinuria has to be assessed with lab value at screening and will be performed on day 1 of cycle 2, and then every second cycle staring with cycle 2 (i.e. cycle 2, 4, 6 etc.)
k. The baseline and subsequent scans to assess response must be performed using an identical technique . Radiological imaging studies to evaluate tumor status will be done after the initial 3 weeks (only applicable to patients receiving induction regorafenib and nivolumab). All patients will undergo CT/MRI scan at week 8, and then every 2 cycles (8 weeks) while the patient is on study, regardless of treatment delays.
l. If treatment is held or otherwise delayed, tumor response assessments should follow a schedule of Q8W, regardless of treatment cycle.
m. For subjects who have entered the survival follow-up period and have not yet experienced progression of disease, every effort should be made to follow up for tumor evaluation by CT/MRI until progression of the malignancy every 8 weeks or until a new anticancer treatment is started.
n. All medication given within 2 weeks before the start of study treatment.
o. Doses of the chemotherapy regimen should be recalculated before each cycle if there has been a change of ≥10% in body weight. Use actual weight.
p. PBMCs will be collected at baseline; cycle 1 day 15; cycle 2 day 1, cycle 3 day 1; every imaging time point; and the time of treatment discontinuation.
q. ctDNA will be collected via MSK Access at baseline, C2D3, C2D17, every imaging time point starting at 8 weeks, and the time of treatment discontinuation.
r. Patients may undergo an optional biopsy of primary tumor during screening (baseline) for generation of PDOs.
s. Tumor markers to be drawn at baseline, every imaging timepoint time point starting at 8 weeks, and the time of treatment discontinuation (CEA, LDH, CA19-9; as clinically appropriate)
t. Tumor markers to be drawn C1D1 if not collected during screening.

Table 4.2. Study flow chart (Induction Omitted)

Procedure	Screening [a]	Cycle 1 (28 days)									Subsequent cycles	EOT [c]	F/U [d]
Days		1	2	3	4 - 14	15	16	17	18 - 21	22 - 28			
Medical hx/ demographics	x	x				x					x[g]	x	x
Urine/serum pregnancy test	x	x											
Archival tumor samples[e]	x												
Optional research biopsy	x[f]												
Physical exam[b]	x	x				x					x[g]	x	x
Performance status	x	x				x					x[g]	x	x
Toxicities, adverse effect assessment	x	Reported from screening throughout all subsequent cycles										x	x[h,i]
Hematology[b]	x	x				x					x[g]	x	
Chemistry[b]	x	x				x					x[g]	x	
Magnesium	x	x				x					x[g]	x	
TSH, T_3, T_4	x	x				x					x[g]	x	
Tumor Markers[s]	x[t]										X[s]	x	
INR, APTT		Monitored per investigator discretion											
Urinalysis	x[j]										x[j]		
CT/MRI assessment[k]	x										X[k,l]	x	x[m]
Concomitant medication[n]	x	All medications taken during study will be documented											
12-lead ECG	x												
Research test: PBMCs	x	x									x[p]	x	
Research test: ctDNA[g]	x			x				x			x[q]	x	
FOLFOX[o]		x	x	x		x	x	x			x[g]		
Nivolumab		x				x					x[g]		
Regorafenib		x	x	x	x	x	x	x	x		x[g]		
Regorafenib dispensing		x									x[g]		
Regorafenib compliance		Compliance will be assessed at every cycle											

ECG=electrocardiogram; EOT=end of treatment; F/U=follow-up; hx=history; TSH= thyroid-stimulating hormone.

a. Radiological imaging studies and archival tissue within 28 days of start of study treatment, other screening evaluation within 2 weeks before start of study treatment.
b. Physical exam (vital signs [BP, heart rate, temperature], weight, and a review of body systems), chemistry, hematology, and physical exam will be performed on the intended days 1 and 15 of each cycle before chemotherapy or ≤72 h before dosing thereafter. Starting at C7D15, and for all subsequent CXD15, physical exam is optional as per investigator discretion – routine labs should still be performed.
c. Within 28 days of tumor progression or study treatment discontinuation.
d. Assessment by the treating medical oncologist. For those patients no longer followed up by an MSK MD, the clinical trials nurse will make a follow-up phone call every 3 months to assess the patient's vital status.
e. A sample of archival tumor biopsy or other available tumor biopsy sample should be submitted for biomarker analysis during screening. A biopsy is required at screening (baseline) if there is no archival tissue available. Tumor biopsy samples may also be submitted for biomarker analysis at any other time during the course of the clinical study.
f. For physical exam/lab assessments, not required if screening assessments were performed within 72 h of first dose.

g. Cycles ≥3: Procedures will be performed identical to cycle 2, day 1. On day 15 of cycles ≥7, patients will receive treatment and labs only. Radiologic tumor assessment will be at the end of every second cycle (cycles 4, 6, etc.) before the next cycle (cycles 5, 7, etc.).
h. AE monitoring should continue for at least 4 weeks after the last dose of study treatment.
i. Only applies to AEs that occur within 30 days following the last study treatment. Those AEs will be followed up until resolution.
j. Proteinuria has to be assessed with lab value at screening and will be performed on day 1 of cycle 2, and then every second cycle staring with cycle 2 (i.e. cycle 2, 4, 6 etc.)
k. The baseline and subsequent scans to assess response must be performed using an identical technique . Radiological imaging studies to evaluate tumor status will be done after the initial 3 weeks (only applicable to patients receiving induction regorafenib and nivolumab). All patients will undergo CT/MRI scan at week 8, and then every 2 cycles (8 weeks) while the patient is on study, regardless of treatment delays.
l. If treatment is held or otherwise delayed, tumor response assessments should follow a schedule of Q8W over a cycle schedule.
m. For subjects who have entered the survival follow-up period and have not yet experienced progression of disease, every effort should be made to follow up for tumor evaluation by CT/MRI until progression of the malignancy every 8 weeks or until a new anticancer treatment is started.
n. All medication given within 2 weeks before the start of study treatment.
o. Doses of the chemotherapy regimen should be recalculated before each cycle if there has been a change of ≥10% in body weight. Use actual weight.
p. PBMCs will be collected at baseline; cycle 1 day 15; cycle 2 day 1, cycle 3 day 1; every imaging time point; and the time of treatment discontinuation.
q. ctDNA will be collected via MSK Access at baseline, C1D3, C1D17, every imaging time point starting at 8 weeks, and the time of treatment discontinuation.
r. Patients may undergo an optional biopsy of primary tumor during screening (baseline) for generation of PDOs.
s. Tumor markers to be drawn at baseline, every imaging timepoint time point starting at 8 weeks, and the time of treatment discontinuation (CEA, LDH, CA19-9; as clinically appropriate)
t. Tumor markers to be drawn C1D1 if not collected during screening.

12.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient develops progressive disease while receiving the combination of FOLFOX chemotherapy, regorafenib, and nivolumab, the patient will be removed from the study unless the treating physician determines that it is of clinical benefit (defined as improvement in the quality of life, function, or general well-being) for the patient to continue receiving the trial therapy. If at least 6 months have elapsed since discontinuation of oxaliplatin, oxaliplatin may be reinitiated at the last dose level for this patient, at the investigator's discretion, for concerns of clinical progression. If after 8 weeks of continued treatment a second scan shows additional disease progression, treatment will be discontinued, and the patient will be taken off study. If at any time the patient develops unacceptable toxicity that fails to resolve after a maximum treatment delay of 12 weeks, they will be removed from treatment and followed up for survival. At the end-of-treatment visit, patients will undergo CT/MRI scan for assessment of response.

A patient will be withdrawn from the study treatment in the following circumstances:

- The patient is no longer able to participate in the study (e.g., AE, surgery, concomitant diagnoses, concomitant therapies, or administrative reasons); in such a case, the treating investigator's reason for a patient's removal must be recorded in the clinical research database
- Patient withdraws consent or elects to discontinue participation in the trial

- Significant deviation from the protocol or eligibility criteria; such patients will be considered to represent protocol violations and will be removed from the study
- Noncompliance with study or follow-up procedures
- Drug-related AE(s) have not resolved after 12 weeks of treatment interruption. An exception to this rule for patients who derive obvious clinical benefit, according to the investigator's judgment, may be considered upon discussion with the PI. The dose-reduction scheme provided should be followed in this case
- Repeated episodes of drug-related toxicity despite appropriate management
- Documented progressive disease

When a patient is removed from the study treatment, the end-of-treatment visit must be performed within 1 to 14 days of the off-treatment date. Every effort should be made to follow up with patients in case an AE is ongoing at the time of withdrawal. Patients who show a clinical benefit (e.g., with either an objective tumor response, absence of disease progression, or presence of clinical benefit in the opinion of the treating investigator) may continue to receive additional treatment courses. Patients with radiologically documented progressive disease should be removed from the study unless the treating investigator judges it to be of clinical benefit for the patient to continue receiving the trial therapy.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

The primary endpoint of the study is 6-month PFS with combination nivolumab, regorafenib, and FOLFOX chemotherapy. If CT/MRI scan shows disease progression by RECIST 1.1, the patient will be removed from the study and followed up for OS. As per RECIST 1.1 criteria, any evidence of progression in non-measurable lesions, measurable lesions, or the development of new lesions, would qualify as disease progression. The treating investigator will determine if there is unequivocal progression of non-measurable lesions sufficient to require change in therapy. Examples of unequivocal progression include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or increase in overall disease burden comparable to magnitude of increase required for disease progression for measurable disease (i.e. an increase in tumor burden representing an additional 73% in volume, which is equivalent to a 20% increase in diameter of a measurable lesion). Any time a patient has intolerable toxicity or declines further treatment, they will go to the event-monitoring phase and will be followed up for OS. OS is defined as the time from the start of treatment until death or last follow-up, whichever comes first; PFS is defined as the time from the start of treatment until disease progression or death, whichever comes first.

The secondary endpoints include response rate, overall clinical benefit, safety, median PFS, and OS. ORR is defined as the percentage of patients who have achieved either an objective complete or partial target lesion response that is confirmed by RECIST 1.1. Overall clinical benefit is defined as SD, CR, or PR. Target lesions must have a minimum size of at least one diameter of 10 mm for liver, soft-tissue lesions, lung, and skin. Pathological nodes must be at least 15 mm in the short axis to be considered target lesions. The primary tumor is not considered measurable disease. Patients will be

assessed with a CT/MRI scan at baseline and after 4 weeks of treatment. Regardless of whether there is a response on postinduction CT/MRI scan, all patients with acceptable toxicities will continue to receive treatment with nivolumab, FOLFOX, and regorafenib. Patients will have a CT/MRI scan at 8 weeks and every 8 weeks thereafter. For toxicity assessment, the type, frequency, severity, timing, and relationship of each AE will be determined in accordance with NCI CTCAE v5.0. Toxicity during cycle 1 and subsequent cycles will be reported.

13.2 Criteria for Study Endpoint Evaluability

All patients who received at least 1 dose of nivolumab, regorafenib, and FOLFOX will be evaluable for toxicity and response. Patients who did not receive at least one dose of all three study components will not be evaluated for toxicity or response and will be replaced by a new patient. Subjects who progress during induction with nivolumab and regorafenib will not be considered for endpoint analysis and therefore replaced but will continue to be followed per protocol for additional secondary analysis.

14.0 BIOSTATISTICS

This is a single-arm, open-label, nonrandomized, single-institution, phase II trial of nivolumab in combination with FOLFOX and regorafenib as first-line therapy for HER2-negative metastatic esophagogastric adenocarcinoma. The primary endpoint is 6-month PFS, as measured from the start of treatment with nivolumab and regorafenib to the date of either documentation of disease progression with FOLFOX, regorafenib, and nivolumab or death. Progression of disease to FOLFOX, regorafenib and nivolumab will be defined according to RECIST 1.1. Patients with measurable and non-measurable disease that is evaluable radiographically will be eligible for entry in the study. Per RECIST 1.1, any evidence of progression in non-measurable or measurable lesions or the development of new lesions qualifies as disease progression. For the primary endpoint analysis, 6 month PFS will be considered as a binary endpoint. Removal of a patient from the study before 6 months, without documented progression, will be considered an event for the primary endpoint of 6-month PFS. Patients who are removed from the study because of toxicity before 6 months, without documented progression, will continue to undergo imaging to obtain 6 months of assessment of progression. Loss to follow-up or withdrawal of consent before 6 months, without documented progression, will be counted as an event for the 6-month PFS endpoint; however, this is expected to be a rare occurrence. Patients who receive at least 1 dose of nivolumab and start regorafenib treatment will be considered evaluable for the primary endpoint of 6-month PFS and all secondary endpoints including safety.

Our previously reported phase II trial of FOLFOX plus regorafenib in patients with metastatic esophagogastric adenocarcinoma observed a 6-month PFS of 53%. With a total of 35 patients with esophagogastric adenocarcinoma and using an exact single-stage binomial design, we will have 80% power to detect an improvement in 6-month PFS from a historical control of 53% to 74%, with a type I error rate of 5%. If ≥24 patients are alive and progression free at 6 months, the combination of FOLFOX, nivolumab, and regorafenib will be considered to be worthy of further investigation. We expect to enroll 2 to 3 patients per month, with completion of accrual in approximately 18 months.

Secondary endpoints include objective ORR, clinical benefit, median PFS, OS (median, 1-year), and safety. ORR is defined as the percentage of patients who have achieved either an objective complete or partial target lesion response by RECIST 1.1. Stable disease is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study. A patient is considered to have SD if at least 12 weeks have lapsed after start of treatment. Clinical benefit is defined as the percentage of patients who achieve SD, PR, or CR. Patients will be assessed with a CT/MRI scan at baseline and at week 4 after initiation of treatment with nivolumab and regorafenib. Regardless of whether there is a response on the postinduction CT/MRI scan, all patients with acceptable toxicities will continue to receive nivolumab, FOLFOX, and regorafenib. Patients will have a CT/MRI scan at 8 weeks and every 8 weeks thereafter.

PFS is defined as the time from the start of treatment until disease progression or death, whichever comes first. Subjects who are alive and progression-free at the data cut-off date will be censored at the date of the last evaluable tumor assessment. Subjects who discontinue from the study without disease progression or death will be censored at the date of last evaluable tumor assessment. Subjects who started any subsequent anti-cancer therapy without prior reported disease progression will be censored at the last tumor assessment prior to or on the initiation of subsequent anti-cancer therapy. Subjects who did not have any on-study tumor assessment and did not die will be censored at the treatment start date.

OS is defined as the time from the start of treatment until death or last follow-up. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

Survival curves will be estimated using the Kaplan-Meier method. Calculation of best RECIST 1.1 response (CR + PR) and overall clinical benefit (SD + CR + PR) will be estimated using binomial proportions along with 95% confidence intervals. AEs of any grade that are considered to be related to study treatment will be summarized descriptively using percentages.

The study protocol will allow for a maximum of 43 patients to be enrolled in order to achieve a total of 35 evaluable patients on the protocol as it is written. To be considered evaluable for endpoint analysis, subjects must have received at least 1 dose of nivolumab, regorafenib, and FOLOX. Provision of additional slots is to account for subjects who progress during the induction period or otherwise do not meet endpoint criteria. These subjects will continue to be followed per protocol, however they will be replaced until 35 evaluable patients can be achieved. To date, 2 patients came off treatment during the induction phase and did not receive FOLFOX. These patients will therefore be replaced by new patients while continuing to be followed per protocol.

Exploratory objectives of the study include:

- Perform correlative analysis of PD-L1 status by CPS and response, defined as either PR or CR. PD-L1 will be associated with response using Fisher's exact test. The log-rank test will be used to compare survival curves between patients with PD-L1–negative (CPS <1) and

PD-L1–positive (CPS ≥1) disease, as well as those with PD-L1–high (CPS ≥10) and PD-L1–low (CPS <10) disease.

- Perform correlative analyses, including exon-capture sequencing (MSK-IMPACT) and whole-exome analysis, to determine associations between treatment response and specific alterations, mutation load, and specific neoantigen landscape. The log-rank test will be used to compare survival between patients with the presence or absence of alterations in individual genes or pathways. The Mann-Whitney test will be used to compare mutational loads of tumors among responders (PR or CR) and nonresponders. The log-rank test will be used to compare survival between patients with low TMB (bottom quartile) and high TMB (top quartile).
- Plasma samples obtained at sequential time points during this trial will be used to evaluate the role of the combination of FOLFOX, nivolumab, and regorafenib on ctDNA clearance and the development of mutations conferring acquired resistance to therapy. The log-rank test will be used to compare survival between patients who clear or do not clear ctDNA, either after the induction cycle or at any timepoint.
- Flow cytometric analysis will be performed on PBMCs at baseline and during treatment to assess changes in the composition and activation status of lymphocyte subsets, including CD8+ and CD4+ T-cell subsets (activated, effector/memory, regulatory) and populations of those cells as defined by the expression of activation, exhaustion, or signaling markers, such as ICOS, HLA-DR, PD-1, CTLA-4, and/or intracellular IFN-γ. We will also assess changes in monocytes including MDSCs. These will be investigated graphically to explore patterns of change over time. Wilcoxon signed rank test will be used to test for differences between pre- and on-treatment specimens.
- Utilize pre-treatment tumor specimens and serially collected PBMCs to assess TCR clonality of tumor-infiltrating and peripheral lymphocytes. TCR clonality will be investigated graphically to explore patterns of change over time. TCR clonality will be compared between treatment responders and non-responders using the Mann-Whitney test.
- Perform correlative analyses on baseline tumor samples with tumor microenvironment analysis (including IHC for immune cell subsets and RNA sequencing). Gene set enrichment analysis will explore pathways associated with response. Deconvolution of immune gene expression to estimate the relative proportion of immune cell subtypes in the tumor microenvironment will be explored using CIBERSORT.
- Use patient biopsy specimens for generation of PDOs. Organoid cultures will be cocultured with pre-treatment and on-treatment PBMCs to assess antitumor immunity and its modulation by treatment, including but not limited to tumor organoid cytotoxicity, T-cell activation, and T-cell cytokine responses. Continuous variables between samples from treatment responders and non-responders will be compared using the Mann-Whitney test.
- Explore the activity of induction regorafenib and nivolumab in patients with metastatic esophagogastric cancer as assessed by pre- and post-induction CT/MRI scan and ctDNA decline. We will also estimate median PFS and OS in patients who received induction regorafenib and nivolumab using the Kaplan-Meier method.

These analyses are exploratory in nature and hypothesis generating due to limited sample size.

Previous clinical trials have reported the frequency of AEs attributable to treatment with FOLFOX, regorafenib, and nivolumab. To reduce risk to patients, the study design includes early termination of the trial in the event of excessive grade ≥4 neutropenia, grade ≥3 diarrhea despite adequate antidiarrheal management (loperamide and diphenoxylate/atropine), or grade ≥3 neuropathy. In addition, the safety analysis will assess the rates of regorafenib-related grade ≥4 liver function test abnormalities, grade ≥3 hand foot syndrome and rash (despite adequate skin management), and persistent grade ≥3 hypertension despite adequate medical management. Presence of grade ≥3 events that, in the clinical judgment of the PI, are believed to be serious, unexpected, and a side effect likely attributable to regorafenib will serve as evidence to reduce the dose. Patients will be continuously monitored for safety per stopping rules in Table 5, derived using repeated significance testing (with low boundary). Each patient can contribute to more than one stopping criteria. Only AEs (possibly, probably, or definitely) related to the study treatment in the first 2 cycles (i.e., 8 weeks) will count toward the excessive toxicity boundaries below. If at any time during the trial we observe 2 fatal adverse events, we will stop enrollment to the trial. The probability of observing 2 or more fatal adverse events out of the 35 patients is 0.05, 0.15, 0.53, 0.88 if the probability of a fatal adverse event is 1%, 2%, 5%, and 10% respectively.

Table 5. Toxicity stopping rules: for each toxicity type, the lower toxicity rate is acceptable rate while the higher toxicity rate is the unacceptable rate.

Toxicity	No. of Toxicities Needed to Stop the Study	Toxicity Rate	Probability Boundary Is Crossed
Grade 4 neutropenia	5 within the first 10 patients 7 within the first 20 patients	.19	.10
	11 within 35 patients	.45	.97
Grade 3-4 diarrhea	4 within the first 10 patients 5 within the first 20 patients	.12	.11
	8 within 35 patients	.35	.97
Grade 3-4 neuropathy	2 within the first 10 patients 3 within the first 20 patients	.05	.13
	5 within 35 patients	.25	.98
Grade 4 liver function test	5 within the first 10 patients 7 within the first 20 patients	.19	.10
	11 within 35 patients	.40	.91
Grade 3 hand foot syndrome	4 within the first 10 patients 5 within the first 20 patients	.12	.11
	8 within 35 patients	.30	.90

Grade 4 rash	4 within the first 10 patients 5 within the first 20 patients	.12	.11
	8 within 35 patients	.30	.90
Grade 4 persistent hypertension	2 within the first 10 patients 3 within the first 20 patients	.04	.1
	4 within 35 patients	.20	.95

15.0 TOXICITIES/RISKS/SIDE EFFECTS

The treating investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart (Section 11.0) and more frequently if clinically indicated. AEs will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE v5.0. Toxicities will be characterized according to seriousness, causality, toxicity grading, and action taken with regard to trial treatment. For subjects receiving treatment with nivolumab, all AEs of unknown etiology associated with nivolumab exposure should be evaluated to determine if it is possibly an event of clinical interest of a potentially immunologic etiology (termed immune-related adverse events [irAEs]).

In the event that one component of the combination regimen is discontinued, patients may continue to receive the other components. For example, in case of discontinuation of oxaliplatin for cumulative toxicity, patients may continue with 5-FU and nivolumab on days 1 and 15 and regorafenib on days 1-21 of each 28-day cycle. If nivolumab is discontinued due to immune-related toxicity, patients may continue to receive regorafenib and FOLFOX (assuming acceptable toxicity). Likewise, if regorafenib is discontinued, patients may continue to receive nivolumab and FOLFOX. If a patient is no longer receiving FOLFOX, nivolumab may be given every 4 weeks at 480 mg IV at the treating physician's discretion.

Dose Modification of Overlapping Toxicities

Based on the known toxicity profiles of regorafenib, nivolumab, 5-FU and oxaliplatin, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, hypertension is a known risk of regorafenib, peripheral neuropathy is a known risk of oxaliplatin, and irAEs are risks of nivolumab. However, certain AEs, such as diarrhea and liver enzyme elevation may be initially considered attributable to multiple study interventions. Therefore, evaluation of attribution is important for determining the study intervention most likely related to the AE, or an alternative etiology, in order to initiate proper clinical management. The investigator may consider timing of AE onset. For example, since regorafenib is administered daily, regorafenib dosing may be interrupted in the middle of a treatment cycle (i.e. between nivolumab and chemotherapy dosing). Refer to section 15.2 for regorafenib reinitiation guidelines. If the subject recovers from an AE in response to regorafenib

interruption, the event is more likely related to regorafenib. Otherwise, after excluding other alternative explanations, an irAE should be considered. Resolution of the AE with initiation of steroids would suggest that the event is related to nivolumab. The treating investigator may consult with the principal investigator for guidance with determining attributions.

The following tables provide guidance for overlapping toxicities such as diarrhea and elevated liver transaminases. Investigators should also consult dose modification guidelines for individual drugs for management of these and other AEs.

Table 6. Dose modification guidelines for diarrhea

Toxicity Grade	Nivolumab	Regorafenib	FOLFOX	Follow-up
Grade 2	- Withhold - Administer oral corticosteroids followed by taper	- Continue administration	- Withhold until diarrhea improves to grade 0 or 1	Monitor for signs and symptoms of enterocolitis and bowel perforation. Participants with ≥ Grade 2 diarrhea, with suspicion of colitis, should consider gastrointestinal consultation and endoscopy to rule out colitis If nivolumab is withheld, nivolumab can be resumed after the AE has been reduced to grade 1 or 0 and corticosteroids have been tapered. Nivolumab should be permanently discontinued if the AE does not resolve within 12 weeks of the last dose or if corticosteroids cannot be reduced to less than 10 mg prednisone or equivalent per day within 12 weeks.
Grade 3	- Withhold - Administer IV corticosteroids followed by taper	- Withhold until improvement to grade 2 or lower. Can be resumed at reduced dose level	- Withhold until diarrhea improves to grade 0 or 1 - Restart FOLFOX with 1 dose-level reduction of 5-FU	
Grade 4	- Permanently discontinue - Administer IV corticosteroids followed by taper	- Permanently discontinue	- Withhold until diarrhea improves to grade 0 or 1 - Restart FOLFOX with 1 dose-level reduction of 5-FU	

Table 7. Dose modification guidelines for elevated AST, ALT and total bilirubin

Toxicity Grade	Nivolumab	Regorafenib	FOLFOX	Follow-up
Grade 2	- Withhold - Administer oral or IV corticosteroids followed by taper	- Continue dosing	- Continue dosing	Monitor with liver function tests (consider weekly or more frequently until liver function tests return to baseline or is stable) If nivolumab is withheld, nivolumab can be resumed after the AE has been reduced to grade 1 or 0 and corticosteroids have been tapered. Nivolumab should be permanently discontinued if the AE does not resolve within 12 weeks of the last dose or if corticosteroids cannot be reduced to less than 10 mg prednisone or equivalent per day within 12 weeks.
Grade 3	- Permanently discontinue - Administer IV corticosteroids followed by taper	- Interrupt dosing if first occurrence. Can be restarted at reduced dose level after liver function tests resolve to Grade 1 - Permanently discontinue if recurrence	- Withhold oxaliplatin until resolves to grade 0 or 1. Resume at 1 dose level reduction. 5-FU can be continued	
Grade 4	- Permanently discontinue - Administer IV corticosteroids followed by taper	- Permanently discontinue	- Withhold until resolves to grade 0 to 1. Restart at 1 dose level reduction.	

15.1 Nivolumab

AEs (both nonserious and serious) associated with nivolumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Nivolumab must be withheld for drug-related toxicities and severe or life-threatening AEs, per Table 8 below. The most-common adverse reactions (≥20%) are fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain.

Table 8. Dose-modification guidelines for drug-related AEs

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/colitis	2-3	Toxicity resolves to grade 0-1	Toxicity does not resolve to <= grade 1 within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or increased bilirubin	2	Toxicity resolves to grade 0-1	Toxicity does not resolve to <= grade 1 within 12 weeks of last dose
	3-4	Permanently discontinue	Permanently discontinue
T1DM (if new onset) or hyperglycemia	T1DM or 3-4	Hold nivolumab for new-onset T1DM or grade 3-4 hyperglycemia associated with evidence of beta-cell failure	Resume nivolumab when patients are clinically and metabolically stable
Hypophysitis	2-3	Toxicity resolves to grade 0-1	Toxicity does not resolve to <= grade 1 within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to grade 0-1	Toxicity does not resolve to <= grade 1 within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with nivolumab can be continued while treatment for the thyroid disorder is instituted	Therapy with nivolumab can be continued while treatment for the thyroid disorder is instituted
Infusion reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to grade 0-1	Toxicity does not resolve to <= grade 1 within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal failure or nephritis	2	Toxicity resolves to grade 0-1	Toxicity does not resolve to <= grade 1 within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All other drug-related toxicity[1]	3 or Severe	Toxicity resolves to grade 0-1	Toxicity does not resolve to <= grade 1 within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
T1DM=type 1 diabetes mellitus. **Note: Permanently discontinue for any severe or grade 3 drug-related AE that recurs or any life-threatening event.** [1]Patients with intolerable or persistent grade 2 drug-related AEs may stop taking the study medication at the treating physician's discretion. Permanently discontinue the study drug for persistent grade 2 adverse reactions for which treatment with the study drug has been stopped that do not recover to grade 0 or 1 within 12 weeks of the last dose.			

15.1.1 Supportive Care

- **Pneumonitis**:
  - For **grade 2**, 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 and 4**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures as needed
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration

- **Diarrhea or 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 diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **grade 2 diarrhea or colitis** that persists >3 days, administer oral corticosteroids.
  - For **grade 3 and 4 diarrhea or colitis** that persists >1 week, treat with IV steroids followed by high-dose oral steroids
  - When symptoms improve to grade ≤1, steroid taper should be started and continued over no less than 4 weeks
  - Nivolumab can be held until the patient is off corticosteroids
  - Additional interventions (i.e. infliximab) for steroid-refractory diarrhea or colitis should be discussed in consultation with gastroenterology

- **T1DM (if new onset, including diabetic ketoacidosis) or grade ≥3 hyperglycemia, if associated with ketonuria or metabolic acidosis:**
  - Insulin replacement therapy is recommended for T1DM and for grades 3 and 4 hyperglycemia associated with metabolic acidosis or ketonuria
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide
  - Subject should be referred to endocrinology

- **Hypophysitis:**
    - For **grade 2** events, treat with corticosteroids. When symptoms improve to grade ≤1, 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 and 4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to grade ≤1, 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
    - Subject should be referred to endocrinology

- **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 on the basis of clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
    - For **grade 2 hyperthyroidism** events (and **grade 2 to 4 hypothyroidism**):
        - For hyperthyroidism, nonselective beta-blockers (e.g., propranolol) are suggested as initial therapy
        - For hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care
    - For **grade 3 and 4 hyperthyroidism:**
        - Treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to grade ≤1, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered
- **Hepatic:**
    - For **grade 2** events, monitor liver function tests more frequently until values have returned to baseline values (consider weekly)
        - Treat with IV or oral corticosteroids
    - For **grade 3 and 4** events, treat with IV corticosteroids for 24 to 48 h.
        - Treat with IV methylprednisone 1 to 4 mg/kg at investigator's discretion.
    - When symptoms improve to grade ≤1, steroid taper should be started and continued over no less than 4 weeks.
    - Gastroenterology should be consulted if hepatic toxicity is unresponsive to steroids for consideration of additional agents (i.e. methotrexate).

- **Renal failure or nephritis:**
    - For **grade 2** events, treat with corticosteroids.
    - For **grade 3 and 4** events, treat with systemic corticosteroids.
    - When symptoms improve to grade ≤1, 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 h of completion of infusion.

15.1.2 Dose Modification and Toxicity Management for irAEs Associated with Nivolumab

AEs associated with nivolumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of nivolumab treatment and may affect >1 body system simultaneously. Therefore, early recognition of irAEs and initiation of treatment is critical to reduce complications. On the basis of existing clinical study data, most irAEs were reversible and could be managed with interruptions of nivolumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests, such as bronchoscopy, endoscopy, and skin biopsy, may be included as part of the evaluation. On the basis of the severity of irAEs, withhold or permanently discontinue nivolumab and administer corticosteroids. Dose-modification and toxicity-management guidelines for irAEs associated with nivolumab are provided in Table 9. Please refer to the investigator's brochure for a complete list of reported AEs. Nivolumab must be withheld for drug-related toxicities and severe or life-threatening AEs, per Table 9.

Table 9. Dose-modification and toxicity-management guidelines for irAEs associated with nivolumab

General instructions:

Corticosteroid taper should be initiated upon the AE improving to grade ≤1 and continue to taper over at least 4 weeks.

For situations where nivolumab has been withheld, nivolumab can be resumed after the AE has been reduced to grade 1 or 0 and corticosteroids have been tapered. Nivolumab should be permanently discontinued if the AE does not resolve within 12 weeks of the last dose or if corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.

For severe and life-threatening irAEs, IV corticosteroids should be initiated first, followed by oral steroids. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken to Nivolumab	irAE Management with Corticosteroids and/or Other Therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 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		

General instructions:

Corticosteroid taper should be initiated upon the AE improving to grade ≤1 and continue to taper over at least 4 weeks.

For situations where nivolumab has been withheld, nivolumab can be resumed after the AE has been reduced to grade 1 or 0 and corticosteroids have been tapered. Nivolumab should be permanently discontinued if the AE does not resolve within 12 weeks of the last dose or if corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.

For severe and life-threatening irAEs, IV corticosteroids should be initiated first, followed by oral steroids. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken to Nivolumab	irAE Management with Corticosteroids and/or Other Therapies	Monitor and Follow-up
Diarrhea or colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (e.g., diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (e.g., peritoneal signs and ileus) Participants with grade ≥2 diarrhea, with suspicion of colitis, should consider gastrointestinal consultation and 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 or ALT elevation or increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returns to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or hyperglycemia	Newly onset T1DM or grade 3 or 4 hyperglycemia associated with evidence	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer antihyperglycemic in	Monitor participants for hyperglycemia or other signs and symptoms of diabetes

General instructions:

Corticosteroid taper should be initiated upon the AE improving to grade ≤1 and continue to taper over at least 4 weeks.

For situations where nivolumab has been withheld, nivolumab can be resumed after the AE has been reduced to grade 1 or 0 and corticosteroids have been tapered. Nivolumab should be permanently discontinued if the AE does not resolve within 12 weeks of the last dose or if corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.

For severe and life-threatening irAEs, IV corticosteroids should be initiated first, followed by oral steroids. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken to Nivolumab	irAE Management with Corticosteroids and/or Other Therapies	Monitor and Follow-up
	of β-cell failure		participants with hyperglycemia	
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 nonselective 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 to 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 to 2 mg/kg or equivalent) followed by taper	Monitor for changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	On the basis of severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other irAEs	Intolerable or persistent grade 2	Withhold	On the basis of severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue		

General instructions: Corticosteroid taper should be initiated upon the AE improving to grade ≤1 and continue to taper over at least 4 weeks. For situations where nivolumab has been withheld, nivolumab can be resumed after the AE has been reduced to grade 1 or 0 and corticosteroids have been tapered. Nivolumab should be permanently discontinued if the AE does not resolve within 12 weeks of the last dose or if corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks. For severe and life-threatening irAEs, IV corticosteroids should be initiated first, followed by oral steroids. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.				
irAE	**Toxicity Grade or Conditions (CTCAE v5.0)**	**Action Taken to Nivolumab**	**irAE Management with Corticosteroids and/or Other Therapies**	**Monitor and Follow-up**
		on the basis of the type of event. Events that require discontinuation include and are not limited to Guillain-Barre Syndrome and encephalitis		
	Grade 4 or recurrent grade 3	Permanently discontinue		

[1]Withhold or permanently discontinue nivolumab at the discretion of the investigator or treating physician.

NOTE: For participants with grade 3 or 4 immune-related endocrinopathy for whom withholding of nivolumab is required, nivolumab may be resumed when the AE resolves to grade ≤2 and is controlled with hormone replacement therapy or metabolic control is achieved (in case of T1DM).

15.1.3 Dose Modification and Toxicity Management of Infusion Reactions Related to Nivolumab

Nivolumab may cause severe or life-threatening infusion reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 h of completion of infusion. Dose-modification and toxicity-management guidelines on nivolumab-associated infusion reactions are provided in Table 10.

Table 10. Nivolumab infusion reaction dose-modification and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	**Stop Infusion** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator If symptoms resolve within 1 h of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve, and the participant should be premedicated for the next scheduled dose Participants who develop grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Participant may be premedicated 1.5 h (±30 min) before infusion of nivolumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine) Acetaminophen 500-1000 mg po (or equivalent dose of analgesic)
Grade 3 or 4 Grade 3: Prolonged (e.g., 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.,	**Stop Infusion** Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator Hospitalization may be indicated **In cases of anaphylaxis, epinephrine should be used immediately **Participant is permanently discontinued from further study drug treatment**	

NSAID=non-steroidal anti-inflammatory drug; po=per OS (orally).
Appropriate resuscitation equipment should be available at the bedside and a physician should be readily available during the period of drug administration.
For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov.

15.1.4 Other Allowed Dose Interruption for Nivolumab

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

Interruptions from the protocol-specified treatment plan for >12 weeks between nivolumab doses for nonstudy medication–related or administrative reasons require consultation between the investigator and the study PI.

15.2 Regorafenib

The starting dose of regorafenib is 80 mg daily on days 1-21 as 2 40-mg coprecipitate tablets. Each cycle consists of 28 days.

Doses will be delayed or reduced for clinically significant hematologic and nonhematologic toxicities that are related to protocol therapy according to the guidelines shown in the table below. Dose modifications will follow predefined dose levels. Dose adjustments for hematologic toxicity are based on the blood counts obtained in preparation for the day of treatment.

Table 11. Regorafenib dose modifications

Dose level 0 (standard starting dose)	80 mg orally daily	Two 40-mg tablets of regorafenib
Dose level -1	40 mg orally daily	One 40-mg tablet of regorafenib

If a subject experiences >1 toxicity, dose reduction should occur on the basis of the toxicity with the highest grade.

In the case of ≥2 toxicities of the same grade, the investigator may reduce dosage on the basis of the toxicity deemed to be the most causally related to the study treatment.

If >1 dose reduction is required, regorafenib only will be discontinued and the rest of the study treatment may be continued. The following tables outline dose adjustments for toxicities related to the study drug, with the exception of HFSR, hypertension, and liver function test abnormalities.

Table 12. Recommended dose modification for toxicities, except HFSR, rash, hypertension, and increase in ALT, AST, or bilirubin

NCI CTCAE v5.0	Dose Interruption	Dose Modification[a]	Dose for Subsequent Cycles
Grade 0 to 2	Treat on time	No change	No change
Grade 3	Delay until grade ≤2[b]	Reduce by 1 dose level	
Grade 4	Discontinue	Discontinue administration	

a. Excludes alopecia, nonrefractory nausea or vomiting, nonrefractory hypersensitivity, and nonclinical and asymptomatic laboratory abnormalities.
b. If there is no recovery after a 4-week delay, treatment should be permanently discontinued unless the subject is deriving clinical benefit.

The table above outlines dose adjustments for hematologic and nonhematologic toxicities related to regorafenib, except HFSR, hypertension, and increases in ALT, AST, and bilirubin. In addition to these recommended dose modifications, subjects who develop diarrhea, mucositis, anorexia, or other events predisposing to fluid loss or inadequate fluid intake should be carefully monitored and rehydrated as clinically necessary to minimize the risk of postural hypotension and renal failure.

Table 13. Grading for HFSR

	Grade 1	Grade 2	Grade 3
NCI CTCAE v5.0 Palmar-plantar erythrodysesthesia syndrome[a]	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters bleeding, edema, or hyperkeratosis) with pain	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain
Further description, examples of skin changes	Numbness, dysesthesia or paresthesia tingling, painless swelling, or erythema of the hands and/or feet	Painful erythema and swelling of the hands and/or feet	Moist desquamation, ulceration, blistering, or severe pain of the hands and/or feet
Effect on activities	Does not disrupt normal activities	Limiting instrumental activities of daily life (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money)	Limiting self-care activities of daily life (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications) and not bedridden

a. Palmar-plantar erythrodysesthesia syndrome is a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of hands or the soles of the feet.

Suggested regorafenib dermatologic toxicity modification

Table 14. Recommended dose modification for HFSR[a] or other skin rash[a]

Grade of event (NCI CTCAE v5.0)	Occurrence	Suggested Dose Modification
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief.
Grade 2	First occurrence	Maintain dose level and immediately institute supportive measures. If no improvement, interrupt therapy for a **minimum of 7 days**, until toxicity resolves to grade 0-1[b, c]
	Second occurrence	Same as first occurrence.
Grade 3	First occurrence	Institute supportive measures immediately. Interrupt therapy for a **minimum of 7 days** until toxicity resolves to grade 0-1.[c] Continue supportive measures and when resuming treatment, resume at same dose level[b, d]
	Second occurrence	Institute supportive measures immediately. Interrupt therapy for a **minimum of 7 days** until toxicity resolves to grade 0-1.[c] Continue supportive measures and when resuming treatment, resume at -1 dose level.

a. More-conservative management is allowed if judged medically appropriate by the investigator.
b. If there is no recovery after a 4-week delay, treatment with regorafenib will be discontinued permanently.
c. Subjects requiring >1 dose reduction should go off protocol therapy for regorafenib only. The other study treatments may be continued.
d. The maximum daily dose is 80 mg.

Reinitiation of regorafenib following treatment hold for rash: As noted in table 14, regorafenib should be held for a minimum of 7 days for any rash or HFSR ≥ grade 3. When the provider determines that it is safe to resume regorafenib after the minimum of 7 days off, the patient will be instructed to start a new cycle of regorafenib, 21 days on/7 days off, with any necessary dose reduction based on toxicity level and recurrence of event. Note that the regorafenib schedule may no longer correlate with the FOLFOX/nivolumab schedule. Labs do not need to be repeated prior to restarting regorafenib.

At the first occurrence of HFSR or other rash, independent of grade, prompt institution of supportive measures such as topical emollients, low-potency steroids, or urea-containing creams should be administered.
Patients with any dermatologic toxicity ≥ grade 1 should be referred to dermatology at MSKCC with Dr. Lacouture. Recommended prevention and management strategies for skin toxicities consistent with HFSR are summarized below:

Preparation for potential rash:
Before initiating treatment with regorafenib:

- Educate patient about the potential for skin rash to develop anywhere on the body and need to call with any sign of rash
- Provide patient with a prescription for clobetasol 0.05% cream 60g topical corticosteroid to be applied twice daily if rash appears. Emphasize the importance of filling the prescription and keeping it at home. However, instruct patient *not* to use this cream unless directed by a medical provider.
- Consider dermatology telehealth referral to Dr. Lacouture for pre-treatment counseling prior to D1 of treatment.

Preparation for HFSR:
Before initiating treatment with regorafenib:
- Check condition of hands and feet.
- Suggest a manicure or pedicure, or visit with a podiatrist, when indicated.

During regorafenib treatment:
- Use thick socks, comfortable shoes, and wear soft slippers at home (no barefoot, no flip-flops).
- Use gloves when doing housework, sports, or hobbies.

Use of creams:
- Use creams containing urea >10% three times a day.
-
- Topical analgesics (e.g., lidocaine 4-5% cream or patches) are to be considered for pain control in areas of blisters or pressure.
- Topical corticosteroids such as clobetasol 0.05% cream twice daily should be recommended for $\geq$ G1. Avoid systemic steroids.

Protecting tender areas:
- Use socks or gloves to cover moisturizing creams.
- Wear well-padded footwear.
- Use insole cushions or inserts (e.g., silicone, gel).
- Foot soaks with cool water.

Hypertension
Hypertension is a known AE associated with regorafenib treatment. Subjects will have their blood pressure (BP) measured at doctor visits during weeks 1 to 3 and will have additional BP monitoring at the investigator's discretion. If additional BP measurements are performed outside of the study site and BP is >140 mm Hg systolic or >90 mm Hg diastolic (NCI CTCAE v5.0), the subject must contact study personnel. The management of hypertension, including the choice of antihypertensive medication, will be performed according to local standards and the usual practice of the investigator. Every effort should be made to control BP by medical

means other than study drug dose modification. If necessary, Table 13 outlines suggested dose reductions.

Table 15. Management of treatment-emergent hypertension

Grade (NCI CTCAE v5.0)	Antihypertensive Therapy	Regorafenib Dosing
1 Prehypertension (systolic BP 120 to 139 mm Hg or diastolic BP 80 to 89 mmHg)	None	Continue regorafenib Consider increasing BP monitoring

2 Systolic BP 140 to 159 mm Hg or diastolic BP 90 to 99 mm Hg OR Symptomatic increase by >20 mm Hg (diastolic) if previously within normal limits	Treat with the aim to achieve diastolic BP ≤90 mm Hg If BP previously within normal limits, start antihypertensive monotherapy If patient already on antihypertensive medication, titrate up the dose	Continue regorafenib If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP ≤90 mm Hg[a] When regorafenib is restarted, continue at the same dose level
3 Systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg OR More than 1 drug or more-intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤90 mm Hg: Start anti-hypertensive medication AND/OR Increase current antihypertensive medication AND/OR Add additional antihypertensive medications	Hold regorafenib until diastolic BP ≤90 mm Hg and, if symptomatic, until symptoms resolve[a] When regorafenib is restarted, continue at the same dose level If BP is not controlled with the addition of new or more-intensive therapy, reduce by 1 dose level[b] If grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, discontinue therapy
4 Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Per institutional guidelines	Discontinue therapy

a. Patients requiring a delay of >4 weeks should go off protocol therapy for regorafenib only. Other treatments can be continued.
b. Patients requiring >1 dose reduction should go off protocol therapy for regorafenib only. Other treatments can be continued.

Liver Function Abnormalities

For patients with observed worsening of serum liver tests considered to be related to regorafenib (i.e., where no alternative cause is evident, such as posthepatic cholestasis or disease progression), the dose modification and monitoring advice in Table 14 should be followed.

Regorafenib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may

occur in patients with Gilbert's syndrome.

Table 16. Dose modification or interruption for ALT and/or AST with or without concurrent bilirubin increases related to study drug

Observed elevations	First Occurrence	Restart	Reoccurrence
AST and/or ALT ≤5X ULN (grade <3)	Continue dosing, with weekly monitoring of liver function until transaminases return to <3X ULN (grade ≤1) or baseline.		
ALT and/or AST >5X ULN (grade ≥3)	Interrupt dosing, with weekly monitoring until transaminases return to <3X ULN or baseline	If the potential benefit for reinitiating regorafenib is considered to outweigh the risk of hepatotoxicity: Reduce 1 dose level and measure serum liver tests weekly for at least 4 weeks	Discontinue
ALT and/or AST >20X ULN (grade ≥4)	Discontinue		
ALT and/or AST >3X ULN (grade ≥2) with concurrent bilirubin >2X ULN	Discontinue treatment and measure serum liver tests weekly until resolution. Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the recommendations outlined above for ALT/AST elevations		

Diarrhea

Diarrhea can be a common side effect of regorafenib. The same dose-modification algorithm used for skin toxicities can be used to address these toxicities. However, the preventive and management strategies for diarrhea should be consistent with local standards (e.g., antidiarrheals and optimized hydration status).

Antidiarrhea medications may be introduced if symptoms occur. Previous trials have shown that diarrhea can be managed with loperamide. The recommended dose of loperamide is 4 mg at first onset followed by 2 mg every 2 to 4 h until diarrhea-free for 12 h.

Proteinuria

Assessment for proteinuria will be conducted as detailed in Table 4.1 and Table 4.2. Guidelines for assessment and management of proteinuria are as follows:

- Grading according to CTCAE v5.0 will be based on the 24-hour urine collection for total protein result.
- If proteinuria ≥ 2+ is detected on urinalysis, study drug is continued and a 24-hour urine collection for total protein will be obtained to assess the grade of proteinuria. If urine protein is >2 gm/24 hours, hold regorafenib and resume at 1 dose level reduction when proteinuria is ≤ 1+ on urinalysis or 24-hour urine collection is < 2 gm/24 hours. If already at lowest dose level, discontinue regorafenib.

15.3 FOLFOX

Initiation of the next cycle of therapy may be delayed by no more than 4 weeks to allow recovery from toxicity. Treatment delay of >4 weeks due to toxicity may lead to removal from study.

Dose reduction of oxaliplatin or 5-FU and leucovorin should be based on the worst toxicity demonstrated during the preceding cycle. Subjects who require >2 dose-reduction steps must permanently discontinue oxaliplatin or 5-FU and leucovorin, or both, depending on the specific toxicity. Regorafenib may be continued at the investigator's discretion.

If the cycle start date is delayed due to toxicity related to FOLFOX, regorafenib will be held and resumed on day 1 of the cycle.

15.3.1 Dose Modifications of FOLFOX

15.3.1.1 Hematologic Toxicity

Colony-stimulating factors
Patients should not routinely receive prophylactic colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor) during cycle 1. Subsequent use will be at the discretion of the treating physician.

Neutropenia
For grade ≥3 neutropenia on the day of treatment, delay treatment (including FOLFOX, regorafenib and nivolumab) until neutropenia improves to grade ≤2, then resume treatment with:

- One dose-level reduction of oxaliplatin for all subsequent cycles.
- One dose-level reduction of 5-FU (bolus and infusion) and leucovorin for all subsequent cycles.
- No dose reduction for regorafenib or nivolumab.
- If treatment is delayed for neutropenia for 4 consecutive weeks, discontinue all protocol treatment.

Thrombocytopenia

For platelet counts of 50,000/mL to 74,000/mL on the day of treatment, delay treatment (including FOLFOX, regorafenib and nivolumab) until platelet counts improve to ≥75,000/mL, then resume treatment as follows:

- One dose-level reduction of oxaliplatin for all subsequent cycles.
- One dose-level reduction of 5-FU (bolus and infusion) and leucovorin for all subsequent cycles.
- No dose reduction for regorafenib or nivolumab.
- *For platelet counts from 50,000/mL to 74,000/mL persisting >7 days, resume treatment with oxaliplatin with 2 dose-level reductions when platelets improve to ≥75,000/mL*

For platelet counts of 25,000/mL to 49,000/mL on the day of treatment, delay treatment until platelet counts improve to ≥75,000/mL, then resume treatment as follows:

- One dose-level reduction of oxaliplatin for all subsequent cycles.
- One dose-level reduction of 5-FU (bolus and infusion) and leucovorin for all subsequent cycles.
- No dose reduction for regorafenib or nivolumab.
- *For platelet counts of 25,000/mL to 49,000/mL persisting >7 days, resume treatment with oxaliplatin with 2 dose-level reductions when platelet count improves to ≥75,000/mL.*

For platelet counts <25,000/mL on the day of treatment, delay treatment until platelet counts improve to ≥75,000/mL, then resume treatment as follows:

- Two dose-level reductions of oxaliplatin for all subsequent cycles.
- Two dose-level reductions of 5-FU (bolus and infusion) and leucovorin for all subsequent cycles.
- No dose reduction for regorafenib or nivolumab.
- *For platelet counts <25,000/mL persisting >7 days, resume treatment with oxaliplatin with 2 dose-level reductions when platelet count improves to ≥75,000/mL.*

15.3.1.2 Neurologic Toxicities

For grade 2 peripheral sensory neuropathy (moderate paresthesia or dysesthesia or limiting instrumental activities of daily living):

- Withhold administration of oxaliplatin. When toxicity resolves to grade ≤1, resume oxaliplatin with 1 dose-level reduction for all subsequent cycles. Continue 5-FU and leucovorin.

If oxaliplatin is withheld for 4 weeks (2 consecutive doses) for neurologic toxicity, discontinue oxaliplatin. Continue 5-FU and leucovorin.

For grade ≥3 peripheral sensory neuropathy (severe paresthesia or dysesthesia or limiting self-care activities of daily living):

- Discontinue oxaliplatin. Continue 5-FU and leucovorin.

15.3.1.3 Gastrointestinal Toxicities

For grade ≥2 diarrhea, withhold administration of FOLFOX until diarrhea improves to grade ≤1.

- Following grade 3 or 4 diarrhea at any time during a cycle: continue FOLFOX with 1 dose-level reduction of 5-FU for all subsequent cycles and the previous dose level of oxaliplatin.
- If FOLFOX is skipped for diarrhea for 4 weeks (2 consecutive cycles), discontinue FOLFOX.

For grade ≥2 oral mucositis present on day 1 of a cycle: delay FOLFOX until mucositis improves to grade <2. Decrease 5-FU by 1 dose level for all subsequent cycles.

If a subject requires a dose delay of oxaliplatin, 5-FU, and leucovorin >4 weeks from the intended next dose, treatment of the specific drug will be permanently discontinued.

Subjects who have had their treatment cycle delayed must be evaluated by those evaluations defined for the intended day 1 of that cycle ≤72 h before actual dosing.

Subjects may also discontinue oxaliplatin following multiple cycles if, in the investigator's judgment, cumulative toxicity is likely to increase over time and become problematic. If oxaliplatin treatment only should be discontinued, in the investigator's judgment, the subject should continue to receive other protocol-specified treatments.

General dose reductions for FOLFOX are outlined in Table 17.

Table 17. FOLFOX dose reductions

Drug	Starting Dose	Dose Modification		
		Dose Level -1	Dose Level -2	Dose Level -3
Oxaliplatin	85 mg/m^2	70 mg/m^2	50 mg/m^2	35 mg/m^2
5-FU	Bolus 5-FU: 400 mg/m^2 Leucovorin: 400 mg/m^2 Infusion 5-FU: 2400 mg/m^2/48 h	Bolus 5-FU: 300 mg/m^2 Leucovorin: 300 mg/m^2 Infusion 5-FU: 2000 mg/m^2/48 h	Bolus 5-FU: 200 mg/m^2 Leucovorin: 200 mg/m^2 Infusion 5-FU: 1600 mg/m^2/48 h	Bolus 5-FU: 150 mg/m^2 Leucovorin: 150 mg/m^2 Infusion 5-FU: 1300 mg/m^2/48 h

* Patients may begin with dose level -1 if deemed necessary per the treating physician's discretion.

15.4 Contraception

Nivolumab may have adverse effects on a fetus *in utero*, and it is not known whether nivolumab has transient adverse effects on the composition of sperm. Subjects should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study. To participate in the study, subjects of childbearing potential must adhere to

the contraception requirement (described in Table 18) from the day of study medication initiation (or 14 days before the initiation of study medication for oral contraception), throughout the study period, up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

For this trial, male subjects will be considered to be of nonreproductive potential if they have azoospermia (due to either a vasectomy or an underlying medical condition).

Female subjects will be considered to be fertile upon menarche and until menopause, unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

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

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal women

A postmenopausal state is defined as the absence of menstruation for 12 months without an alternative medical cause.

- A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with 2 follicle-stimulating hormone measurements in the postmenopausal range is required.

Women taking hormone replacement therapy whose menopausal status is in doubt will be required to use a nonhormonal, highly effective contraception method if they wish to continue their hormone replacement therapy during the study. Otherwise, they must discontinue hormone replacement therapy to allow confirmation of postmenopausal status before study enrollment.

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol-defined time frame:

- Remain abstinent from penile-vaginal intercourse on a long-term and persistent basis
- Use a male condom in conjunction with their partner's use of a contraceptive method with a failure rate of <1% per year, as described in Table 18, when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

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

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception with a low user dependency consistently and correctly, as described in Table 18, during the protocol-defined time frame.

Table 18. Contraceptive methods

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly*
● Male or female condom with or without spermicide ● Cervical cap, diaphragm, or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly*
• Combined (estrogen- and progestogen-containing) hormonal contraception o Oral o Intravaginal o Transdermal o Injectable
• Progestogen-only hormonal contraception o Oral o Injectable
Highly Effective Methods with Low User Dependency *Failure rate of <1% per year when used consistently and correctly*
• Progestogen-only contraceptive implant • Intrauterine hormone-releasing system • Intrauterine device • Bilateral tubal occlusion
Vasectomized partner Vasectomy is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant

Use in pregnancy

If a subject becomes pregnant while on treatment, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy

will be reported to the sponsor without delay and within 24 h to the sponsor if the outcome is a serious AE (e.g., death, spontaneous loss of pregnancy (miscarriage, stillbirth), congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the sponsor.

Use in nursing women
It is unknown whether nivolumab is excreted in human milk. Since many drugs are excreted in human milk and because of the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment.

15.5 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred

- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
  - An explanation of how the AE was handled
  - A description of the participant's condition
  - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

15.6 External SAE Reporting

Definitions and Adverse Event Collection and Reporting Information for Interventional Protocols:

DEFINITIONS

ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

A ***non-serious adverse event*** is an AE not classified as serious.

The protocol must include a definition for Serious Adverse Events (SAE)**.**

SERIOUS ADVERSE EVENTS

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and

scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.
- Unusual Failure in Efficacy (for Phase IV Canadian studies)

Although pregnancy and potential drug-induced liver injury (DILI), are not always serious by regulatory definition, however, these events must be reported within the SAEs timeline.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

NOTE: (PI determines if this information regarding hospitalizations are considered SAEs and should be included in the protocol. This is supplemental information that is included in BMS-sponsored trials)

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

ADVERSE EVENT Collection and REPORTING INFORMATION:

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- An SAE report should be completed for any event where doubt exists regarding its seriousness;
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

  An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS. If you prefer to use your own Institutional form, it must be reviewed by the BMS Protocol Manager prior to study initiation to ensure that at a minimum all of the data elements on the CIOMS form are present. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.
- CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
- The MedWatch form is available at: MedWatch 3500 Form
- The Sponsor will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).
- The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
- GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
- The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).
- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).
- In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.
- Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data

monitoring committee, or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.

- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS. BMS will perform due diligence follow-up using the BMS Pregnancy Form which the investigator must complete.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

NONSERIOUS ADVERSE EVENT

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from following the subject's written consent to participate in the study.

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin following the subject's written consent to participate in the study. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event and complete one of the following forms within 24 hours of awareness of the event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch, BMS Pregnancy Surveillance Form, **or** approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

16.0 PROTECTION OF HUMAN PARTICIPANTS

The responsible principal investigator will ensure that this study is conducted in agreement with the declaration of Helsinki. The study will seek to protect the rights of human subjects in every way. The potential risks, including adverse drug reactions and potential benefits in terms of pain control will be discussed in detail with the patients.

Potential side effects as outlined above will be discussed with the patients. No patient will be required to participate in the study and participation, or refusal to do so, will not affect the patient's care or treatment.

The patient will not incur any financial cost as a result of participation in the study. Patients will be given up to $100 per treatment visit (for up to 1 year) for travel related expenses incurred while on study.

Participation will be purely voluntary, patient confidentiality will be maintained. No results of the study will be presented or discussed in a fashion that will allow identification of a particular patient in the study. All adverse events will be fully reported to the IRB in a timely fashion as required.

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the

Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.2 Data Management

Data to be collected include documentation from all outpatient visits, laboratory, pharmacy, and treatment records. Data will be collected and stored in Medidata.

At MSKCC a Clinical Research Associate (CRA) and/or Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRA and/or CRC include confirmation of patient eligibility, project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team. Source documentation will be available to support computerized patient records.

Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

16.3 Quality Assurance

Data and project enrollment will be monitored on an ongoing basis by the Principal Investigator. The CRA or CRC will inform the PI about the number of patients enrolled, the number of patients randomized, the number of patients in follow-up, and any other outstanding issues. A log will be maintained of eligible vs. enrolled patients. The study data will be assessed for completeness. Random-sample data quality and protocol compliance audits will be conducted by the study team at minimum of two times per year or more frequently if problems are encountered.

16.4 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

17.0 REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-386.

2. De Lisi V, Cocconi G, Tonato M, Di Costanzo F, Leonardi F, Soldani M. Randomized comparison of 5-FU alone or combined with carmustine, doxorubicin, and mitomycin (BAFMi) in the treatment of advanced gastric cancer: a phase III trial of the Italian Clinical Research Oncology Group (GOIRC). *Cancer Treat Rep*. 1986;70(4):481-485.

3. Catalano V, Labianca R, Beretta GD, Gatta G, de Braud F, Van Cutsem E. Gastric cancer. *Crit Rev Oncol Hematol*. 2009;71(2):127-164.

4. Cavanna L, Artioli F, Codignola C, et al. Oxaliplatin in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in patients with metastatic gastric cancer (MGC). *Am J Clin Oncol*. 2006;29(4):371-375.

5. Luo H-Y, Xu R-H, Zhang L, et al. A pilot study of oxaliplatin, fluorouracil and folinic acid (FOLFOX-6) as first-line chemotherapy in advanced or recurrent gastric cancer. *Chemotherapy*. 2008;54(3):228-235.

6. Oh SY, Kwon H-C, Lee S, et al. A Phase II study of oxaliplatin with low-dose leucovorin and bolus and continuous infusion 5-fluorouracil (modified FOLFOX-4) for gastric cancer patients with malignant ascites. *Jpn J Clin Oncol*. 2007;37(12):930-935.

7. Comella P, Massidda B, Filippelli G, et al. Randomised trial comparing biweekly oxaliplatin plus oral capecitabine versus oxaliplatin plus i.v. bolus fluorouracil/leucovorin in metastatic colorectal cancer patients: results of the Southern Italy Cooperative Oncology study 0401. *J Cancer Res Clin Oncol*. 2009;135(2):217-226.

8. Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol*. 2008;26(9):1435-1442.

9. Louvet C, André T, Tigaud JM, et al. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. *J Clin Oncol*. 2002;20(23):4543-4548.

10. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med*. 2008;358(1):36-46.

11. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol*. 2006;24(31):4991-4997.

12. Al-Batran S-E, Hartmann JT, Hofheinz R, et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. *Ann Oncol*. 2008;19(11):1882-1887.

13. Enzinger PC, Burtness BA, Niedzwiecki D, et al. CALGB 80403 (Alliance)/E1206: A Randomized Phase II Study of Three Chemotherapy Regimens Plus Cetuximab in Metastatic Esophageal and Gastroesophageal Junction Cancers. *J Clin Oncol*. 2016;34(23):2736-2742.

14. Moy RH, Dos Santos Fernandes G, Jonsson P, et al. Regorafenib in Combination with First-Line Chemotherapy for Metastatic Esophagogastric Cancer. *Oncologist*. 2020;25(1):e68-e74.

15. Lieto E, Ferraraccio F, Orditura M, et al. Expression of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) is an independent prognostic indicator of worse outcome in gastric cancer patients. *Ann Surg Oncol*. 2008;15(1):69-79.

16. Maeda K, Chung YS, Ogawa Y, et al. Prognostic value of vascular endothelial growth factor expression in gastric carcinoma. *Cancer*. 1996;77(5):858-863.

17. Ebos JML, Kerbel RS. Antiangiogenic therapy: impact on invasion, disease progression, and metastasis. *Nat Rev Clin Oncol*. 2011;8(4):210-221.

18. Li X, Kumar A, Zhang F, et al. VEGF-independent angiogenic pathways induced by PDGF-C. *Oncotarget*. 2010;1(4):309-314.

19. Lieu C, Heymach J, Overman M, Tran H, Kopetz S. Beyond VEGF: inhibition of the fibroblast growth factor pathway and antiangiogenesis. *Clin Cancer Res*. 2011;17(19):6130-6139.

20. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol*. 2014;15(11):1224-1235.

21. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2014;383(9911):31-39.

22. Fuchs CS, Shitara K, Di Bartolomeo M, et al. Ramucirumab with cisplatin and fluoropyrimidine as first-line therapy in patients with metastatic gastric or junctional adenocarcinoma (RAINFALL): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(3):420-435.

23. Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol*. 2011;29(30):3968-3976.

24. Shen L, Li J, Xu J, et al. Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study). *Gastric Cancer*. 2015;18(1):168-176.

25. Huynh H, Ong R, Zopf D. Antitumor activity of the multikinase inhibitor regorafenib in patient-derived xenograft models of gastric cancer. *J Exp Clin Cancer Res*. 2015;34:132.

26. Schmieder R, Hoffmann J, Becker M, et al. Regorafenib (BAY 73-4506): antitumor and antimetastatic activities in preclinical models of colorectal cancer. *Int J Cancer*. 2014;135(6):1487-1496.

27. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-312.

28. Demetri GD, Reichardt P, Kang Y-K, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):295-302.

29. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10064):56-66.

30. Pavlakis N, Sjoquist KM, Martin AJ, et al. Regorafenib for the Treatment of Advanced Gastric Cancer (INTEGRATE): A Multinational Placebo-Controlled Phase II Trial. *J Clin Oncol*. 2016;34(23):2728-2735.

31. Argilés G, Saunders MP, Rivera F, et al. Regorafenib plus modified FOLFOX6 as first-line treatment of metastatic colorectal cancer: A phase II trial. *Eur J Cancer*. 2015;51(8):942-949.

32. Ma C-J, Huang C-W, Chang T-K, et al. Oncologic Outcomes in Metastatic Colorectal Cancer with Regorafenib with FOLFIRI as a Third- or Fourth-Line Setting. *Transl Oncol*. 2019;12(3):502-512.

33. Fuchs CS, Doi T, Jang RW, et al. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. *JAMA Oncol*. 2018;4(5):e180013.

34. Shitara K, Özgüroğlu M, Bang Y-J, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2018;392(10142):123-133.

35. Kang Y-K, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;390(10111):2461-2471.

36. Makker V, Rasco D, Vogelzang NJ, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2019;20(5):711-718.

37. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2019;380(12):1116-1127.

38. Abou-Elkacem L, Arns S, Brix G, et al. Regorafenib inhibits growth, angiogenesis, and metastasis in a highly aggressive, orthotopic colon cancer model. *Mol Cancer Ther*. 2013;12(7):1322-1331.

39. Fukuoka S, Hara H, Takahashi N, et al. Regorafenib Plus Nivolumab in Patients With Advanced Gastric or Colorectal Cancer: An Open-Label, Dose-Escalation, and Dose-Expansion Phase Ib Trial (REGONIVO, EPOC1603). *J Clin Oncol*. Published online April 28, 2020:JCO1903296.

40. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;378(22):2078-2092.

41. Tesniere A, Schlemmer F, Boige V, et al. Immunogenic death of colon cancer cells treated with oxaliplatin. *Oncogene*. 2010;29(4):482-491.

42. Martins I, Kepp O, Schlemmer F, et al. Restoration of the immunogenicity of cisplatin-induced cancer cell death by endoplasmic reticulum stress. *Oncogene*. 2011;30(10):1147-1158.

43. Janjigian YY, Maron SB, Chatila WK, et al. First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2020;21(6):821-831.

44. Sasaki A, Kawazoe A, Eto T, et al. Improved efficacy of taxanes and ramucirumab combination chemotherapy after exposure to anti-PD-1 therapy in advanced gastric cancer. *ESMO Open*. 2020;4(Suppl 2).

45. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014;513(7517):202-209.

46. Cancer Genome Atlas Research Network, Analysis Working Group: Asan University, BC Cancer Agency, et al. Integrated genomic characterization of oesophageal carcinoma. *Nature*. 2017;541(7636):169-175.

47. Zehir A, Benayed R, Shah RH, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nat Med*. 2017;23(6):703-713.

48. Stadler ZK, Battaglin F, Middha S, et al. Reliable Detection of Mismatch Repair Deficiency in Colorectal Cancers Using Mutational Load in Next-Generation Sequencing Panels. *J Clin Oncol*. 2016;34(18):2141-2147.

49. Sanchez-Vega F, Hechtman JF, Castel P, et al. EGFR and MET Amplifications Determine Response to HER2 Inhibition in ERBB2-Amplified Esophagogastric Cancer. *Cancer Discov*. 2019;9(2):199-209.

50. Janjigian YY, Sanchez-Vega F, Jonsson P, et al. Genetic Predictors of Response to Systemic Therapy in Esophagogastric Cancer. *Cancer Discov*. 2018;8(1):49-58.

51. Samstein RM, Lee C-H, Shoushtari AN, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nat Genet*. 2019;51(2):202-206.

52. Greally M, Chou JF, Chatila WK, et al. Clinical and Molecular Predictors of Response to Immune Checkpoint Inhibitors in Patients with Advanced Esophagogastric Cancer. *Clin Cancer Res*. 2019;25(20):6160-6169.

53. Remark R, Merghoub T, Grabe N, et al. In-depth tissue profiling using multiplexed immunohistochemical consecutive staining on single slide. *Sci Immunol*. 2016;1(1):aaf6925.

54. Ganesh K, Wu C, O'Rourke KP, et al. A rectal cancer organoid platform to study individual responses to chemoradiation. *Nat Med*. 2019;25(10):1607-1614.

55. Vlachogiannis G, Hedayat S, Vatsiou A, et al. Patient-derived organoids model treatment response of metastatic gastrointestinal cancers. *Science*. 2018;359(6378):920-926.

18.0 APPENDICES

Appendix 1. Correlative Collection Table

Specimen	Collection Time Points	Mandatory or Optional?	SOC or Research (RNB)?	Analysis (reason for specimen collection)	Collection Amount	Specimen Processing Location	Shipping/Storage Details	Storage
Tumor tissue	Screening	Mandatory (Screening),	RNB	TCR sequencing PD-L1 expression via IHC (CPS) Tumor environment analysis via IHC Vectra PDO generation	**TISSUE SECTIONING REQUESTS ARE TO BE MADE IN BATCH ONLY** TCR sequencing: 10 x 5µm FFPE tissue curls are to be collected from each biopsy. Curls are to be cut serially and kept in a DNAse/RNAse free screw-top microtube. PD-L1: 5 x 5µm serial sections are to be cut from each biopsy. Sections are to be mounted on charged slides (5 slides), one section per slide. Slides should be numbered to differentiate section sequence (e.g., 1/5, 2/5, etc). Tumor Microenviornment analysis via IHC Vectra: 5 x 5µm	TCR sequencing: MSK IMF lab PD-L1: MSK Pathology Lab Tumor environment analysis via IHC Vectra: Dr. Taha Merghoub/Jedd Wolchok lab (MSKCC) PDO: Dr. Karuna Ganesh lab (MSKCC)	TCR sequencing: FFPE tissue samples ship ambient, Fresh-frozen tissue shipped on dry ice. PD-L1: FFPE tissue samples ship ambient, Fresh-frozen tissue shipped on dry ice. Tumor microenvironment analysis via IHC Vectra: FFPE tissue samples ship ambient, Fresh-frozen tissue shipped on dry ice PDO: Fresh tissue samples will be collected on ice and processed immediately in the Ganesh lab for culture in organoid media	For future use

Specimen	Collection Time Points	Mandatory or Optional?	SOC or Research (RNB)?	Analysis (reason for specimen collection)	Collection Amount	Specimen Processing Location	Shipping/Storage Details	Storage
					serial sections are to be cut from each biopsy. Sections are to be mounted on charged slides (5 slides), one section per slide. Slides should be numbered to differentiate section sequence (e.g., 1/5, 2/5, etc). Patient-derived organoid (PDO): Primary tumor issue fragments are to be collected fresh from biopsy			
Plasma for ctDNA	Screening, imaging timepoints, EOT	Mandatory	RNB	ctDNA	2x 10mL cell free DNA blood collection tubes (screening and all other time points)	Department of Molecular Pathology at MSK	Ambient, shipped immediately by courier to Department of Molecular Pathology at MSK	For future use
Whole blood for PBMC (Non-Organoid Subjects)	Screening, C1D1, C1D15, C2D1, C3D1, each imaging timepoint(up to 48 weeks), EOT	Mandatory	RNB	PBMC	4 x 8-mL BD sodium heparin cell-preparation tubes	MSK: Center Ludwig Center for Cancer Immunotherapy Immune Monitoring Core Facility	Ambient, shipped immediately by courier to IMC Facility at MSK Ludwig Cancer for processing	Stored frozen at -20º for future use

Specimen	Collection Time Points	Mandatory or Optional?	SOC or Research (RNB)?	Analysis (reason for specimen collection)	Collection Amount	Specimen Processing Location	Shipping/Storage Details	Storage
Whole blood for PBMC (Organoid subjects)	Screening, C1D1, C1D15, C2D1, C3D1, each imaging timepoint(up to 48 weeks), EOT	Mandatory	RNB	PBMC	6 x 8-mL BD sodium heparin cell-preparation tubes	MSK: Zuckerman Research Center Room Z1741 Lab of Dr. Karuna Ganesh	Ambient, shipped immediately by courier to Zuckerman Research Center Room Z1741	Stored frozen at -20º for future use