ECOG-ACRIN cancer research group
Reshaping the future of patient care

EA2183

A Phase III Study of Consolidative Radiotherapy in Patients with Oligometastatic HER2 Negative Esophageal and Gastric Adenocarcinoma (EGA)

STUDY CHAIR: Nataliya V. Uboha, M.D., Ph.D.
STUDY STATISTICIAN: Noah Graham, M.B.
STUDY CO-CHAIR: Lakshmi Rajdev, M.D., M.S.
STUDY CO-CHAIR: Michael K. Gibson, M.D., Ph.D, FACP
STUDY CO-CHAIR: George A. Fisher, M.D.
COMMUNITY CO-CHAIR: Xin Yao, MD
RADIATION ONCOLOGY CO-CHAIR: Steven H. Lin, M.D., Ph.D.
RADIATION ONCOLOGY COMMITTEE CHAIR: A. Bapsi Chakravarthy, M.D.
GI COMMITTEE CHAIR: Peter J. O'Dwyer, M.D.

Version Date: October 17, 2024

STUDY PARTICIPANTS

ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology
SWOG / SWOG

NCTN STUDY CHAMPIONS

ALLIANCE: Jon F. Strasser, MD
NRG: Kimberley S. Mak, MD, MPH
SWOG: David P. Horowitz, MD

ACTIVATION DATE

February 6, 2020
Addendum #1
Addendum #2
Addendum #3
Addendum #4
Addendum #5
Addendum #6
Addendum #7

Agents	NSC#	Supply
5-Fluorouracil (5-FU)	19893	Commercial
Capecitabine	712807	Commercial
Oxaliplatin	266046	Commercial
Leucovorin	3590	Commercial
Nivolumab	748726	Commercial
Docetaxel	628503	Commercial
Irinotecan	616348	Commercial
Pembrolizumab	776864	Commercial
Cisplatin	119875	Commercial

Study Exempt from IND Requirements per 21 CFR 312.2(b).

Table of Contents

STUDY CHAIR

Nataliya V. Uboha, M.D., Ph.D.
University of Wisconsin
Carbone Cancer Center
600 Highland Avenue
Madison, WI 53792
Phone: (608) 265-9966
Fax: (608) 265-8133
Email: Nvuboha@medicine.wisc.edu

STUDY CO-CHAIR

Michael Gibson, M.D., Ph.D., FACP
Vanderbilt Division of Hematology & Oncology
2220 Pierce Avenue
Nashville, TN 37232
Phone: (615) 936-8422
Fax: (615) 343-8668
Email: Mike.gibson.1@vumc.org

STUDY CO-CHAIR

Lakshmi Rajdev, M.D., M.S.
Mount Sinai Hospital
1000 Tenth Avenue
New York, NY 10019
Phone: (212) 523-7275
Email: lakshmi.rajdev@mountsinai.org

STUDY CO-CHAIR

George A. Fisher, M.D.
Stanford University Medical Center
CCSR Building Room 1115
269 Campus Drive
Stanford, CA 94305
Phone: (650) 723-9057
Fax: (650) 725-9113
Email: georgeaf@stanford.edu

STUDY CHAIR LIAISON (SCL)

Renae Quale, BSN, RN
University of Wisconsin
Carbone Cancer Center
600 Highland Avenue
Madison, WI 53792
Phone: (608) 265-2789
Fax: (608) 263-8613
Email: rmq@medicine.wisc.edu

RADIATION ONCOLOGY CO-CHAIR

Steven H. Lin, M.D., Ph.D.
MD Anderson Cancer Center
Division of Radiation Oncology
1515 Holcombe Boulevard
Houston TX, 77030
Phone: (713) 563-8490
Fax: (713) 606-3836
Email: shlin@mdanderson.org

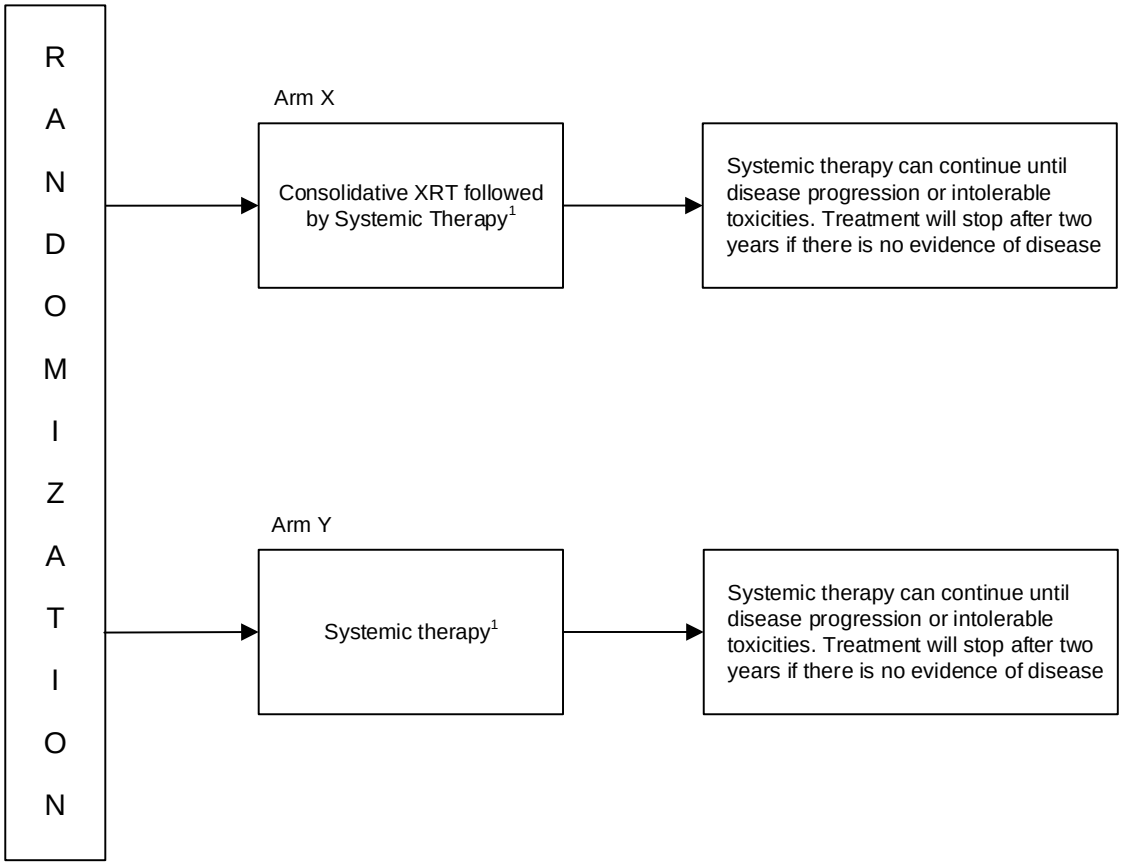
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878)), or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

Schema

Stratification Factors:

- Number of metastatic sites: 1-2 vs. 3 or more at the time of diagnosis of advanced disease.
- Prior use of anti-PD1 agents (IO) during first-line treatment of advanced disease vs. no prior IO during first-line treatment of advanced disease
- Triplet vs. doublet first-line chemotherapy backbone



N = 216

1. Systemic therapy will consist of standard FDA approved systemic therapy for HER2 negative esophageal and gastric adenocarcinoma as per NCCN guidelines and with the options outlined in Section **5.1**. The selection of the systemic therapy regimen used is at the discretion of the treating physician and in agreement with the patient. Once the regimen has been declared and started, patients may not switch to another regimen option.

1. Introduction

1.1 Disease Background

Esophageal and gastric adenocarcinoma (EGA) is a major health problem worldwide. Each year, an estimated 300,000 people are diagnosed with GI cancers, with over 150,000 people dying annually[1]. In Western countries, lower esophageal adenocarcinoma, which frequently involves the gastroesophageal junction (GEJ), is the most common site and histological subtype of esophageal cancer. The incidence of this cancer in both males and females is on the rise in the Western world[2]. Despite recent developments, overall survival (OS) for advanced disease remains about 12 months[3]. Patients with EGA experience rapid clinical deterioration after progression on first-line treatments, which limits the physician's ability to provide subsequent therapies. Close to 50% of patients with EGA do not tolerate subsequent lines of treatment[3]. Maximizing the duration of disease control during first-line treatment is critical. Intensification of first-line therapies has been explored in the past, with multiple regimens demonstrating clinical activity, but at the cost of significant toxicities [3-6]. Hence, novel approaches are needed to improve outcomes in this patient population.

1.2 First-Line Treatments of Metastatic HER2 Negative EGA

In the US, a doublet chemotherapy, combination of a fluoropyrimidine and platinum [FOLFOX (5-fluoropyrimidine (5-FU), leucovorin, and oxaliplatin)) or CAPOX (capecitabine and oxaliplatin)] is part of the standard first-line treatments for metastatic EGA without HER2 amplification. Triple drug regimens, such as FLOT (5-FU, leucovorin, oxaliplatin and docetaxel) or DCF (docetaxel, cisplatin, and 5-FU), can also be used in patients who are medically fit. However, administration of these regimens is difficult because of significant associated toxicities. Response rates to first-line doublet chemotherapy are ~40-50%. An additional ~25% of patients have disease stability with current treatments.

More recently, incorporation of immune checkpoint inhibitors has become part standard treatment of EGA in first-line setting. Nivolumab is now approved for advanced EGA based on the results from CheckMate 649, a randomized phase 3 trial.[4] The study had two primary endpoints: progression free survival (PFS) and overall survival (OS) in the biomarker defined patient population whose tumors had PDL1 CPS 5 or greater. This study demonstrated that first-line treatment with the combination of nivolumab plus chemotherapy (FOLFOX or CAPOX) improved OS and PFS in patients with advanced gastroesophageal adenocarcinoma with PDL1 CPS score of 5 or greater, 14.4 vs. 11.1 months with hazard ratio (HR) of 0.71 (0.59-0.86, $p < 0.0001$).[4] Among 1581 randomized patients, 60% had tumors with PDL1 CPS of 5 or more. In addition, OS was also improved in patients with tumors with PDL1 CPS 1 or greater and in all randomized patients, although the differences between the experimental groups and control groups were less pronounced with the inclusion of patients whose tumors had negative or lower PDL1 (CPS < 5) expression. Based on the results of this study, the Food and Drug Administration (FDA) approved nivolumab (Opdivo, Bristol-Myers Squibb Company) in combination with fluoropyrimidine- and platinum-containing chemotherapy for advanced or metastatic gastric, GEJ, and esophageal adenocarcinoma, regardless of PDL1 expression.

It is important to note that only 17% of all enrolled patients had tumors negative for PDL1 expression. In subgroup analysis by PDL1 CPS subpopulations presented in the supplemental section of the publication, in PDL1 negative group the OS in chemotherapy plus nivolumab vs. chemotherapy group was 13.2 vs. 12.5 months with HR of 0.92 (0.70-1.23). In patients with tumors with PDL1 CPS < 5, OS was 12.4 vs. 12. 3 with chemotherapy plus nivolumab vs. chemotherapy alone group with HR of 0.94 (0.78-1.13). These results raise a question as to whether these subgroups of patients derive any benefit from immunotherapy. While there is clear benefit with 3.3 months survival advantage when nivolumab is added to chemotherapy in those with PDL1 CPS ≥5 tumors, the benefits are less clear in the rest of the patients. As such, approach to treatment should involve detailed discussions of risks and benefits with individual patients. Pembrolizumab with chemotherapy is approved in first-line setting for untreated esophageal cancer.[5] Similarly, to nivolumab, activity of this agent is primarily seen in patients with PDL1 CPS positive tumors.

In general, continuation of systemic regimens past 4-6 months is challenging because of chemotherapy-induced neuropathy and cumulative toxicities. There are no unifying guidelines regarding treatment of responders beyond this time point. Treatments for neuropathy are also limited. As such, in the past maintenance chemotherapy with 5-FU or capecitabine was often employed, with small studies demonstrating the benefit of this approach compared to supportive measures alone[5-7]. However, fluoropyrimidines or immunotherapy alone cannot control disease for extended periods of time, and thus better strategies are needed in first-line setting[9].

1.3 Oligometastatic EGA

Based on clinical experience and published data, we estimate that at least 10-15% of all EGA patients have oligometastatic disease at the time of diagnosis[8]. There is a body of literature that suggests that aggressive treatment of select patients with limited metastatic sites may result in improved outcomes[9]. However, prospective randomized trials evaluating locoregional therapy in oligometastatic upper EGA are lacking. There are also no unified guidelines on how to define and/or manage oligometastatic disease. However, resection and consolidation radiotherapy (XRT) are under study.

Surgical resection of oligometastatic disease has been attempted in multiple institutions with promising efficacy [10-13]. There is an ongoing randomized phase III trial in Europe (RENAISSANCE, NCT02578368) that is studying whether surgical debulking of oligometastatic disease improves outcomes[14]. Patients with protocol-defined oligometastatic disease are treated with 2 months of induction FLOT and are subsequently randomized to resection of all metastases followed by continuation of FLOT versus continuation of FLOT alone. There are also a number of small case series and single institution reports that describe an aggressive approach to oligometastatic EGA. Okano *et al* reviewed 807 gastric cancer cases in Kagawa Medical University, Japan[15]. Nineteen patients underwent liver metastatectomy with curative intent. Survival rates at 1, 3, and 5 years respectively were 77%, 34%, and 34%. Three patients survived more than 5 years after resection. Makino *et al* reported similar survival data in 63 patients with gastric cancer who underwent hepatic metastatectomy[16]. Koga *et al* and Baek *et al* described long-term survivors after hepatic resection of metastases from gastric cancer[17,18]. Hiyoshi *et al* reported on metastatectomy for recurrent

esophageal cancer[19]. Fourteen patients who underwent surgery (some with repeated resections) had favorable outcomes. Ghaly *et al* described the outcomes of 56 esophageal cancer patients who underwent definitive treatment (surgery or radiation) of recurrent metastasis after esophagectomy [20]. Median survival after recurrence treatment was 25.8 months, which compared favorably to historical references. Schmidt *et al* reported on 112 patients with oligometastatic EGA who underwent resection of the primary tumor and metastatic sites. Patients with an R0 resection and those who received pre-operative therapy had the best outcomes[21].

There are also promising data with regards to consolidative XRT. A case series from the MD Anderson Cancer Center described 101 long-term survivors with oligometastatic EGA who received consolidative XRT to all sites of disease during their treatment continuum[22]. Those who received induction chemotherapy prior to consolidation had the best outcomes. Kim *et al* described the role of Stereotactic Body Radiation Therapy (SBRT) in 7 patients with isolated paraaortic lymph node metastases after gastrectomy[23]. Three-year OS and PFS rates were 43% and 29% after SBRT.

There are also a number of radiation studies that evaluated the role of consolidative radiation to a limited number of metastases across disease types. Although these reports are not disease specific, they produced hypothesis generating results that are worth investigating further in prospective disease-specific and randomized studies. Bigntardi *et al* demonstrated the feasibility and safety of SBRT to metastatic abdominal lymph nodes, which resulted in encouraging disease free survival (DFS) rates in metastatic patient population. This study had a small number of patients with UGI malignanies[24]. A Randomized Phase 2 trial SABR-COMET (Stereotactic Radiation for the Comprehensive Treatment of Oligometastatic Cancers enrolled patients with oligometastatic cancers of any origin[25]. Patients (N=99) were randomized in a 2:1 fashion to an ablative approach with SBRT versus palliative radiation as per standard of care after a period of systemic therapy. This trial demonstrated an OS of 50 months with SBRT versus 28 months in a control cohort[26]. These results warrant further investigation of the role of consolidative radiation therapy in a disease specific setting.

1.4 Trial Importance

There is a subset of EGA patients with limited burden of metastatic disease who are undertreated with current strategies and who may benefit from more aggressive approaches early in the course of their disease. This is the first study to prospectively define the potential benefits of locoregional debulking with XRT in oligometastatic EGA and to define oligometastatic EGA. It has the potential to prolong OS and maintain quality of life for patients with an otherwise extremely poor prognosis.

1.5 Study Design

This is a randomized phase III study evaluating the role of consolidative XRT in oligometastatic EGA. Patients with ≤ 5 metastases and who have completed 3-6 months of systemic therapy without disease progression will be eligible for enrollment. Patients will be randomized to receive either systemic therapy or XRT to all disease sites followed by systemic therapy. All patients will continue on systemic therapy until disease progression or development of significant

toxicities. Systemic therapy can be modified per standard of care (SOC) guidelines as interpreted by the primary physician (for example, stopping oxaliplatin due to peripheral neuropathy).

2. Objectives

The primary objective of this protocol is to establish superiority of consolidative radiation therapy over continuation of systemic therapy alone in patients with oligometastatic EGA that does not progress on first-line therapy.

2.1 Primary Objective

2.1.1 Overall survival (OS)

2.2 Secondary Objectives

2.2.1 Safety and tolerability of consolidative radiation therapy in the treatment of oligometastatic EGA.

2.2.2 Progression-free survival (PFS)

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@ecog-acrin.org) or the Group's Regulatory Officer (EA.RegOfficer@ecog-acrin.org).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Patient must be ≥ 18 years of age.

_____ 3.1.2 Patient must have histologically confirmed HER2 negative metastatic esophageal or gastric adenocarcinoma (AJCC 8th edition) with known PDL1 CPS expression.

_____ 3.1.3 Patient must have received 3-6 months of first-line systemic therapy for advanced disease within 4 weeks of the date of protocol randomization. Patient must have at least stable disease, with no evidence of disease progression on first-line systemic therapy to be eligible.

_____ 3.1.4 Patient must have oligometastatic disease at the time of diagnosis of metastatic disease and prior to initiation of the first-line systemic therapy, which is defined as the following:

3.1.4.1 One to five (1-5) radiologically visible metastatic lesions (not sites), in addition to the primary site. CT or MRI scans will be performed for staging purposes. Patients with oligometastatic sites that are only detected with PET/CT will be eligible for participation. Malignant lymph node must be at least 1 cm in short axis or biopsy proven involved by disease.

3.1.4.2 Anatomically defined lymphadenopathy will be considered as 1 metastatic-lesion. For example, 2 enlarged paraaortic lymph nodes will be considered as one lesion, and 2 additional lesions will be allowed to meet protocol definition of oligometastatic disease. However, if supraclavicular or cervical nodes are involved for distal esophageal tumors or gastric tumors, these are counted separately from intrathoracic nodes. For upper thoracic/cervical esophageal tumors, the involvement of celiac nodes are counted separately from intrathoracic nodes. Intrathoracic nodes, defined as hilar and mediastinal nodes, will be collectively counted as one.

3.1.4.3 Patients with radiologically evident peritoneal metastasis are not eligible.

_____ 3.1.5 Patient must have received at least 2 chemotherapy agents during their first-line treatment.

_____ 3.1.6 Consultation with radiation oncology must be performed to confirm eligibility. Patient must not have any contraindications to radiation therapy. Prior palliative or definitive radiation or chemoradiation to the primary site is allowed.

_____ 3.1.7 Patient must have an ECOG Performance Status 0-1.

_____ 3.1.8 Patient must not be pregnant or breast feeding due to the potential harm to unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.

A patient of child bearing potential must have a serum or urine pregnancy test to rule out pregnancy within 14 days prior to randomization.

A patient of childbearing potential is defined as anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Patient of child bearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.9 Patient must not expect to conceive or father children by using accepted and effective method(s) of contraception or by abstaining from sexual intercourse for the duration of their participation in this study. Patients of childbearing potential must continue contraception measures for 5 months after the last dose of protocol treatment. Investigators must counsel all patients on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

_____ 3.1.10 Patient must have adequate organ function, obtained within 28 days prior to randomization, as defined below:

_____ Hemoglobin (Hgb) ≥ 8 g/dL

Hgb:_____ Date of Test:_____

_____ Platelets ≥ 75,000/µL

Platelets:_____ Date of Test:_____

_____ Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L

ANC:_____ Date of Test:_____

_____ AST/ALT ≤ 3.0 × institutional upper limit of normal (ULN)

AST:_____ Institutional ULN:_____

Date of Test:_____

ALT:_____Institutional ULN:_____

Date of Test:_____

_____ Bilirubin ≤ 1.5 x institutional ULN (unless suspected Gilbert's disease per treating physician)

Bilirubin:_____ Institutional ULN:_____

Date of Test:_____

Suspected Gilbert's disease?_____(Yes or No)

_____ Serum creatinine ≤ 1.5 x institutional ULN or Creatinine Clearance ≥ 30 mL/min (estimated using Cockcroft and Gault formula or measured) See Appendix V for calculation information.

Serum creatinine _____Date of Test:_____

Institutional ULN:_____

Creatinine Clearance:_____Date:_____

_____ 3.1.11 Patient must be able to understand and willing to sign and date the written voluntary informed consent form prior to any protocol-specific procedures. Patients with impaired decision-making capacity (IDMC) who have a legally authorized representative (LAR) or caregiver and/or family member available will also be considered eligible.

_____ 3.1.12 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this protocol.

_____ 3.1.13 Patients who had prior definitive treatment for early stage EGA are eligible for participation as long as recurrent disease developed at least 6 months after completion of all prior therapies.

NOTE: Patients previously treated with radiosensitizing 5-FU and oxaliplatin will be eligible for participation as long as adequate time has elapsed from past treatments. For prior definitive treatments with curative intent, recurrent disease

must be diagnosed at least 6 months after treatment completion.

NOTE: Patients who received systemic chemotherapy or immunotherapy as part of the treatment for their locoregional disease (for example, induction therapy before chemoradiation or adjuvant therapy after resection) are eligible for participation, as long as all definitive therapy has been completed at least 6 months prior to developing recurrent disease.

_____ 3.1.14 Any major surgery must have been completed ≥ 4 weeks prior to randomization.

_____ 3.1.15 Patient must not have any known CNS metastasis.

_____ 3.1.16 Patient must not have any uncontrolled intercurrent illness including, but not limited to ongoing or active infection requiring treatment, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

_____ 3.1.17 Patient must not have had live vaccines within 4 weeks prior to randomization. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Patients are permitted to receive inactivated vaccines and any non-live vaccines including those for the seasonal influenza and COVID-19 (Note: intranasal influenza vaccines, such as Flu-Mist® are live attenuated vaccines and are not allowed). If possible, it is recommended to separate study drug administration from vaccine administration by about a week (primarily, in order to minimize an overlap of adverse events).

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Registration and Randomization Procedures

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five-person registration types.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

CTSU Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

IRB Approval:

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an Active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org);
- Click on *Protocols* in the upper left of the screen:
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *[Corresponding Organization]*, and protocol number *[NCI Protocol #]*.
- Click on *Documents, Protocol Related Documents,* and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Protocol-Specific Requirements For EA2183 Site Registration:

- This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU members' website.
- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

Site's registration status may be verified on the CTSU members' website.

- Click on the Regulatory tab at the top of your screen;
- Click on the Site Registration tab;
- Enter the site's 5-character CTEP Institution Code and click on Go
- Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

NOTE: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patient must not start protocol treatment prior to randomization.

Treatment must start within fourteen days, including holidays and weekends, after randomization.

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

4.1 Randomization

4.1.1 The following information will be captured at time of randomization

4.1.1.1 Protocol Number

4.1.1.2 Site/Investigator Identification

- Institution CTEP ID
- Treating Investigator
- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.1.1.3 Patient Identification

- Patient's initials (first and last)
- Patient Demographics
  - Gender

- Birth date (mm/yyyy)
- Race
- Ethnicity
- Method of payment
- Country of residence

4.1.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.1.3 Stratification Factors

- Number of metastatic sites: 1-2 vs. 3 or more at the time of diagnosis of advanced disease
- Prior use of anti-PD1 agents (IO) during first-line treatment of advanced disease vs. no prior IO during first-line treatment of advanced disease
- Triplet vs. doublet first-line chemotherapy backbone

4.2 Additional Requirements

4.2.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.2.2 Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator

Rave Role Requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associates (A) registration type

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted

and study access in Rave will be automatically granted. Site staff will not be able to access the study in Rave until all required Medidata and study-specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the Tasks pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the Studies pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will replace the eLearning link under the study name.

No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Pending study invitations (previously sent but not accepted or declined by a site user) will be automatically accepted and study access in Rave will be automatically granted for the site user. Account activation instructions are located on the CTSU website in the Data Management section under the Data Management Help Topics > Rave resource materials (Medidata Account Activation and Study Invitation). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

4.2.3 Digital RT Data Submission Using TRIAD

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR; and
- TRIAD Site User role on an NCTN, ETCTN, or other relevant roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installations:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

4.3 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EA2183 Forms Completion Guidelines.

5. Treatment Plan

Overview of First-Line Systemic Therapy

Eligible patients will have received 3-6 months of standard first-line systemic therapy. For both arms, systemic therapy after randomization will be chosen at the discretion of the treating physician and can consist of either chemotherapy alone or chemotherapy in combination with an FDA approved immunotherapy as defined the table in Section 5.1. After enrollment, these patients will be treated with one of the standard of care regimens from the table below as determined by the treating provider. All administration doses and dose adjustments will be per local standards of care. Omission of one of the agents, for example oxaliplatin, because of cumulative toxicities will be allowed at the discretion of a treating physician.

5.1 Administration Schedule

Patients will be randomized into one of the following treatment arms:

Arm X: Consolidative XRT followed by Systemic Therapy.

Arm Y: Consolidative Systemic Therapy.

Allowable Options for Systemic Therapy (Both Arms X & Y)	
Chemotherapy + Immunotherapy	**Chemotherapy**
• FOLFOX + nivolumab • FOLFOX + pembrolizumab • CAPOX + nivolumab • CAPOX + pembrolizumab • CF + nivolumab • CF + pembrolizumab	• FOLFOX • CAPOX • CF • FLOT • FOLFIRI
Description of Chemotherapy Regimens: FOLFOX: Oxaliplatin[1], Leucovorin[2], Fluorouracil[3] (14-day cycle) CAPOX: Capecitabine, Oxaliplatin[1] (21-day cycle) CF: Cisplatin, Fluorouracil[4] (21-day or 28-day cycle) FLOT: Docetaxel, Oxaliplatin, Leucovorin[2], Fluorouracil[4] (21-day cycle) FOLFIRI: Irinotecan, Leucovorin[2], Fluorouracil[3] (14-day cycle) **Description of Immunotherapy Agents:** Pembrolizumab: May be added to FOLFOX, CAPOX, or CF at the discretion of the investigator. See Section 8 for dose specifics. Nivolumab: May be added to FOLFOX, CAPOX, or CF at the discretion of the investigator. See Section 8 for dose specifics. **NOTES:** 1. Oxaliplatin may be omitted for patients experiencing cumulative toxicities. 2. Leucovorin may be omitted at the discretion of the investigator. 3. Fluorouracil may be given as a continuous infusion with or without fluorouracil bolus at the discretion of the investigator.	

Allowable Options for Systemic Therapy (Both Arms X & Y)	
Chemotherapy + Immunotherapy	**Chemotherapy**
4. Fluorouracil is given as a continuous infusion.	

5.1.1 Arm X: Consolidative Radiation (XRT) followed by Systemic Therapy

Patients will receive consolidative radiotherapy (XRT) as specified in Section 5.1.2. There will be at least a 1 week break after completion of the systemic therapy that was previously given (prior to enrollment) before starting the consolidative radiotherapy. When the patient's consolidative XRT has been completed, they will resume systemic therapy. This therapy may be a continuation of what they received previously in the first line (or similar regimen) as determined by the investigator. To allow adequate recovery for patients in Arm X, the systemic regimen should start 2-4 weeks after the completion of the consolidative radiotherapy.

5.1.2 Arm X: Radiation Therapy

The goal of radiation is to consolidate gains made by the systemic therapy that was previously given (prior to enrollment) by delivering a dose that maintains the greatest tumor control probability that is also safe to deliver given the anatomic and normal tissue constraints. Radiation therapy is administered using external beam photon radiation therapy, with either three-dimensional conformal radiation therapy (3D-CRT), Intensity Modulated RT (IMRT), stereotactic body radiation therapy (SBRT), or stereotactic radiosurgery (SRS), photon therapy, at the discretion of the treating radiation oncologist. Proton therapy is allowed as well at the discretion of treating physicians. Credentialing requirements are described in in the table below.

Radiotherapy (XRT) must be performed at a participating site of the study. The choice of dose and fractionation will be based on the judgment of the treating radiation oncologist. The suggested dose and fractionations are provided below.

- All therapy units used on this protocol must have their calibrations verified by the IROC Houston QA Center.
- IMRT/VMAT – Institutions treating with IMRT and not previously credentialed for use of IMRT in ECOG-ACRIN trials must irradiate IROC Houston's lung phantom and a phantom treated using IMRT. Contact IROC Houston (http://irochouston.mdanderson.org) for information about their phantoms.
- Proton Therapy - Each beam line used to treat patients on this study must be approved for clinical use by the IROC Houston QA Center. The proton therapy method may be scattering, uniform scanning, or pencil beam scanning depending on institutional availability and approval status for that mode of operation. Investigators using proton beam radiation must comply with current NCI proton therapy guidelines as outlined in the Guidelines for the Use of Proton Radiation Therapy in NCI Sponsored Cooperative Group Clinical Trials, available at

http://rpc.mdanderson.org/RPC/home_page/Proton_guidelines.htm.

RT Credentialing Requirements	**Web Link for Credentialing Procedures and Instructions http://irochouston.mdanderson.org**		
	Treatment Modality		
	3D	IMRT	Key Information
Facility Questionnaire	X	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	X	X	To determine if your institution has completed the requirements, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org).
Phantom Irradiation	X	X	The IROC Lung phantom and an IROC HN phantom treated using IMRT must be successfully completed. Non-standard units such as Tomotherapy or CyberKnife must be credentialed individually. Instructions for requesting and irradiating the phantoms are found on the IROC Houston web site (http://irochouston.mdanderson.org).
IGRT Verification Study	X	X	Institutions must be credentialed for boney and soft tissue IGRT by IROC Houston. Find details on the IROC Houston QA Center website (http://irochouston.mdanderson.org) Institutions that have previously been approved for IGRT may not need to repeat credentialing.
Credentialing Notification Issued to:			
Institution			Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and ECOG-ACRIN that all desired credentialing requirements have been met.

5.1.2.1 Definition of Target Volumes

Target volumes will be approved by the treating radiation oncologist, using the information obtained through clinical examination, radiologic images, the simulation planning study, and histologic specimens. When feasible and

necessary, the patient's diagnostic images (CT scan, MRI study, or PET/CT imaging) will be fused with the simulation scan to delineate the suggested target volumes below.

- Gross Tumor Volume (GTV) – All known disease detected by the above methods, including nodal disease.
- Internal Gross Tumor Volume (iGTV) – GTV plus internal motion, if 4D scanning is obtained at the time of simulation.
- Clinical Target Volume (iCTV) – iGTV plus the region at risk for microscopic spread. This target volume will be added at the physician's discretion, given that all patients in this study will have metastatic disease and thus the utility of accounting for microscopic spread is limited.
- Planning Target Volume (PTV) – iGTV or iCTV plus a margin to account for patient movement and daily setup error.
- Organ at Risk Volumes (OAR) – Delineation of the pertinent organs at risk, to include the lung, heart, esophagus, spinal cord, kidney, and liver.

5.1.2.2 Dose Specifications

NOTE: ICRU-50, ICRU-62, and ICRU-78 prescription methods and nomenclature shall be utilized for this study.

The prescription volume is the PTV.

CT-based treatment planning is required. Calculations that take into account tissue heterogeneity shall be used. Acceptable calculation algorithms such as the superposition/convolution are listed at http://rpc.mdanderson.org/RPC/home.htm. Pencil-beam or Clarkson algorithms should not be used.

Generally, patients who have a metastatic spine lesion will be treated with stereotactic spine radiosurgery (SSRS) with linac-based radiosurgery. Patients who received no prior radiation treatment to their primary tumor should be treated with up to 45 Gy in 15 fractions. Previously irradiated sites may be retreated if the composite dose constraints are met. General guidelines for dose and fractionation are provided below. These guidelines are generally consistent with the current national and practices.

Table of Suggested Radiation Regimes

Disease site	**Recommended Dose**
Osseous Sites	
Spine	18-24 Gy in 1 fraction or 24 Gy-27 in 3 fractions
Bone non-spine	12 Gy for ≥4-cm lesions or 16 Gy for ≤4-cm lesions, in 1 fraction, or 25-30 Gy in 5 fractions. (In the event that the bone lesion is at a high risk of fracture, orthopedic fixation will be allowed followed by adjuvant radiation to 25 Gy in 5 fractions.)
Non-Osseous Sites	
Peripherally positioned lung, liver, or other soft tissue sites	50 Gy in 5 fractions
Centrally positioned lung, liver, or visceral sites like adrenal/kidney	60 Gy in 10 fractions
Centrally positioned sites near critical structures (e.g primary esophagus, trachea, duodenum), large matted lymph nodes, primary esophageal site and adjacent nodes	45 Gy in 15 fractions (near critical structures), prescribed to the PTV with an optional simultaneous integrated and/or sequential boost to 52.5 or 60 Gy to the iGTV. When feasible it is recommended that the entire LN chain containing a metastatic lesion receives an elective radiation dose, per the discretion of the treating radiation oncologist.

Treatment dose will be prescribed to the planning target volume (PTV) for all treatment arms. It is required that the prescribed isodose line should cover 100% of the internal gross tumor volume (iGTV) and more than 95% of the PTV. For lesions close to critical structures, compromised PTV coverage is allowed in order to meet normal tissue dose constraints, pending clinical judgments regarding optimal target coverage and normal tissues sparing by the treating physician. Motion management including 4D simulation, abdominal compression, breath-gating, and/or breathhold techniques will be utilized at the discretion of the treating radiation oncologist and will be recommended for the treatment of lung lesions and abdominal lesions close to the diaphragm.

There is no or little aperture margin recommended for SBRT radiation plans. The external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning, which typically ranges from 70-95%. Higher isodoses (hotspots; (~10-20%) are encouraged (and must be manipulated to occur within the GTV and not in adjacent normal tissues. Heterogeneity correction should be applied for planning as part of standard of care.

5.1.2.3 Recommended Normal Tissue Constraints for 1 to 15 Fraction Regimens

All plans will undergo radiation section-specific QA per department/section policies at which time dose constraints violations will be reviewed. Constraint violations will be allowed pending the clinical judgment of the treating radiation oncologist:

Table of Recommended Radiation Dose Constraints for 1-15 fraction regimens

Standard Name	Description	1 fraction	3 fraction	5 fraction	10 fraction	15 fraction
OpticNrv_R, OpticNrv_L, OpticChiasm	Optic pathway	Dmax ≤10 Gy	Dmax ≤17.4 Gy	Dmax ≤25 Gy	Dmax ≤32 Gy	Dmax ≤42 Gy
Cochlea_R, Cochlea_L	Rt and Lt Cochlea	Dmax ≤9 Gy	Dmax ≤17.1 Gy	Dmax ≤22 Gy	Dmax ≤30 Gy	Dmax ≤33 Gy
Brainstem	Brainstem	Dmax ≤15 Gy	Dmax ≤23.1 Gy	Dmax ≤25 Gy	Dmax ≤36 Gy	Dmax ≤42 Gy
SpinalCord	Spinal Cord	Dmax ≤10 Gy	Dmax ≤21.9 Gy	Dmax ≤30 Gy	Dmax ≤36Gy	Dmax ≤42 Gy
BrachialPlexus	Brachial Plexus	Dmax ≤17.5 Gy	Dmax ≤24 Gy	Dmax ≤30.5 Gy	Dmax ≤50.6 Gy	Dmax ≤50.6 Gy
Heart	Heart/Pericardium	Dmax ≤22 Gy, V16≤15cc	Dmax ≤30 Gy, V24≤15cc	Dmax ≤38 Gy, V32≤15cc	Dmax ≤ 45Gy, V32≤15cc	Dmax ≤ 48.9 Gy; V42≤15cc
Trachea, Bronchus_Main	Trachea and Large Bronchus	Dmax ≤20.2 Gy	Dmax ≤30 Gy	Dmax ≤40 Gy	Dmax ≤ 50Gy	Dmax ≤ 52.5Gy
Esophagus	Esophagus	Dmax ≤15.4 Gy	Dmax ≤25.2 Gy	Dmax ≤35 Gy	Dmax ≤ 50Gy	Dmax ≤ 55.3 Gy, MED ≤ 34Gy
Lungs	Total Lung	Keep 1000cc ≤ 7 Gy	Keep 1000cc ≤ 12.4 Gy	Keep 1000cc ≤ 13.5 Gy	mean dose ≤ 9 Gy, V40 ≤ 7%	Mean ≤ 20Gy, V20Gy ≤ 35%
Skin	Skin	Dmax ≤26 Gy	Dmax ≤33 Gy	Dmax ≤39.5 Gy	Dmax ≤46 Gy	Dmax ≤57 Gy
Duodenum	Duodenum	Dmax ≤12 Gy	Dmax ≤22 Gy	Dmax ≤26 Gy	Dmax ≤ 32 Gy	Dmax ≤ 40 Gy
Kidney_Cortex	Renal Cortex (both right and left)	200 cc > 9.5 Gy	200cc ≤ 15 Gy	700cc ≤ 21 Gy	V10Gy ≤ 33% (each)	V20 Gy ≤ 32%
Rectum	Rectum	Dmax ≤18.4 Gy	Dmax ≤28.2 Gy	Dmax ≤38 Gy	Dmax ≤ 45 Gy	Dmax ≤ 61 Gy

Dmax: Max point dose

V(X): Volume (or percent volume from that structure) receiving X dose. E.g. V20 is volume receiving 20 Gy

5.1.2.4 Primary Site (Primary Esophageal or Gastric Primary and Regional Nodal Sites)

Radiation to the primary site and regional nodal sites can be done at the discretion of the treating radiation oncologist. Standard simulation for treatment to the primary site involves immobilization with an upper body cradle and the arms over the head (if tolerable). 4D simulation done to assess respiratory tumor motion is highly recommended. The radiation dose to the primary site and regional nodes will be determined by the treating physician and based on normal tissue tolerance and institutional standards.

5.1.2.5 Quality Assurance Documentation

Digital Submission

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan, and dose files. Submission via TRIAD is preferred (see Section 4.2.3), but alternatively sites may use sFTP. Instructions for data submission via sFTP are on the IROC Rhode Island web site at http://irocri.qarc.org under "Digital Data." Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data via TRIAD or sFTP or submitted separately. Screen captures are preferred to hard copy for items that are not part of the digital plan.

The following items are to be submitted within one week of the completion of radiotherapy:

- RT treatment plans in DICOM format, including CT, structures, dose, and plan files.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
- Copies (in DICOM Format) and reports of all imaging studies used to define the target volume.
- RT-1 Dosimetry Summary Form.
- Motion Management Reporting Form (if applicable).
- RT-2 Radiotherapy Total Dose Record form
- Copy of the patient radiotherapy record including prescription and daily and cumulative doses to all targeted volumes and critical organs.

Non DICOM data may be included with the DICOM RT submissions via TRIAD or sFTP or emailed to DataSubmission@QARC.org.

Questions regarding the dose calculations or documentation should be directed to:

Protocol Dosimetrist at physics@QARC.org or 401.753.7600

5.1.3 Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the screening and treatment phase of this protocol. The eligibility criteria describes other medications that are prohibited in this protocol.

- Anti-cancer systemic chemotherapy or biological therapies that are not part of the protocol
- Chemotherapy not specified in this protocol
- XRT not specified by the protocol
- Patients who, in the assessment by the site investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the protocol treatment
- There are no prohibited therapies during post-treatment follow-up

5.1.4 Arms X and Y: Systemic Therapy

Patients will receive systemic therapy with one of the treatment regimens from the list in 5.1. This may be a continuation of what they received previously in first line (or a similar regimen) as determined by the investigator.

NOTES FOR BOTH ARMS:

- Systemic Therapy may continue until disease progression, intolerable toxicities, or a maximum of 2 years on consolidation therapy.
- Chemotherapy doses can be adjusted by the treating investigator as per local treatment standards to account for cumulative chemotherapy toxicities. For example, oxaliplatin can be stopped or dose-reduced for development of oxaliplatin-induced neuropathy.
- Immune mediated toxicities should be managed according to local standards, relying on ASCO guidelines29. Patients may remain on study treatment with chemotherapy alone if immunotherapy has to be permanently discontinued due to toxicities.
- Treatment premedication should be administered as per institutional guidelines.
- Patients receiving oxaliplatin on this study should be counseled to avoid cold drinks, chewing of ice chips, and exposure to cold water or air because the neurotoxicity often seen with oxaliplatin appears to be exacerbated by exposure to cold. The period of time during which the patient is at risk for these cold-induced sensory neuropathies is not well documented. Patients should exercise caution regarding cold exposure during the treatment period. Peripheral sensory neuropathies can

occur at any time after receiving oxaliplatin therapy but are usually cumulative.

5.1.5 Allowed Treatment Locations

5.1.5.1 Drug Therapy: All study drug agents and standard of care medications are available commercially and may be administered at a local facility to accommodate logistical needs of the patient or parent institution (registering site). The local facility must be able to share all study related information with the investigator or have a transparent electronic health record (EHR) that is easily accessible to the primary investigator (PI). Only drugs and standard of care supportive agents may be given at the local facility. Radiation (XRT) that is study related must be performed at a participating registered site of the study (See Section 5.1.2).

Regulatory Requirements for local facility administration: It is the responsibility of the registering site/primary investigator to ensure:

- The patient is registered (4.1) randomized (4.2) has met eligibility requirements (4.2.2) and has informed consent prior to any study related treatment at the local facility.
- All study related data collection, adverse event (AE) reporting, including SAE reporting where applicable, must be reported by the registering site/PI into Medidata Rave as outlined in Section 4.2.
- If treatment at the local facility differs from protocol requirements, this must be reported by the registering site/PI as a deviation.
- The registering site PI and local facility treating physician should have a written agreement in place and open lines of communication to ensure the protocol is being followed as outlined in Section 5.1. Dose modifications must follow Section 5.4.1 of the protocol.
- The local facility may not require IRB approval, unless otherwise dictated by local institutional guidelines.
- The patient must authorize in writing that the registering site may access medical records related to treatments at the local facility- unless a formal HIPPA document is already in place that fulfills this requirement.

5.1.5.2 Radiation Therapy: Consolidative radiotherapy (XRT) must be performed at a participating registered site of the study. Study related XRT may not be performed at a local facility that is not registered.

5.1.5.3 Registration visit, including informed consent, must be performed IN-PERSON. After these have been completed, telemedicine assessments are allowed to meet the logistical needs of the patient or investigator. If a physical exam cannot be completed via telemedicine, this must be documented in the patient record and is considered a minor deviation. Telemedicine may NOT be used for more than two visits in succession without an in-person visit. Visits at which study-required blood draws or scans are required, must be performed in-person. When a visit is completed via telemedicine, the site must still arrange for protocol-required laboratory tests to be performed.

5.2 Adverse Event Reporting Requirements

All toxicity grades described throughout this protocol and all reportable adverse events that patients may experience on this protocol will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

5.2.2 **Routine reporting:** Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to Section 4 of the protocol for more information on how to access the Medidata Rave system and the EA2183 forms packet for instructions on where, when and what adverse events are to be reported routinely on this protocol.

5.2.3 **Expedited reporting:** In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). Section 5.2.5 outlines the procedures for expedited reporting of adverse events on this protocol.

5.2.4 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans, whether or not considered agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to protocol treatment.
Unlikely	The AE is *doubtfully related* to protocol treatment.
Possible	The AE *may be related* to protocol treatment.
Probable	The AE is *likely related* to protocol treatment.
Definite	The AE is *clearly related* to protocol treatment.

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol, Investigator's Brochure or drug package insert

5.2.5 Expedited Adverse Event Reporting Procedure

Adverse events requiring expedited reporting will use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov., so that ECOG-ACRIN and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900)
- the FDA (1-800-FDA-1088)

An electronic report MUST be submitted via CTEP-AERS immediately upon re-establishment of internet connection.

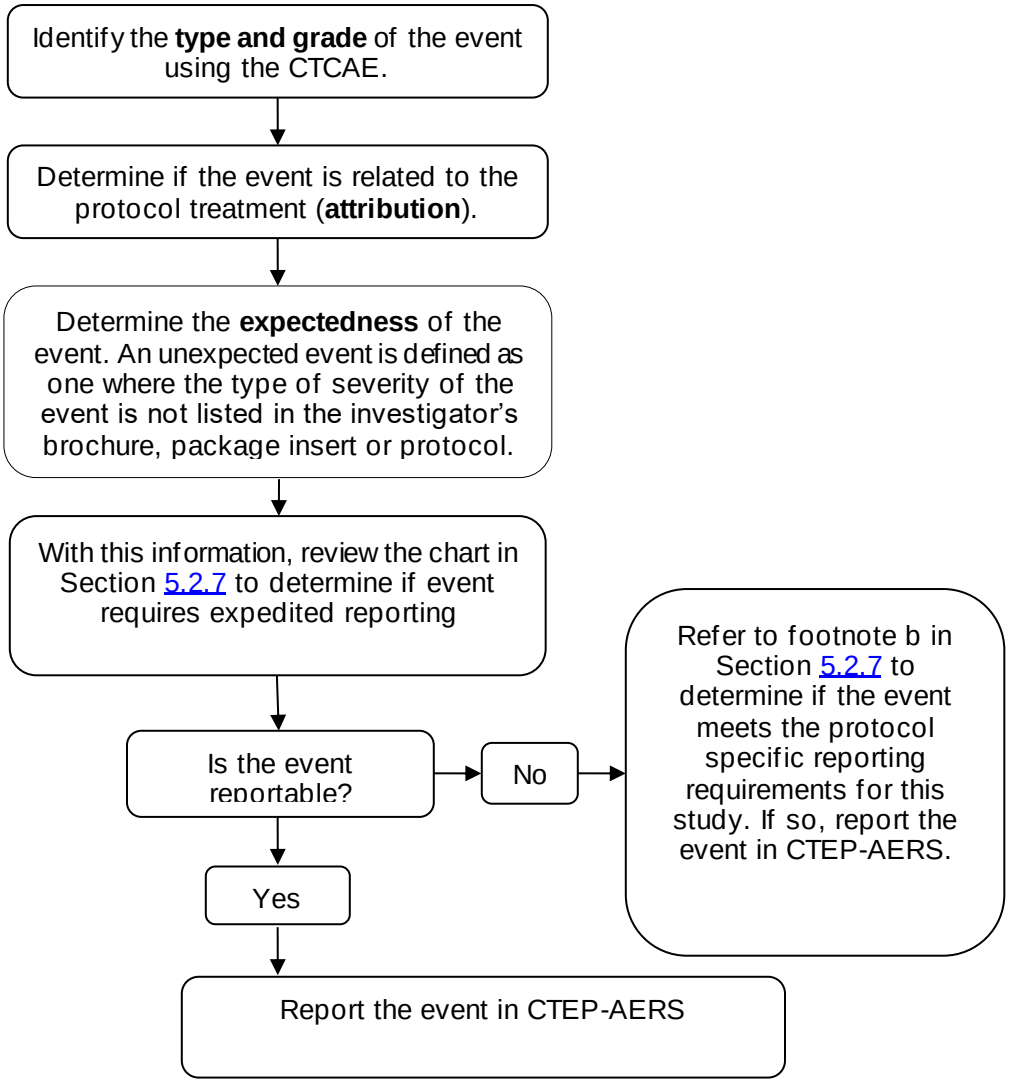
Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to FDA (800-332-0178) in the same timeframe. Supporting and follow up documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please

contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

Many factors determine the requirements for expedited reporting of adverse events on each individual protocol. The instructions and tables in the following sections have been customized for protocol EA2183 and outline the specific expedited adverse event reporting requirements for study EA2183.

5.2.6 Steps to determine if an event is to be reported in an expedited manner – Arms X and Y.



5.2.7 Expedited Reporting Requirements for Arms X and Y on protocol EA2183

Agents: Oxaliplatin, Leucovorin, 5-FU, Capecitabine, Nivolumab, Pembrolizumab, Cisplatin, Docetaxel, Irinotecan

Other Treatment: Radiation

Expedited reporting requirements for adverse events experienced by patients on arm(s) with IND exempt/commercial agents only

Attribution	**Grade 4**		**Grade 5[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a A death occurring while on study treatment or within 30 days of the last dose of study treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

NOTE: Any death that occurs > 30 days after the last dose of study treatment and is attributed possibly, probably, or definitely to the study treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported in CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

Infusion Reactions: All Grade 4 infusion reactions must be reported in CTEP-AERS within 7 calendar days of learning of the event.

Immune Related Adverse Events (IRAE): Any grade 3 or higher immune related adverse events must be reported in CTEP-AERS Rave within 7 calendar days of learning of the event. If available, please submit any supporting data as well (e.g.: autoimmune serology tests or biopsy reports). Any questions regarding if an event qualifies as an IRAE can be directed to the study chair.

NOTE: In to appropriately report these events to regulatory agencies, please be sure to state that the event being reported is an IRAE in the 'Description of Event' section of the CTEP-AERS report

5.2.8 Other recipients of adverse event reports and supplemental data

Adverse events determined to require expedited reporting must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.9 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported as follows:

- **A <u>second malignancy</u> is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Report the diagnosis on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

     NOTE: When reporting attribution on the AE Form, assess the relationship between the secondary malignancy and the current protocol treatment ONLY (and NOT relationship to any anti-cancer treatment received either before or after protocol treatment).
  3. Report the diagnosis in CTEP-AERS at http://ctep.cancer.gov.
  4. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  5. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the

associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted in CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR)

5.3.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Nivolumab

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. *Frequency is provided based on 2096 patients.* Below is the CAEPR for Nivolumab.

Version 2.5, June 10, 2023[1]

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
		Blood and lymphatic system disorders - Other (lymphatic dysfunction)
CARDIAC DISORDERS		
		Cardiac disorders - Other (cardiomyopathy)
		Myocarditis
		Pericardial tamponade[2]
		Pericarditis
ENDOCRINE DISORDERS		
	Adrenal insufficiency[3]	
	Hyperthyroidism[3]	
	Hypophysitis[3]	
	Hypothyroidism[3]	
EYE DISORDERS		
		Blurred vision
		Dry eye
		Eye disorders - Other (diplopia)[3]
		Eye disorders - Other (Graves opthalmopathy)[3]
		Eye disorders - Other (optic neuritis retrobulbar)[3]
		Eye disorders - Other (Vogt-Koyanagi-Harada)[3]
	Uveitis	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis[3]	
		Colonic perforation[3]
	Diarrhea	
	Dry mouth	
		Enterocolitis
		Gastritis
		Mucositis oral
	Nausea	
	Pancreatitis[4]	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue		
	Fever	
	Injection site reaction	
HEPATOBILIARY DISORDERS		
		Hepatobiliary disorders - Other (Immune-related hepatitis)
IMMUNE SYSTEM DISORDERS		
		Allergic reaction[3]
		Autoimmune disorder[3]
		Cytokine release syndrome[5]
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]
		Immune system disorders - Other (sarcoid granuloma, sarcoidosis)[3]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction[7]	
INVESTIGATIONS		
	Alanine aminotransferase increased[3]	
	Aspartate aminotransferase increased[3]	
	Blood bilirubin increased[3]	
	CD4 lymphocytes decreased	
	Creatinine increased	
	Lipase increased	
	Lymphocyte count decreased	
	Neutrophil count decreased	
	Platelet count decreased	
	Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
		Hyperglycemia
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
		Musculoskeletal and connective tissue disorder - Other (polymyositis)
		Myositis
		Rhabdomyolysis
NERVOUS SYSTEM DISORDERS		
		Encephalopathy[3]
		Facial nerve disorder[3]
		Guillain-Barre syndrome[3]
		Myasthenia gravis[3]
		Nervous system disorders - Other (demyelination myasthenic syndrome)

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Nervous system disorders - Other (encephalitis)[3]
		Nervous system disorders - Other (meningoencephalitis)
		Nervous system disorders - Other (meningoradiculitis)[3]
		Nervous system disorders - Other (myasthenic syndrome)
		Peripheral motor neuropathy
		Peripheral sensory neuropathy
		Reversible posterior leukoencephalopathy syndrome[3]
RENAL AND URINARY DISORDERS		
		Acute kidney injury[3]
		Renal and urinary disorders - Other (Immune-related nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Pleural effusion[3]	
	Pneumonitis[3]	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia (BOOP))[3]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
		Erythema multiforme[3]
	Pruritus[3]	
	Rash maculo-papular[3]	
		Skin and subcutaneous tissue disorders - Other (bullous pemphigoid)
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3]	
	Skin hypopigmentation[3]	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3]Nivolumab being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune

hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[4]Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[5]Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[6]Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving Nivolumab. These complications may occur despite intervening therapy between receiving Nivolumab and allo-SCT.

[7]Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

Adverse events reported on Nivolumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Nivolumab caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia

EAR AND LABYRINTH DISORDERS - Vestibular disorder

EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema

GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain

HEPATOBILIARY DISORDERS - Bile duct stenosis

IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)

INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection

INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Histiocytic necrotizing lymphadenitis)

NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage

PSYCHIATRIC DISORDERS - Insomnia

RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)

VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

NOTE: Nivolumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.3.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pembrolizumab (MK-3475, NSC 776864)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. *Frequency is provided based on 3793 patients.* Below is the CAEPR for Pembrolizumab (MK-3475).

Version 2.8, August 14, 2024[1]

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia[2]	
		Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura)[2]
		Blood and lymphatic system disorders - Other (autoimmune hemolytic anemia)[2]
	Lymph node pain[2]	
CARDIAC DISORDERS		
		Myocarditis[2]
		Pericarditis[2]
ENDOCRINE DISORDERS		
	Adrenal insufficiency[2]	
		Endocrine disorders - Other (hypoparathyroidism)[2]
	Endocrine disorders - Other (thyroiditis)[2]	
	Hyperthyroidism[2]	
	Hypophysitis[2]	
	Hypopituitarism[2]	
	Hypothyroidism[2]	
EYE DISORDERS		
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)
		Uveitis[2]
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis[2]	
	Diarrhea[2]	

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
		Enterocolitis[2]
		Gastritis[2]
		Gastrointestinal disorders - Other (exocrine pancreatic insufficiency)
	Mucositis oral[2]	
	Nausea	
	Pancreatitis[2]	
	Small intestinal mucositis[2]	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
Fatigue		
	Fever[2]	
HEPATOBILIARY DISORDERS		
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]	
		Hepatobiliary disorders - Other (sclerosing cholangitis)
IMMUNE SYSTEM DISORDERS		
		Anaphylaxis[2]
		Cytokine release syndrome[2]
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]
	Immune system disorders - Other (sarcoidosis)[2]	
		Serum sickness[2]
INFECTIONS AND INFESTATIONS		
		Myelitis[2]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction	
INVESTIGATIONS		
	Alanine aminotransferase increased[2]	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased[2]	
	Blood bilirubin increased	
		GGT increased
		Lipase increased
		Serum amylase increased
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hyponatremia	
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia[2]	

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
	Arthritis[2]	
	Back pain	
	Joint range of motion decreased	
	Myalgia[2]	
	Myositis[2]	
NERVOUS SYSTEM DISORDERS		
		Guillain-Barre syndrome[2]
		Myasthenia gravis
		Nervous system disorders - Other (autoimmune neuropathy)[2]
		Nervous system disorders - Other (demyelination)[2]
		Nervous system disorders - Other (myasthenic syndrome)[2]
		Nervous system disorders - Other (nerve paresis)[2]
		Nervous system disorders - Other (neuromyopathy)[2]
		Nervous system disorders - Other (non-infectious encephalitis)[2]
		Nervous system disorders - Other (non-infectious meningitis)[2]
		Nervous system disorders - Other (non-infectious myelitis)
		Nervous system disorders - Other (optic neuritis)
		Nervous system disorders - Other (polyneuropathy)[2]
		Paresthesia
		Peripheral motor neuropathy[2]
RENAL AND URINARY DISORDERS		
		Acute kidney injury
		Renal and urinary disorders - Other (autoimmune nephritis)[2]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
		Pneumonitis[2]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Bullous dermatitis[2]	
		Erythema multiforme[2]
	Erythroderma	
		Palmar-plantar erythrodysesthesia syndrome
	Pruritus[2]	
	Rash acneiform[2]	
	Rash maculo-papular[2]	
		Skin and subcutaneous tissue disorders - Other (Drug reaction with eosinophilia with systemic symptoms [DRESS])[2]
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]	

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
	Skin hypopigmentation[2]	
		Stevens-Johnson syndrome[2]
		Toxic epidermal necrolysis[2]
	Urticaria[2]	
VASCULAR DISORDERS		
		Vasculitis[2]

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions have been reported in patients receiving Pembrolizumab (MK-3475). Adverse events potentially related to Pembrolizumab (MK-3475) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of Pembrolizumab (MK-3475), administration of corticosteroids and supportive care.

[3]Acute graft-versus-host disease has been observed in patients treated with Pembrolizumab (MK-3475) who received hematopoeitic stem cell transplants.

Adverse events reported on Pembrolizumab (MK-3475) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Pembrolizumab (MK-3475) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia

EYE DISORDERS - Eye pain

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastrointestinal disorders - Other (intussusception); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain

INVESTIGATIONS - CPK increased; Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Joint effusion2; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity

NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor

PSYCHIATRIC DISORDERS - Agitation; Confusion

RENAL AND URINARY DISORDERS - Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pleuritic pain[2]; Pneumothorax; Respiratory failure

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)

VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

NOTE: Pembrolizumab (MK-3475) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.4 Dose Modifications

5.4.1 Chemotherapy Regimens

(FOLFOX, CAPOX, FLOT, FOLFIRI, FC)

All treatment dose modifications will be per standard of care. Dose reductions and/or schedule modifications in both Arms X and Y will occur based on the treating physician's discretion and managed according to institutional standard of practice (SOP). If a patient experiences toxicity requiring a dose reduction, the dose may remain reduced for subsequent cycles. Dose re-escalations will be permitted at the treating physician's discretion. Doses may be delayed at the discretion of the treating physician. Additionally, refer to the FDA labeling package insert for individual agents for complete details on safety and treatment considerations.

Maximum treatment delays for toxicity are 28 days.

Treatment break due to exposure/isolation or infection should not exceed 4 weeks (28 days) during chemotherapy treatment.

Patients who are treated with nivolumab or pembrolizumab in combination with chemotherapy are allowed to continue with chemotherapy administration in the event nivolumab or pembrolizumab is held due immune mediated toxicities (and with permanent immunotherapy discontinuation), as long as it is safe to do so in the opinion of the treating physician. Refer to table in Section 5.4.2 for guidance on immune related toxicity.

5.4.2 Immunotherapy Agents

(Pembrolizumab and Nivolumab)

There are no dose reductions allowed for nivolumab or pembrolizumab. If there is a treatment delay or toxicity that is related only to immunotherapy, chemotherapy may continue at the

investigator's discretion. If the patient has toxicity from immunotherapy requiring it be discontinued per the Table below, chemotherapy may continue, and the patient may remain on study.

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

Adverse events (both nonserious and serious) associated with exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of immunotherapy agent, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue immunotherapy agent (pembrolizumab or nivolumab) and administer corticosteroids. Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Immunotherapy must be withheld for drug-related toxicities and severe or life-threatening AEs as described in the Table below.

Note that non-irAEs will be managed as appropriate, following clinical practice recommendations.

General instructions:

1. For non-endocrine-related severe and life-threatening irAEs, investigators should consider the use of IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. Some non-endocrine irAEs do not require steroids. For example, celiac disease induced by immunotherapy can be controlled by diet alone.
2. For non-endocrine-related toxicities, pembrolizumab/nivolumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 8 weeks of the last immunotherapy treatment.
3. Generally, when corticosteroids are used, investigators should begin a taper when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab or nivolumab has been withheld due to a non-endocrine irAE, they may resume after the irAE has decreased to ≤ Grade 1 after a corticosteroid taper.

Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions related to Immunotherapy (Nivolumab or Pembrolizumab)

irAEs	Toxicity grade (CTCAE V5.0)	Action	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics for opportunistic infections.	Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper. Patients who do not respond to corticosteroids should be seen by a gastroenterologist for confirmation of the diagnosis and consideration of secondary immune suppression.	Monitor patients for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood, or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus) Specifically assess for celiac disease serologically and exclude Clostridium difficile infection. Patients with ≥Grade 2 diarrhea suspecting enterocolitis should consider GI consultation and performing endoscopy to rule out enterocolitis and assess mucosal severity. Patients with diarrhea/colitis should be advised to drink liberal quantities of
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions related to Immunotherapy (Nivolumab or Pembrolizumab)				
irAEs	**Toxicity grade (CTCAE V5.0)**	**Action**	**Corticosteroid and/or other therapies**	**Monitoring and follow-up**
				clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions				
irAEs	**Toxicity grade (CTCAE V5.0)**	**Action**	**Corticosteroid and/or other therapies**	**Monitoring and follow-up**
AST or ALT elevation or Increased Bilirubin	Grade 2[a]	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 returned to baseline or is stable)
	Grade 3[b] or 4[c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Grade 1 or 2	Continue	Initiate treatment with insulin If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (e.g. anion gap, ketones, blood pH, etc.) reported	Investigate for diabetes. In the absence of corticosteroids or diabetes medication non-adherence, any grade hyperglycemia may be an indication of beta-cell destruction and pembrolizumab-induced diabetes akin to type 1 diabetes. This should be treated as a Grade 3 event. Given this risk, exercise caution in utilizing non-insulin hypoglycemic agents in this setting. After a thorough investigation of other potential causes, which may involve a referral to an endocrinologist, follow institutional guidelines. Monitor glucose control.
	New onset T1DM (evidence of β-cell failure)	Withhold d Resume immunotherapy		Monitor for glucose control Strongly consider referral to endocrinologist

Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions				
irAEs	**Toxicity grade (CTCAE V5.0)**	**Action**	**Corticosteroid and/or other therapies**	**Monitoring and follow-up**
	or Grade 3 or 4 hyperglycemia	when symptoms resolve and glucose levels are stable		Obtain C-peptide level paired with glucose, autoantibody levels (e.g. GAD65, islet cell autoantibodies), and hemoglobin A1C level
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) Provide adrenal insufficiency precautions including indications for stress dose steroids and medical alert jewelry Strongly consider referral to endocrinologist
	Grade 3 or 4	Withhold or permanently discontinue		
Hyperthyroidism	Grade 2	Consider withholding. Resume immunotherapy when symptoms are controlled, and thyroid function is improving	Treat with nonselective beta-blockers (e.g., propranolol) or thionamides as appropriate Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed	Monitor for signs and symptoms of thyroid disorders Strongly consider referral to endocrinologist
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function Strongly consider referral to nephrologist
Cardiac Events (including	Asymptomatic cardiac enzyme	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes

Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions				
irAEs	**Toxicity grade (CTCAE V5.0)**	**Action**	**Corticosteroid and/or other therapies**	**Monitoring and follow-up**
myocarditis, pericarditis, arrhythmias, impaired ventricular function, vasculitis)	elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1), or Grade 1			Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month
	Grade 2, 3 or 4	Permanently discontinue	Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent Initiate treatment per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), or pericardiocentesis as appropriate	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month
Suspected SJS, TEN, or DRESS	ANY	Withhold		

Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions				
irAEs	**Toxicity grade (CTCAE V5.0)**	**Action**	**Corticosteroid and/or other therapies**	**Monitoring and follow-up**
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE, administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes. Strongly consider referral to dermatologist Consider skin biopsy for evaluation of etiology.
All Other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event e		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Infusion Reactions	**NCI CTCAE Grade**	**Treatment**	**Premedication at subsequent dosing**
Mild reaction: infusion interruption not indicated; intervention not indicated	Grade 1	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic	Grade 2	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs	Patients may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
medications indicated for ≤24 hrs.		• Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study immunotherapy treatment	
Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Grade 3	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids (e.g. methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) • Increase monitoring of vital signs as medically indicated until the participant is deemed	No subsequent dosing.

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
		medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Patient is permanently discontinued from further study immunotherapy treatment.	
Life-threatening; pressor or ventilator support indicated	Grade 4	Admit patient to intensive care unit (ICU) and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. Follow Grade 3 recommendations as applicable.	No subsequent dosing.

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; ECMO=extracorporeal membrane oxygenation; GI=gastrointestinal; ICU=intensive care unit; IO=immuno-oncology; ir=immune related; IV=intravenous; MRI=magnetic resonance imaging; PO=per os; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal; VAD=ventricular assist device.

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

a AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal;
bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

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

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

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

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

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.

Neurological Toxicities

Event	Management
Immune-mediated neuropathy, Grade 1	Continue immunotherapy (pembrolizumab or nivolumab) Investigate etiology. Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, including facial paresis, Grade 2	Withhold immunotherapy for up to 12 weeks after event onset.[a] Investigate etiology and refer patient to neurologist. Initiate treatment as per institutional guidelines. For general immune-mediated neuropathy: If event resolves to Grade 1 or better, resume.[b] If event does not resolve to Grade 1 or better while withholding immunotherapy, permanently discontinue immunotherapy.[c] For facial paresis: If event resolves fully, resume immunotherapy.[b] If event does not resolve fully while withholding immunotherapy, permanently discontinue immunotherapy.[c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	Permanently discontinue immunotherapy.[c] Refer patient to neurologist. Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	Permanently discontinue immunotherapy.[c] Refer patient to neurologist. Initiate treatment as per institutional guidelines. Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Pembrolizumab or nivolumab (immunotherapy) may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤10 mg/day oral prednisone before pembrolizumab can be resumed.

[c] Resumption of immunotherapy may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab or nivolumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate).

Event	Management
Immune-mediated myelitis, Grade 1	Continue immunotherapy unless symptoms worsen or do not improve. Investigate etiology and refer patient to a neurologist.

Event	Management
Immune-mediated myelitis, Grade 2	Permanently discontinue immunotherapy. Investigate etiology and refer patient to a neurologist. Rule out infection. Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	Permanently discontinue immunotherapy. Refer patient to a neurologist. Initiate treatment as per institutional guidelines.

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue immunotherapy. [a] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.
a Resumption of pembrolizumab or nivolumab (immunotherapy) may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with immunotherapy should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate).	

5.5 Supportive Care

Patients should receive appropriate supportive care measures as deemed appropriate by the treating investigator.

All supportive measures consistent with optimal patient care will be given throughout the study.

5.5.1 Concomitant Medications

A comprehensive medication review should be performed at baseline to assess any treatment concerns related to the patient's current medications. These do not need to be recorded in the study file.

All treatments the site investigator considers necessary for a patient's welfare may be administered at the discretion of the site investigator in keeping with the local standards of medical care.

5.5.2 Prohibited Medications

5.5.2.1 Corticosteroids (systemic): May diminish the therapeutic effect of Immune Checkpoint Inhibitors. If the patient is on a regimen containing pembrolizumab or nivolumab, carefully consider the need for corticosteroids at doses of a prednisone-equivalent of 10 mg or more per day. Doses of

prednisone-equivalent >10 mg per day for uses other than treating immunotherapy related toxicity are prohibited.

Use of corticosteroids to treat immune related adverse events is still recommended. Intranasal and inhaled corticosteroids are permitted.

5.5.2.2 Live vaccines are prohibited during study treatments. Attenuated vaccines will be allowed. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Patients are permitted to receive inactivated vaccines and any non-live vaccines including those for the seasonal influenza and COVID-19 (Note: intranasal influenza vaccines, such as Flu-Mist® are live attenuated vaccines and are not allowed). If possible, it is recommended to separate study drug administration from vaccine administration by about a week (primarily, in order to minimize an overlap of adverse events).

5.6 Duration of Therapy

Patients will stop protocol therapy under the following circumstances:

- Documented disease progression.
- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EA2183 Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Patient has no radiological evidence of disease for 2 years after randomization.

5.7 Duration of Follow-up

All patients will be followed for 5 years post-randomization.

6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be followed with restaging scans about every 3 months or earlier if clinically indicated.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST.

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

NOTE: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

Evaluable Non-Target Disease Response

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

6.1.2 Disease Parameters

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as

≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

NOTE: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be

≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

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

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum

of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

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

6.1.3 Methods for Evaluation of Disease

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

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

Clinical Lesions

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

Chest X-ray

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

Conventional CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans) such as severe contrast allergy precluding safe use of contrasted CT.

Tumor Markers

Tumor markers alone cannot be used to assess response.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR)

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

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of one or more new lesions is also considered progression, See Section 6.1.4.3.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 6 weeks.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis)

Non-CR/Non-PD

Persistence of one or more non-target lesion(s.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (see Section 6.1.4.3). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from "trace" to "large", an increase in nodal disease from "localized" to "widespread", or an increase sufficient to require a change in therapy.

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

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) increases in size to ≥ 15 mm in the short axis, or

b) there is new pathological confirmation that it is disease (regardless of size).

New effusion or ascites that appears during treatment should only be reported as a new lesion (and therefore progressive disease) if it has cytological confirmation of malignancy.

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

Target Lesions	Non-Target Lesions	New Lesions*	Best Overall Response	Remarks
CR	CR	No	CR	
CR	Non-CR/Non-PD***	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	

Target Lesions	Non-Target Lesions	New Lesions*	Best Overall Response	Remarks
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 6 weeks from study entry
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD***	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

7. Study Parameters

7.1 Therapeutic Parameters and Study Calendar: 14 and 28 Day Cycles

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within ≤ 4 weeks prior to randomization.
2. Prestudy CBC (with differential and platelet count) must be done ≤ 4 weeks prior to randomization.
3. All required prestudy chemistries, as outlined in Section 3, must be done ≤ 4 weeks prior to randomization.

Treatment days may be delayed up to 3 days to account for logistical issues, such as scheduling and travel difficulties, weather, holidays. Local standard practices should be applied when these scheduling changes are made. Treatment delays due to exposure/isolation or infection should not exceed 4 weeks (28 days) for chemotherapy treatment.

	Prior to Randomization	End of XRT	Every Chemo Cycle (post-RT)[10,11]		End of Treatment[9]	Follow-Up[8]
			D1	D15		
Medical History, Baseline Assessment, Height	X					
Weight, Vitals [1]	X		X	X	X	
Physical Examination, ECOG Performance Status	X		X			
CBC with Differential[2]			X	X	X	
Serum Comprehensive Panel[3]			X	X	X	
Adverse Event Assessment		X	X		X	
Tumor PDL1 CPS						
Pregnancy Test[4]	X					
Imaging[5]	X		X[6]			X
Radiation Oncology Evaluation[6]	X[7]					

1. Vitals will include temperature, heart rate, respiratory rate and blood pressure
2. CBC with differential and platelet count (which includes WBC, ANC, platelets, Hgb and Hct) required for protocol therapy must be done < 72 hours prior to each treatment day.

3. CMP to include sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, liver function tests (AST, ALT, total bilirubin, alkaline phosphatase) and albumin. CMP must be done <72 hours prior to each treatment day. For patients who are treated with immunotherapy in addition to chemotherapy, TSH should be checked on day 1 of every odd cycle. Free T4 should only be checked if TSH is abnormal. TSH and free T4 results are not required prior to dosing.
4. All patients of childbearing potential must have a negative [blood test or urine test] within 14 days prior to randomization. to rule out pregnancy.
5. During treatment, restaging CT or MRI scans (CT or MRI chest and contrast enhanced CT or MRI abdomen and pelvis with IV and PO contrast) should be performed every 3 months (+/- 14 days) after randomization.
6. Radiation oncologist consultation will be prior to enrollment. Radiation Oncologist evaluations may be performed by telemedicine if needed. If radiation interrupted for 7 days or less after initiation due to logistical reasons, patient may continue on study as prior, record as minor deviation. XRT interruptions > 7 days must be reviewed with study chair and statistician.
7. End of treatment visit should occur 30 days (+/-7 days) after last dose of protocol treatment (or earlier if new therapy is initiated).
8. All patients will be followed for 5 years post-randomization. When the patient is in follow up, scans should be performed every 3 months (+/- 14 days) for the first two years after randomization, and every 6 months (+/- 28 days) for years 3-5.
9. Telemedicine assessments are allowed except during screening for eligibility purposes. If a physical exam cannot be completed via telemedicine, this must be documented in the patient record and is considered a minor deviation. Telemedicine may NOT be used for more than two visits in succession without an in-person visit. Visits at which study-required blood draws or scans are required, must be performed in-person. When a visit is completed via telemedicine, the site must still arrange for protocol-required laboratory tests to be performed.
10. Post-RT chemotherapy should be started 2-4 weeks after the completion of the consolidative radiotherapy to allow for adequate recovery from toxicities.
11. Omit Day 15 timepoints for regimens with 14-day cycles.

7.2 Therapeutic Parameters and Study Calendar: 21 Day Cycles

Treatment days may be delayed up to 3 days to account for logistical issues, such as scheduling and travel difficulties, weather, holidays. Local standard practices should be applied when these scheduling changes are made.

	Prior to Randomization	End of XRT	Every Chemo Cycle (post-RT)[10]	End of Treatment[9]	Follow-Up[8]
			D1		
Medical History, Baseline Assessment, Height	X				
Weight, Vitals[1]	X		X	X	
Physical Examination, ECOG Performance Status	X		X		
CBC with Differential[2]			X	X	
Serum Comprehensive Panel[3]			X	X	
Adverse Event Assessment		X	X	X	
Tumor PDL1 CPS					
Pregnancy Test (if applicable)[4]	X				
Imaging[5]	X		X[6]		X
Radiation Oncology Evaluation[6]	X[7]				

1. Vitals will include temperature, heart rate, respiratory rate and blood pressure.
2. CBC and platelet count (which includes WBC, ANC, platelets, Hgb and Hct) required for protocol therapy must be done < 72 hours prior to each treatment cycle.
3. CMP to include sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, liver function tests (AST, ALT, total bilirubin, alkaline phosphatase) and albumin. CMP must be done <72 hours prior to each treatment cycle. For patients who are treated with immunotherapy in addition to chemotherapy, TSH should be checked on day 1 every 3 cycles (about every 9 weeks). Free T4 should only be checked if TSH is abnormal. TSH and free T4 results are not required prior to dosing.
4. All patients of childbearing potential must have a negative [blood test or urine test] within 14 days prior to randomization to rule out pregnancy.
5. During treatment, restaging CT or MRI scans (CT or MRI chest and contrast enhanced CT or MRI abdomen and pelvis should be performed every 3 months (+/- 14 days) after randomization.
6. Radiation oncologist consultation will be required prior to registration. Radiation Oncologist evaluation may be performed by telemedicine if needed. If radiation is interrupted for 7 days or less after initiation due to logistical reasons, patient may continue on study as prior, record as minor deviation. XRT interruptions > 7 days must be reviewed with study chair and statistician.
7. Cycle 1 Day 1 assessments do not have to be repeated if done within 7 days of treatment initiation.

8. All patients will be followed for 5 years post-randomization. Follow up scans should be performed every 3 months (+/- 14 days) for the first two years after randomization, and every 6 months (+/- 28 days) for years 3-5.
9. Telemedicine assessments are allowed with the exception of screening visit for eligibility purposes. If a physical exam cannot be completed via telemedicine, this must be documented in the patient record and is considered a minor deviation. Telemedicine may NOT be used for more than two visits in succession without an in-person visit. Visits at which study-required blood draws or scans are required, must be performed in-person. When a visit is completed via telemedicine, the site must still arrange for protocol-required laboratory tests to be performed.
10. Post-RT chemotherapy should be started 2-4 weeks after the completion of the consolidative radiotherapy to allow for adequate recovery from toxicities.

8. Drug Formulation and Procurement

All agents utilized in this study will be obtained commercially. Please refer to the package insert or institutional preparation guidelines for additional information for each agent. All dose modifications and supportive care medications will be used based on local guidelines and standard of care practices (SOP).

8.1 5-Fluorouracil (5-FU) (NSC #19893)

8.1.1 Classification

Antimetabolite

8.1.2 Mode of Action

Fluorouracil is a nucleoside metabolic inhibitor that interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA); these affect rapidly growing cells and may lead to cell death. Fluorouracil is converted to three main active metabolites: 5-fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP), 5-fluorouridine-5′-triphosphate (FUTP) and 5-fluoro-2′-deoxyuridine-5′-triphosphate (FdUTP). These metabolites have several effects including the inhibition of thymidylate synthase by FdUMP, incorporation of FUTP into RNA and incorporation of FdUTP into DNA.

8.1.3 Storage and Stability

Although 5-FU solution may discolor slightly during storage, the potency and safety are not adversely affected. Store at room temperature (68-77°F). Protect from light. If a precipitate occurs due to exposure to low temperatures, resolubilize by heating to 140°F with vigorous shaking; allow to cool to body temperature before using

8.1.4 Availability

5-FU is available commercially.

8.1.5 Dose Specifics

FOLFOX, FOLFIRI, FLOT, CF: All dosing and schedules will follow institution SOP for each specific regimen. Administration of 5-FU bolus, and/or continuous infusion therapy should follow local institutional standards.

8.1.6 Dose Formulation

5-FU is available in various sizes and dosage forms. Any FDA approved dosage form may be used for this study.

8.1.7 Route of Administration

5-FU should be only by the intravenous route taking care to avoid extravasation. May be administered by IV push, IV bolus, or continuous infusion. Refer to institutional SOP for infusion times of specific preparations.

8.1.8 Side Effects

The spectrum of toxicity includes stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea with cramping and/or bleeding, anorexia, nausea and emesis are commonly seen during therapy. Leukopenia usually follows every course of adequate therapy with fluorouracil. The lowest white blood cell counts are commonly observed between the 9th and 14th days after the first dose, although uncommonly the maximal depression may be delayed for as long as 20 days. By the 30th day the count has usually returned to the normal range. Alopecia and dermatitis may be seen. The dermatitis most often seen is a pruritic maculopapular rash usually appearing on the extremities and less frequently on the trunk. Other side effects include myocardial ischemia, angina, lethargy, malaise, headache, allergic reactions, disorientation, confusion, euphoria, dizziness, uncoordination, visual changes, photosensitivity (eyes and skin), nail changes including loss of nails, skin thickening, cracking, dryness or sloughing, vein pigmentation, biliary sclerosis, or acaculous cholecystitis.

Refer to Package Insert for a complete list of Adverse Events.

8.1.9 References

Fluorouracil (5-FU) package insert.

8.2 Capecitabine (NSC #712807)

8.2.1 Other Names

Xeloda

8.2.2 Classification

Cytotoxic chemotherapy, anti-metabolite

8.2.3 Mode of Action

Capecitabine is a fluoropyrimidine carbamate that is an orally active prodrug of 5-FU. Normal cells, as well as tumor cells, metabolize 5-FU into 5-fluoro-2'deoxyuridinemonophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). Both are metabolites that cause cell injury by two different mechanisms. FdUMP and the folate factor, N5-10-methylenetetrahydrofolate, bine to tyhmidylate synthase (TS) to inhibit the formation of thymidylate. This deficiency of thymidylate causes cell cycle division to halt. This is because thymidylate is necessary for thymidine triphosphate production, which is essential for DNA synthesis. FUTP works by incorporating itself into transcription in place of uridine triphosphate therefore interfering with RNA transcription and protein synthesis.

8.2.4 Storage and Stability

Capecitabine is stored at 25 degrees C, with excursions permitted to 15 to 30 degrees C.

8.2.5 Availability

Capecitabine is available commercially.

8.2.6 Dose Specifics

CAPOX: Dosing is at the discretion of the investigator and will follow institutional standards of practice.

The investigator's chosen dose in mg/m² will be calculated by the patient's body surface area (BSA) and will be rounded to the nearest dose using 150 mg and 500 mg available strengths.

8.2.7 Preparation

Commercially available as 500 mg and 150 mg tablets

8.2.8 Route of Administration

Capecitabine needs to be taken orally within 30 minutes after a meal

8.2.9 Side Effects

Hematologic: anemia, neutropenia, thrombocytopenia

Cardiovascular: edema, venous thrombosis

Constitutional: fatigue, pyrexia, swelling in hands, feet or abdomen, pain, chest pain

Dermatologic: hand-foot syndrome, dermatitis, skin discoloration, alopecia

Gastrointestinal: diarrhea, nausea, vomiting, stomatitis, abdominal pain, gastrointestinal motility disorder, constipation, taste disturbance, upper GI inflammatory disorders, gastrointestinal hemorrhage, ileus

Hepatic: hyperbilirubinemia

Infections: bacterial or viral

Metabolic: appetite decreased, dehydration

Musculoskeletal: back pain, arthralgia

Neurologic: peripheral sensory neuropathy, headache, dizziness, insomnia

Ocular: eye irritation, visual abnormalities

Psychiatric: mood alteration, depression

Pulmonary: dyspnea, cough, pharyngeal disorder, epistaxis, sore throat

Vascular: venous thrombosis

Refer to Package Insert for a complete list of Adverse Events.

8.2.10 Nursing/Patient Implications

- Monitor CBC and platelet count prior to drug administration.
- Symptom management of expected nausea, vomiting, diarrhea, and hand-foot skin syndrome
- Administer doses at least 12 hours (+/- 2 hours) apart.
- Capecitabine tablets should be swallowed with water within 30 minutes after a meal.

- Capecitabine tablets may not be crushed.

8.2.11 References

Capecitabine package insert

8.3 Oxaliplatin (NSC #266046)

8.3.1 Other Names

Eloxatin®, trans-l-diaminocyclohexane oxalatoplatinum, cis-[oxalato(trans-l-1,2-diaminocyclohexane)platinum(II)]

8.3.2 Classification

Alkylating agent

8.3.3 Mode of Action

The mechanism of action of oxaliplatin is similar to cisplatin. The main site of action is intrastrand cross-linking, therefore inhibiting DNA replication and transcription.

8.3.4 Storage and Stability

Please refer to the package insert.

8.3.5 Availability

Oxaliplatin is available commercially.

8.3.6 Dose Specifics

All dosing will follow institutional standards. The typical starting doses/schedule are below:

FOLFOX: Oxaliplatin 85 mg/m^2 IV every 14 days

CAPOX: Oxaliplatin 130 mg/m^2 IV every 21 days

FLOT: Oxaliplatin 85 mg/m^2 IV every 21 days

Doses may be omitted or reduced for cumulative toxicities at the discretion of the investigator.

8.3.7 Preparation

Please refer to the package insert. Dilution with D5W (250 or 500 mL) is required prior to administration.

8.3.8 Route of Administration

Intravenous over 2 hours or 1 mg/m^2/min per SOP. The infusion time may be extended up to 6 hours for acute toxicity/hypersensitivity.

When used in combination with a fluoropyrimidine (eg, 5-FU), infuse oxaliplatin first.

May infuse concomitantly with leucovorin through a Y-Site per institutional SOP.

8.3.9 Incompatibilities

Oxaliplatin may degrade in the presence of aluminum-containing needles or IV infusion sets or alkaline medications (such as

fluorouracil). Oxaliplatin is incompatible with sodium chloride solutions. Flush infusion line with D5W prior to administration of any concomitant medication.

8.3.10 Side Effects

The most commonly observed oxaliplatin toxicities include neurotoxicity, GI toxicity, and myelosuppression.

Acute pharyngolaryngeal dysesthesia is reported to occur in 1-2% of patients. This syndrome is characterized by a subjective sensation of difficulty breathing or swallowing without laryngospasm or bronchospasm or objective evidence of hypoxia. Avoidance of cold drinks, food and air is suggested in order to minimize pharyngolaryngeal dysesthesia. Antianxiety agents (e.g., lorazepam) may be used to treat pharyngolaryngeal dysesthesias once oxygen saturation has been documented to be normal.

Peripheral neuropathy persisting > 14 days is characterized by paresthesias, dysesthesias, and hypothesia. Abnormalities in proprioception may also be seen. Symptoms of persistent neuropathy may improve upon discontinuation of oxaliplatin.

Gastrointestinal toxicities include nausea, vomiting (oxaliplatin is considered to be moderately emetogenic) and diarrhea.

Neutropenia is reported in 73% of patients receiving oxaliplatin with 5-FU and leucovorin (44% grade 3 or 4). Grade 3 or 4 thrombocytopenia is reported to occur in 4% of patients receiving the combination.

Allergic reactions, similar to those seen with other platinum compounds, have also been observed in patients treated with oxaliplatin. Reactions range from rash to anaphylaxis.

Rarely, oxaliplatin has been associated with pulmonary fibrosis, which may be fatal. Oxaliplatin should be discontinued in the presence of unexplained pulmonary symptoms (e.g. nonproductive cough, dysphagia) or pulmonary infiltrates until interstitial lung disease or pulmonary fibrosis have been ruled out.

Veno-occlusive disease (VOD) of the liver is a rare complication associated with oxaliplatin and 5-FU. Clinical manifestations of VOD include hepatomegaly, ascites, and jaundice. Histologically, VOD is characterized by diffuse damage in the centrilobular zone of the liver. Sequelae of VOD include hepatomegaly, splenomegaly, portal hypertension, and esophageal varices.

For more information on toxicities associated with oxaliplatin, please see the package insert.

8.3.11 Nursing Implications

- Do not use needles or intravenous infusion sets containing aluminum for the administration of oxaliplatin.
- Monitor for neurologic symptoms.
- Administer antiemetics as indicated by the investigator.

- Monitor complete blood cell and platelet count prior to each administration.
- Monitor for hypersensitivity reaction.

8.3.12 References

Investigator's Brochure: Oxaliplatin. Sanofi Winthrop, Nov. 1996.

Eloxatin® (oxaliplatin injection) Prescribing Information. Sanofi-Aventis, May 2006.3. Neurologic: Peripheral neuropathy (related to cumulative dose, dose-limiting toxicity), laryngopharyngeal dysesthesia (decreased incidence and severity with prolonged infusion duration).

8.4 Leucovorin (NSC #3590)

8.4.1 Other Names

Leucovorin Calcium, Wellcovorin, citrovorum factor, folinic acid, 5-formyl tetrahydrofolate, LV, LCV.

8.4.2 Classification

Tetrahydrofolic acid derivative.

8.4.3 Mode of Action

Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin.

Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase.

8.4.4 Storage and Stability

Store at room temperature (20º-25ºC, 68º-77ºF). Protect from light.

8.4.5 Availability

Leucovorin is available commercially.

8.4.6 Dose Specifics

FOLFOX, FOLFIRI, FLOT: Doses will follow institutional guidelines (SOP). The typical starting dose is below:

Leucovorin 200-400 mg/m^2 IV

8.4.7 Route of Administration

Intravenous infusion over 15-120 minutes, depending on regimen.

May infuse concurrently through a Y-Site with oxaliplatin or irinotecan per SOP.

8.4.8 Side Effects

- Hematologic: Thrombocytosis
- Dermatologic: Skin rash
- Gastrointestinal: Nausea, upset stomach, diarrhea
- Allergic: Skin rash, hives, pruritus
- Pulmonary: Wheezing (possibly allergic in origin)
- Other: Headache; may potentiate the toxic effects of fluoropyrimidine therapy, resulting in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects

Refer to Package Insert for a complete list of Adverse Events.

8.4.9 References

FDA approved package insert

8.5 Irinotecan NSC #616348)

Please refer to the package insert or institutional preparation guidelines for additional information.

8.5.1 Other Names/Classification

Camptosar

8.5.2 Classification

Topoisomerase I inhibitor

8.5.3 Mode of Action

Causes single stranded DNA breakage by inhibition of the intranuclear enzyme toposisomerase-1. Leads to apoptotic cell death via defects in DNA repair.

8.5.4 Storage and Stability

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. Keep the vial in the carton until the time of use.

Inspect the vial for damage and visible signs of leaks before removing from the carton. If damaged, incinerate the unopened package.

8.5.5 Dose Specifics

FOLFIRI: dosing follows standard institutional practice (SOP). The usual starting dose is below:

Irinotecan 150-180 mg/m^2 IV every 14 days.

8.5.6 Preparation

Dilute in D5W (preferred) or NS to a final concentration of 0.12 to 2.8 mg/mL per SOP.

8.5.7 Route of Administration

Infuse over 60-90 minutes per SOP.

8.5.8 Incompatibilities

Do not mix with any other compound.

8.5.9 Availability

This drug is commercially available.

8.5.10 Side Effects

- Hematologic: Leukopenia, neutropenia, anemia, thrombocytopenia, neutropenic fever, hemorrhage
- Gastrointestinal: Diarrhea (early and late – see administration above), nausea and vomiting, anorexia, abdominal pain, flatulence, stomatitis, dyspepsia, dehydration
- Hepatic: Elevated transaminases.
- Cardiovascular: Vasodilation, hypotension, myocardial infarction, stroke, edema
- CNS: Dizziness, confusion, somnolence, insomnia, back pain
- Respiratory: Pulmonary embolism,
- Dermatologic: Alopecia, rash
- Other: Asthenia, thrombophlebitis, sweating, weight loss, chills

8.5.11 Nursing/Patient Implications

Premedicate with antiemetics in anticipation of mild to moderate nausea and vomiting. When used in combination with 5-fluroruracil and leucovorin the nausea and vomiting will likely be worse.

Fatalities have been reported with thromboembolic events and neutropenic sepsis in patients receiving 5-fluorouracil, leucovorin and irinotecan.

Monitor for diarrhea. Diarrhea occurring within one hour of irinotecan has been treated with atropine 0.25 to 1mg IV or SC. Loperamide has been effective in treating later diarrhea and the patient should be instructed on its immediate use at the first loose stool following the irinotecan.

Monitor CBC, platelets, and liver function tests.

Dose modifications per the protocol or the package insert should be followed for hematologic and gastrointestinal toxicity.

Advise patient of likely post-treatment neutropenia and instruct in appropriate neutropenic precautions.

8.6 Cisplatin (NSC #119875)

8.6.1 Other Names

Cis-diaminedichloroplatinum Cis-diaminedichloroplatinum (II), diaminedichloroplatinum, cis-platinum, platinum, Platinol, Platinol-AQ, DDP, CDDP, DACP, NSC 119875 R R

8.6.2 Classification

Antineoplastic Alkylating Agent, Platinum Analog

8.6.3 Mode of Action

Cisplatin inhibits DNA synthesis by the formation of DNA cross-links; denatures the double helix; covalently binds to DNA bases and disrupts DNA function; may also bind to proteins; the cis-isomer is 14 times more cytotoxic than the trans-isomer; both forms cross-link DNA but cis-platinum is less easily recognized by cell enzymes and, therefore, not repaired. Cisplatin can also bind two adjacent guanines on the same strand of DNA producing intrastrand cross-linking and breakage.

8.6.4 Storage and Stability

Refer to specific product labeling:

Lyophilized powder: Store intact vials at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Store in original carton prior to reconstitution to protect from light. The reconstituted solution is stable for 20 hours at 20°C to 25°C (68°F to 77°F); do not refrigerate. Solution removed from amber vial should be protected from light if not used within 6 hours.

Solution: Store intact vials at 20°C to 25°C (68°F to 77°F). Protect from light. Do not refrigerate solution (precipitate may form). According to the manufacturer, after initial entry into the vial, solution is stable for 28 days protected from light or for at least 7 days under fluorescent room light at room temperature.

When diluted for administration in D51/4NS, D51/2NS, D5NS, 1/4NS, 1/3NS, 1/2NS, or NS, cisplatin stability is dependent on the chloride ion concentration.

8.6.5 Dose Specifics

CF: Cisplatin dosing follows standard institutional practice (SOP)

8.6.6 Preparation

Refer to package insert or institutional standard of practice (SOP). The desired dose of cisplatin is diluted with 250-1000 ml of saline solution. Varying concentrations of 0.225-5% sodium chloride may be used.

8.6.7 Route of Administration

Intravenous Infusion over 60 minutes (+40 minutes to allow for SOP)

May administer 1 mg/min to meet institution SOP.

Hydration (+/- electrolytes and/or mannitol) will be given pre/post cisplatin per institution SOP.

8.6.8 Incompatibilities

Do not use needles or IV administration sets that contain aluminum for cisplatin preparation or administration; aluminum may react with cisplatin resulting in precipitate formation and loss of potency.

8.6.9 Availability

Commercially available

8.6.10 Side Effects

1. Renal: A dose-related, cumulative renal tubular injury can occur; adequate hydration and diuresis usually minimize the risk. Saltwasting nephropathy and/or orthostatic hypotension with hyporeninemic hypoaldosteronism can occur in up to 10% of patients.
2. Neurologic: A dose-related ototoxicity, manifested by high frequency hearing loss and tinnitus, occurs in about 30% of patients. Paresthesias, decreased vibratory, position, and touch sensations are less common; particularly at cumulative doses <400 mg/m^2
3. Hematologic: Mild leukopenia and thrombocytopenia occur in 25-30% of patients, but are rarely dose-limiting; anemia is less common. A potentially fatal hemolytic uremic syndrome has been reported.
4. Gastrointestinal: Severe, dose-limiting nausea and vomiting occur in almost 100% of patients unless adequate antiemetic prophylaxis is given. Even with successful prophylaxis of acute nausea a delayed (72-96 hour) reaction, requiring additional therapy may occur. Anorexia and taste changes may also occur.
5. Hypersensitivity: Allergic reactions are reported in up to 20% of patients Symptoms include: rash, facial edema, wheezing, hypotension, and tachycardia. Severe anaphylaxis is rare.
6. Other: Electrolyte wasting (magnesium, potassium and sodium), papilledema, optic neuritis, retrobulbar neuritis are reported.

8.6.11 Nursing/Patient Care Implications

- Monitor CBC w/ differential and CMP with electrolytes and SCr prior to each dose.
- Assess peripheral neuropathy and auditory status prior to each dose.
- Assess urine output per institution SOP prior to each dose.
- Hydration (+/- electrolytes and/or diuretics) will be given pre and/or post cisplatin per institution SOP.
- Premedication (recommended*):
  - NK-1 antagonist (aprepitant, fosaprepitant or equivalent)
  - 5HT3 antagonist (palonosetron, ondansetron or equivalent)
  - Dexamethasone
  - +/- olanzapine, +/- prochlorperazine
- *Refer to NCCN Guidelines for Supportive Care “Highly Emetogenic” for a list of acceptable agents. Institution SOP antiemetics for high dose cisplatin are allowed. Patients should also be prescribed antiemetics as needed (PRN) for breakthrough nausea to be available at home. Infusion site must be closely monitored to reduce potential for extravasation.
- Monitor potassium and magnesium each cycle and replete per SOP.

- Reproductive: May cause fetal harm. Nurses must use appropriate precautions when administering.

8.6.12 References

Cisplatin package insert. Lexicomp®

8.7 Docetaxel (NSC #628503)

8.7.1 Other Names

Taxotere, RP-56976

8.7.2 Classification

Antineoplastic agent, Antimicrotubular agent. Taxane derivative.

8.7.3 Mode of Action

Docetaxel promotes the assembly of microtubules from tubulin dimers and inhibits the depolymerization of tubulin which stabilizes microtubules in the cell. This results in inhibition of DNA, RNA, and protein synthesis. Most activity occurs during the M phase of the cell cycle.

8.7.4 Description

Docetaxel, USP is a white to almost-white powder with molecular formula of C43H53NO14, and a molecular weight of 807.88. It is highly lipophilic and practically insoluble in water.

8.7.5 Storage and Stability

Storage and stability may vary by manufacturer, refer to specific prescribing information. Follow USP 797 recommendations for beyond use dates based on the level of risk for preparation.

8.7.6 Availability

Docetaxel is commercially available.

8.7.7 Dose Specifics

FLOT: dosing follows standard institutional practice (SOP). The usual starting dose is:

Docetaxel 50 mg/m^2 IV every 21 days

8.7.8 Preparation

Preparation instructions may vary by manufacturer, refer to specific prescribing information. Must be further diluted in 100- 500 mL of NS or D5W for infusion in a non-DEHP container to a final concentration of 0.3 to 0.74 mg/mL. Gently rotate and invert manually to mix thoroughly; avoid shaking or vigorous agitation.

8.7.9 Route of Administration

Infuse over 1 hour through non-sorbing polyethylene lined (non-DEHP) tubing.

8.7.10 Drug Interactions

Major substrate of CYP3A4.

Do not administer live vaccines during therapy.

Refer to package insert for a comprehensive list of drug interactions.

8.7.11 Side Effects

Anemia, neutropenia, alopecia, fatigue, and fluid retention are common. Hypersensitivity (mild to severe) may occur.

Refer to the package insert for a comprehensive list of side effects.

8.7.12 Nursing and Patient Care Implications

- Check CBC with differential and CMP prior to each dose
- Premedication with corticosteroid, H1/H2 histamine blockers are recommended prior to each dose.
- Monitor patient for infusion reactions per SOP. Emergency medications should be readily available.
- May cause fetal harm- nurses should use precautions when handling.
- Patients who could become pregnant should use effective contraceptive measures before beginning treatment, during therapy, and for 2 months after the last docetaxel dose. Patients with partners who could become pregnant should use effective contraceptives during therapy and for 4 months after the last docetaxel dose.
- Patients should not breastfeed during treatment and for at least 1 week after the last docetaxel dose.

8.8 Pembrolizumab NSC #776864)

8.8.1 Other Names

MK-3475, SCH 900475, KEYTRUDA®

8.8.2 Classification

Anti-PD-1 MAb

8.8.3 Mode of Action

The programmed cell death 1 (PD-1) receptor is an inhibitory receptor expressed by T cells. When bound to either of its ligands, PD-L1 or PD-L2, activated PD-1 negatively regulates T-cell activation and effector function. The pathway may be engaged by tumor cells to suppress immune control. Pembrolizumab (MK-3475) blocks the negative immune regulatory signaling by binding to the PD-1 receptor, inhibiting the interaction between PD-1 and its ligands.

8.8.4 Description

Pembrolizumab is a humanized MAb of the IgG4/kappa isotype.

8.8.5 How Supplied

Pembrolizumab is commercially supplied.

8.8.6 Storage and Stability

Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light by storing in the original box.

Stability: Refer to the package label for expiration.

8.8.7 Dose Specifics

Pembrolizumab 200 mg IV every 3 weeks

OR

Pembrolizumab 400 mg IV every 6 weeks

All dosing and schedules of pembrolizumab will follow institutional guidelines (SOP). For a list of allowable regimens with additional pembrolizumab, refer to table in Section 5.1.

8.8.8 Preparation

Pembrolizumab solution must be diluted prior to administration. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles is observed. To prepare the infusion solution add the dose volume of pembrolizumab to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently invert the bag 10-15 times to mix the solution. The final concentration must be between 1 mg/mL to 10 mg/mL.

8.8.9 Route of Administration

IV: Infuse over 30 minutes through a 0.2 to 5 micron sterile, nonpyrogenic, low-protein binding inline or add-on filter. Do not infuse other medications through the same infusion line.

8.8.10 Drug Interactions

Corticosteroids (systemic): May diminish the therapeutic effect of Immune Checkpoint Inhibitors.

Management: Daily doses of a prednisone-equivalent of 10 mg or more per day is prohibited unless it is being used to treat an immune related adverse event (irAE). Use of corticosteroids to treat immune related adverse events is still recommended.

8.8.11 Side Effects

See Section 5.3.2 for the Comprehensive Adverse Event and Potential Risks (CAEPR) list.

8.8.12 Nursing/Patient Care Implications

Monitor patients closely for immune-mediated adverse reactions including pneumonitis, nephritis, hypo or hyperthyroidism, colitis, hepatitis, infusion reactions, and hypophysitis; instruct patients to report any of these signs or symptoms.

Refer to the protocol for information on evaluation and management of potential immune-related adverse events. (Section 5.4.2)

Patients should not become pregnant or father a child by using highly effective birth control during treatment and for 5 months after their last dose.

Patients should not breastfeed during treatment and for 5 months after their last dose.

8.9 Nivolumab (NSC #748726)

8.9.1 Other Names

Opdivo, BMS-936558; MDX1106

8.9.2 Classification

Anti-PD-1MAb

8.9.3 Mode of Action

Nivolumab targets the programmed death-1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

8.9.4 Description

Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5).

8.9.5 Storage and Stability

Nivolumab should be stored under refrigeration at 2°C to 8°C (36°F to 46°F). It should be protected from light by storing in the original package until time of use. Do not freeze or shake.

8.9.6 Availability

Nivolumab is available commercially.

8.9.7 Dose Specifics

Nivolumab 240 mg IV every 2 weeks

OR

Nivolumab 480 mg IV every 4 weeks

OR

Nivolumab 360mg IV every 3 weeks

See Section 5.1 for a table of allowable regimens using nivolumab. Dosing and schedule will follow institutional standard of practice (SOP) and may be tailored to the specific regimen.

8.9.8 Preparation

Withdraw the required nivolumab volume and transfer into an IV container. Dilute with either NS or D5W to a final concentration of 1 to 10 mg/mL; the total volume of infusion must not exceed 160 mL for patients ≥40 kg (or 4 mL/kg for patients <40 kg). Mix by gentle inversion; do not shake.

8.9.9 Route of Administration

Administer as an IV infusion over 30 minutes. Refer to protocol for infusion rates in off-label dosing. Infuse through a line with a sterile, nonpyrogenic, low protein binding 0.2 to 1.2 micrometer in-line filter. If administering as part of a combination regimen, use separate infusion bags and filters for each infusion. Do not administer other medications through the same IV line. Flush IV line at the end of the infusion.

8.9.10 Method of Administration

Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding in-line filter.

8.9.11 Potential Drug Interactions

Corticosteroids (systemic): May diminish the therapeutic effect of Immune Checkpoint Inhibitors.

Management: Daily doses of a prednisone-equivalent of 10 mg or more per day is prohibited unless being used in the setting of treating an irAE. Use of corticosteroids to treat immune related adverse events is still recommended.

8.9.12 Side Effects

Refer to Comprehensive Adverse Events and Potential Risks list (CAEPR) in Section 5.3.

8.9.13 Patient Implications

Monitor patients closely for immune-mediated adverse reactions including pneumonitis, nephritis, hypo or hyperthyroidism, colitis, hepatitis, infusion reactions, and hypophysitis; instruct patients to report any of these signs or symptoms.

Refer to the protocol for information on evaluation and management of potential immune-related adverse events.

Patients should not become pregnant or father a child by using highly effective birth control during treatment and for 5 months after their last dose.

Patients should not breastfeed during treatment and for 5 months after their last dose.

8.9.14 References

Product Information: OPDIVO (nivolumab) injection, for intravenous use. Bristol-Myers Squibb Company, Princeton, NJ. FDA-label March 2015.

9. Statistical Considerations

This is a randomized phase III study evaluating the role of consolidative XRT in patients with oligometastatic EGA (at most 5 metastatic sites at the time of diagnosis of advanced disease, as detailed in the eligibility section of the protocol). Patients with stable disease after 3-6 months of first-line systemic therapy will be randomized to continuation of systemic therapy versus consolidative XRT to all sites of disease plus continuation of systemic therapy.

We estimate that patients in the control arm (continuation of systemic therapy without consolidative XRT) will have overall survival (OS) of 12 months from the time of randomization. We hypothesize that consolidative XRT will result in improvement in OS from 12 to 18.7 months (HR=0.64). This trial will need to randomize 216 patients in a 2:1 ratio to detect this difference with 85% power using a stratified log rank test with 0.05 one-sided type I error. Interim analyses will follow the ECOG-ACRIN standard approach with a group sequential design and efficacy and futility analyses starting at 30% information time and following every 6 months coinciding with ECOG-ACRIN DSMC meetings. A truncated O'Brien-Fleming boundary function will be used to control type I error for the interim analyses. Total information is at 165 deaths, projected to occur at 54 months post study start, with 36 months of enrollment (depending upon the actual accrual rate to the target population) and 18 months of follow-up. The following table provides the expected interim analyses, corresponding information time and O'Brien-Fleming boundary values to maintain the stated power and one-sided type I error.

Analysis	Information Time	O'Brien-Fleming Boundary (Z)
Interim 1	0.30	3.0902
Interim 2	0.45	2.7312
Interim 3	0.62	2.2793
Interim 4	0.77	2.0185
Interim 5	0.89	1.8857
Final	1.00	1.7882

The study will enroll 216 patients. It is expected that 6 patients per month will accrue to the target patient population.

Toxicity will be evaluated in all treated patients. Interim analyses of toxicity will be performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 2. With 72 and 144 patients in the control and experimental arms, respectively, the maximum width of any binomial 95% confidence interval will be no wider than 24.0% or 16.8%, respectively, and there is at least 80% chance of observing one or more rare (2.5% or 1.2% true probability, respectively) events in either arm.

Stratification at Randomization

Stratification factors include:

- Number of metastatic sites: 1-2 vs. 3 or more at the time of diagnosis of advanced disease.
- Prior use of anti-PD1 agents (IO) during first-line treatment of advanced disease vs. no prior IO during first-line treatment of advanced disease

- Triplet vs. doublet first-line chemotherapy backbone

9.1 Gender and Ethnicity

Based on previous data from E2208 the anticipated accrual in subgroups defined by gender and race is:

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	2	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	5	2	0	0	7
White	39	166	0	2	207
More Than One Race	0	0	0	0	0
Total	44	170	0	2	216

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

10. Electronic Data Capture

Please refer to the **EA2183** Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

NOTE: This study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

11. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

12. References

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A Phase III Study of Consolidative Radiotherapy in Patients with Oligometastatic Esophageal and Gastric Adenocarcinoma

Appendix I

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

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Appendix II

Patient Pill Calendar

Pill Calendar Directions

1. Take your scheduled doses of capecitabine at the same time each day.
2. If a dose is missed or vomited, continue with the next scheduled dose; do not administer an additional dose.
3. Please bring the pill calendar to your next clinic visit.
4. When taking capecitabine:
    - Capecitabine pills are to be swallowed whole with water within 30 minutes after a meal
    - Do not crush or cut Capecitabine pills
    - Use the pill calendar note space to record any side effects, new symptoms, or anything you'd like to talk to your doctor about.

Staff Contact Name and Phone Number : _____

Patient Pill Calendar

This is a calendar on which you are to record the time and number of capecitabine you take each day. You should take your scheduled dose of each pill. **Note the times and the number of pills that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused pills and your completed pill calendar to your doctor's visits.

You should take ____ pills each day in the AM, and ____ pills each day in the PM

DAY	Date Month Day Year			Time pills taken AM	 PM	Number of pills taken AM	 PM	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
1								
2								
3								
4								
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A Phase III Study of Consolidative Radiotherapy in Patients with Oligometastatic Esophageal and Gastric Adenocarcinoma

Appendix III

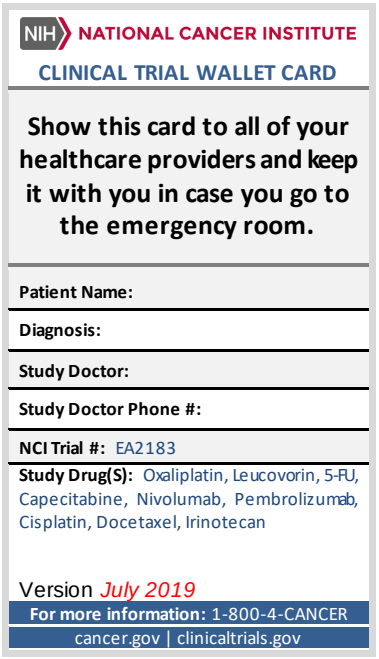
ECOG Performance Status

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

A Phase III Study of Consolidative Radiotherapy in Patients with Oligometastatic Esophageal and Gastric Adenocarcinoma

Appendix IV

Patient Clinical Trial Wallet Card



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: EA2183

Study Drug(S): Oxaliplatin, Leucovorin, 5-FU, Capecitabine, Nivolumab, Pembrolizumab, Cisplatin, Docetaxel, Irinotecan

Version *July 2019*

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Appendix V

Formula to Estimate Renal Function Using Serum Creatinine

Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dL)} \{\times 0.85\ for\ female\ patients\}$$

References:

Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. Nephron. 16:31-41.