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CCTG: IND.235

HEALTH CANADA SUBMISSION

CANCER RESEARCH INSTITUTE (CRI) & CANADIAN CANCER TRIALS GROUP (CCTG)

A PHASE II OPEN LABEL, RANDOMIZED NON-COMPARATIVE TRIAL OF NIVOLUMAB ALONE OR IN COMBINATION WITH IPILIMUMAB FOR THE TREATMENT OF PATIENTS WITH ADVANCED HYPERMUTATED SOLID TUMORS DETECTED BY A BLOOD BASED ASSAY

Nivolumab Ipilimumab in Patients with HyperMutated Cancers Detected in BLood (NIMBLe)

CRI-CCTG Protocol Number: **0001**
CCTG Protocol Number: IND.235

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(For contact information of study personnel see Final Page.)

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STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

I understand that this protocol contains information that is confidential and proprietary to Cancer Research Institute, Bristol Myers Squibb, and PGDx.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, in accordance with any modifications that may occur over the duration of the study, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by CCTG to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB/IRB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of the Cancer Research Institute, Bristol Myers Squibb, PDGx and CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to the Cancer Research Institute, Bristol Myers Squibb, PDGx and CCTG of any such disclosure.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to CCTG. The study may be terminated at any time by CCTG or the Cancer Research Institute, Bristol Myers Squibb, and PDGx with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to the Cancer Research Institute, Bristol Myers Squibb, PDGx and CCTG and must be kept in confidence in the same manner as the contents of this protocol.

_____ _____

Qualified Investigator
(printed name and signature)

Date

Protocol Number: CRI-CCTG-0001

CENTER: _____

TREATMENT SCHEMA

This is an international multi-center, open-label, randomized phase II non-comparative trial of nivolumab alone or in combination with ipilimumab for the treatment of patients with advanced hypermutated solid tumors detected by a blood based assay. The biomarker selection of eligible patients will initially be based on detection of either POLE or POLD1 mutations by cfDNA or tumor testing.

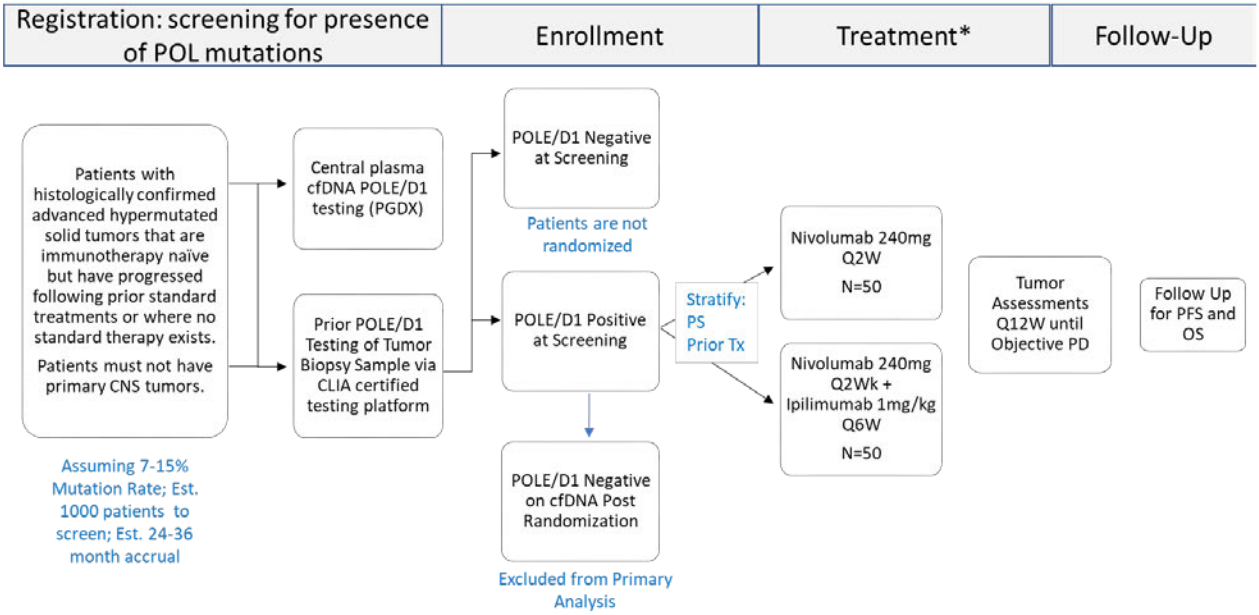
Tumor testing may be conducted in a clinical laboratory as part of standard assessment.

For patients that do not have tumor testing, eligible and consenting patients will undergo screening for POL mutations by testing of cfDNA.

Eligible and consenting patients with POLE or POLD1 mutations will be randomized 1:1 into two arms.

Stratification

- ECOG performance status (0, 1)
- Number of prior treatments (0, 1-2, 3 or more)



1.0 OBJECTIVES

1.1 Primary Objective

To evaluate efficacy as measured by objective response rate by RECIST 1.1 of nivolumab monotherapy and of nivolumab combined with ipilimumab in randomized patients with advanced solid tumors with detectable POLE or POLD1 mutations as determined by plasma cfDNA.

1.2 Secondary Objectives

- To evaluate efficacy as measured by objective response rate of nivolumab monotherapy and of nivolumab combined with ipilimumab in all treated patients with detectable POLE or POLD1 mutations in either plasma cfDNA or tumor tissue.
- To evaluate duration of response of nivolumab monotherapy, and of nivolumab combined with ipilimumab, in those patients with advanced solid tumors with detectable POLE or POLD1 mutations in either plasma cfDNA or tumor tissue.
- To assess the safety and characterize toxicities of nivolumab monotherapy and of nivolumab combined with ipilimumab in all patients.
- To assess the correlation between POLE or POLD1 mutations in tumor and POLE or POLD1 mutations in blood.
- To evaluate response by iRECIST.

1.3 Exploratory Objectives

- To determine Progression Free Survival and Overall Survival of nivolumab monotherapy and of nivolumab combined with ipilimumab in patients with advanced solid tumors with detectable POLE or POLD1 mutations as determined by plasma cfDNA, and in all treated patients (detectable mutations in tissue or plasma cfDNA).
- To determine the correlation between POLE or POLD1 mutations occurring within or outside of the exonuclease domain and tumor mutation load as determined by whole exome and RNA sequencing.
- To determine the correlation between tumor mutation burden assessed in plasma cfDNA and assessed directly in tumor tissue.

2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 DNA Repair Defects and Tumorigenesis

In eukaryotes, DNA integrity is maintained through a diverse array of pathways including base excision repair, mismatch repair, nucleotide excision repair, and double-strand break repair. These robust defense systems play a crucial role in combating the estimated tens of thousands of DNA-damaging events that take place on a daily basis *[Dexheimer 2013]*. Increased mutagenicity due to disruption of these pathways can drive carcinogenesis through the acquisition of multiple oncogenic mutations and loss of tumor suppressor genes. This hypermutated phenotype can be seen in sporadic malignancies as well as a number of hereditary cancer syndromes such as Ataxia-telangiectasia (double-strand break repair), Xeroderma pigmentosum (nucleotide excision repair), and Lynch syndrome (mismatch repair) *[Lange 2011]*.

During DNA replication, in particular, there is an increased risk for base substitution due to replicative errors caused by DNA polymerases, which have error rates of approximately 10^{-5} per base pair per cell division *[Dexheimer 2013]*. Two mechanisms exist to counteract these errors. The first involves real-time proofreading via exonuclease activity present in both DNA polymerase ε, which synthesizes the leading strand and is encoded by POLE, and DNA polymerase δ, which is involved in lagging strand synthesis and encoded by POLD1 *[Albertson 2009]*. Errors that escape such proofreading can be corrected by the second mechanism – the DNA mismatch repair (MMR) pathway. With intact DNA damage repair machinery the spontaneous mutation rate during DNA replication is therefore very low, at less than 10^{-9} per base pair per cell division *[McCulloch 2008]*. However, when these highly conserved systems are disrupted, cells can develop high levels of mutations including deleterious, carcinogenic frameshift and nonsense mutations.

2.2 POLE and POLD1 Mutations in Solid Tumors

While germline mutations of both POLE and POLD1 have been reported in association with microsatellite stable (MSS) colorectal adenomas and carcinomas, as well as endometrial cancers and brain tumors, somatic mutations of these genes can be seen demonstrated in a heterogeneous group of tumors *[Briggs 2013; Palles 2013; Shlien 2015]*. The Cancer Genome Atlas (TCGA) studies of colorectal and endometrial carcinomas identified sporadic POLE mutations in 3% and 7% of these tumors, respectively *[Atlas 2012; Cancer Genome Atlas 2013]*. For the most part these tumors were associated with high rates of tumor mutational burden (TMB) frequently harboring more than 100 mutations per megabase. POLE mutations have also been seen in tumors of the brain, pancreas, ovary, breast, lung, and stomach as well as in uterine carcinosarcomas *[Rayner 2016]*. POLD1 mutations are less prevalent though have been shown to be present in patients with highly mutated non-small cell lung cancer (NSCLC) and brain tumors *[Shlien 2015; Rizvi 2015]*. Combining data from multiple comprehensive genomic profiling studies shows that a wide variety of tumors are affected by these mutations with prevalence rates ranging from 5-10% in an assortment of tumors (Fig 1A and 1B).

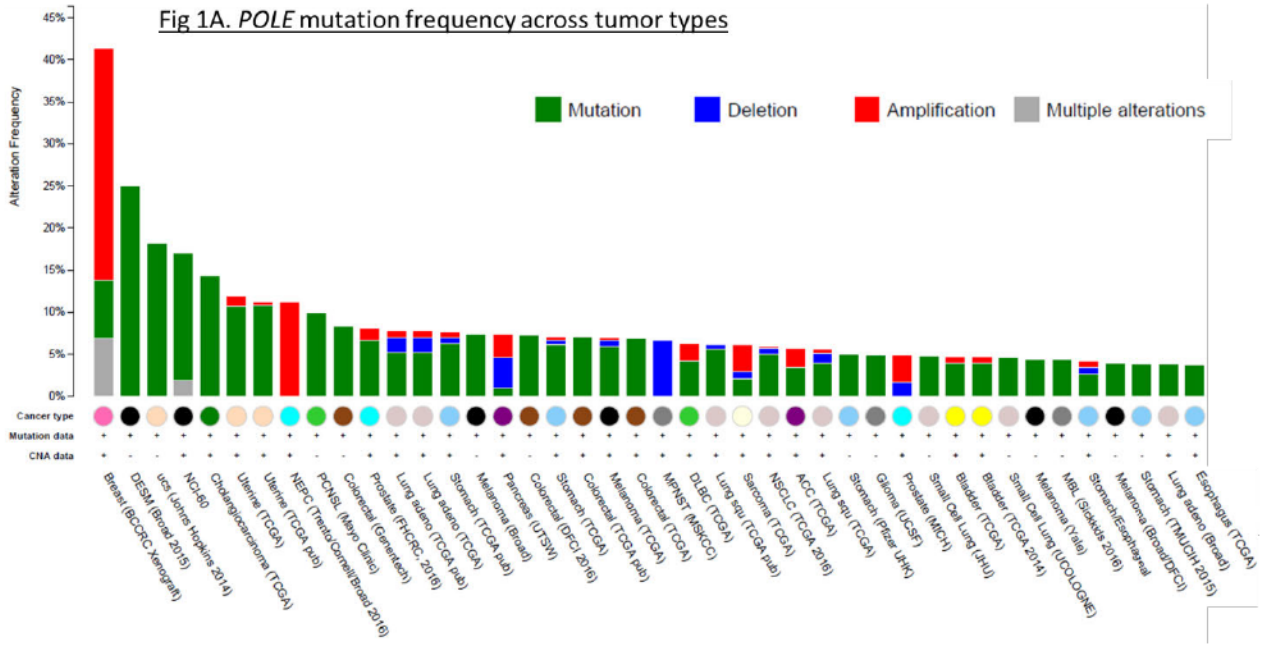


Fig 1A. POLE mutation frequency across tumor types
Mutation
Deletion
Amplification
Multiple alterations
Alteration Frequency
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
Cancer type
Mutation data
CNA data
Breast (BCCRC Xenograft)
DESM (Broad 2015)
ucs (Johns Hopkins 2014)
NCI-60
Cholangiocarcinoma (TCGA)
Uterine (TCGA)
Uterine (TCGA pub)
NEPC (Trento/Cornell/Broad 2016)
PCNSL (Mayo Clinic)
Colorectal (Genentech)
Prostate (FHCRC, 2016)
Lung adeno (TCGA pub)
Lung adeno (TCGA)
Stomach (TCGA pub)
Melanoma (Broad)
Pancreas (UTSW)
Colorectal (DFCI 2016)
Stomach (TCGA)
Colorectal (TCGA pub)
Melanoma (TCGA)
Colorectal (TCGA)
MPNST (MSKCC)
DLBC (TCGA)
Lung squ (TCGA pub)
Sarcoma (TCGA)
NSCLC (TCGA, 2016)
ACC (TCGA)
Lung squ (TCGA)
Stomach (Pfizer UHK)
Glioma (UCSF)
Prostate (MSCH)
Small Cell Lung (JHU)
Bladder (TCGA)
Bladder (TCGA 2014)
Small Cell Lung (UCOLOGNE)
Melanoma (Yale)
MBL (Sickkids 2016)
Stomach/Esophageal
Melanoma (Broad/DFCI)
Stomach (TMUCIH 2015)
Lung adeno (Broad)
Esophagus (TCGA)

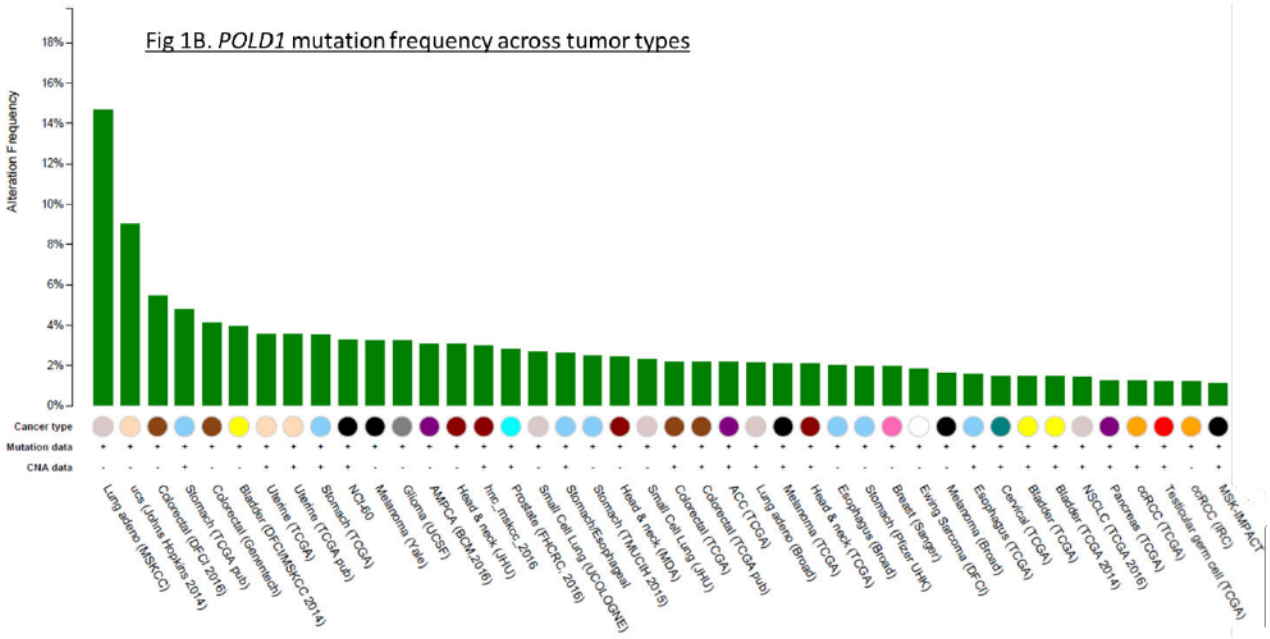


Fig 1B. POLD1 mutation frequency across tumor types
Alteration Frequency
18%
16%
14%
12%
10%
8%
6%
4%
2%
0%
Cancer type
Mutation data
CNA data
Lung adeno (MSKCC)
ucs (Johns Hopkins 2014)
Colorectal (DFCI 2016)
Stomach (TCGA pub)
Colorectal (Genentech)
Bladder (DFCI/MSKCC 2014)
Uterine (TCGA)
Uterine (TCGA pub)
Stomach (TCGA)
NCI-60
Melanoma (Yale)
Glioma (UCSF)
AMPCA (BCM 2016)
Head & neck (JHU)
Inv., malicc, 2016
Prostate (FHCRC, 2016)
Small Cell Lung (UCOLOGNE)
Stomach/Esophageal
Stomach (TMUCIH 2015)
Head & neck (MDA)
Small Cell Lung (JHU)
Colorectal (TCGA)
Colorectal (TCGA pub)
ACC (TCGA)
Lung adeno (Broad)
Melanoma (TCGA)
Head & neck (TCGA)
Esophagus (Broad)
Stomach (Pfizer UHK)
Breast (Sanger)
Ewing Sarcoma (DF-CI)
Melanoma (Broad)
Esophagus (TCGA)
Cervical (TCGA)
Bladder (TCGA)
Bladder (TCGA)
NSCLC (TCGA 2014)
Pancreas (TCGA)
ccRCC (TCGA)
Testicular germ cell (TCGA)
ccRCC (IRC)
MSK-IMPACT

2.3 Immune Checkpoint Blockade in Tumors with High Mutational Burden

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death *[Schumacher 2015; Chen 2017]*. These cancer-specific peptides resulting from neoantigens can be targets for T-cell recognition and effector responses. Tumors harboring defects in DNA repair proteins develop strikingly high rates of base substitutions during DNA replication with a subsequent mutation burden that is 10-20 fold higher than in tumors without these insults *[Rayner 2016]*. In NSCLC and melanoma, it has previously been shown that tumor mutational burden associates with sensitivity to checkpoint blockade with PD-1 blockade *[Rizvi 2015; Snyder 2014]*. In a cohort of 34 NSCLC patients, we found tumors with durable clinical benefit to anti-PD-1 therapy demonstrated high levels of nonsynonymous mutations and four cases (12%) harbored deleterious POLE and POLD1 exonuclease domain mutations. Pan-cancer genomic profiling of tumors also reveals a clear association between a hypermutated phenotype and mutations affecting DNA damage repair proteins (MMR deficient tumors and POLE mutated tumors seen in Figure 2 *[Chalmers 2017; Zehir 2017]*.These highly mutated tumors provoke a brisk immune infiltrate that is impaired through upregulation of inhibitory T-cell signaling via the programmed death -1 (PD-1) receptor pathway in the tumor microenvironment and cytotoxic T-lymphocyte Antigen 4 (CTLA-4) pathway in lymph nodes *[Domingo 2016]*. Given high levels of somatic mutations and increased tumor infiltrating lymphocytes (TILs), POLE and POLD1 mutated tumors present an attractive target for immune checkpoint blockade and case reports of POLE-mutated endometrial cancer and colorectal cancer (CRC) have shown a response to pembrolizumab *[Castellucci 2017; Mehnert 2016]*.

Immune checkpoint blockade has revolutionized the treatment of advanced, microsatellite unstable (MSI-H) tumors. The phase II trial evaluating the efficacy of anti-PD-1 therapy with pembrolizumab in previously treated patients with MSI-H advanced CRC (n=11) and MSI-H non-CRC tumors (n=9) demonstrated improved immune-related ORRs (irORR, 40% and 70%, respectively) and immune-related PFS (irPFS, 78% and 67%, respectively) compared to microsatellite stable tumors (irORR 0%, irPFS 11%) *[Le 2015]*. An expansion study evaluating pembrolizumab in 86 MSI-H patients across 12 different tumor types demonstrated a 53% ORR (46/86 patients) and a remarkable 21% complete response rate (18/86 patients) *[Le 2017]*. Recently, the Food and Drug Administration granted a landmark approval for pembrolizumab in MSI-H tumors regardless of histology in May 2017. Durable outcomes have also been demonstrated for MSI-H CRC patients treated with nivolumab with a reported 12-month OS (OS) of 74% *[Overman 2017]*. Furthermore, combined CTLA-4 and PD-1 inhibition may drive deeper, more robust anti-tumor responses than single agent therapy in this setting. Preliminary data from CheckMate 142, a multi-cohort phase II study of nivolumab with or without ipilimumab in advanced MSI-H CRC, presented at ASCO this year demonstrated a 31% ORR for nivolumab alone compared to 55% for combination therapy with a median duration of response that was not reached for either arm *[Andre 2017]*.

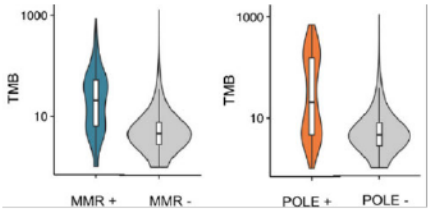


Fig 2. Tumor mutation burden (TMB) in mismatch repair deficient (MMR+) tumors and *POLE* mutated (POLE+) tumors compared specimens without such mutations [16].

2.4 Nivolumab

Nivolumab is a fully humanized IgG4 monoclonal antibody that binds to the immune checkpoint molecule PD-1 with high affinity blocking its interaction with PD-L1 (B7-H1) and PD-L2 (B7-DC). PD-1 blockade may lead to a reversal of tumor-induced T cell related immunosuppression (T-cell exhaustion). Nivolumab has been shown to block PD-1 and reverse the immunosuppression mediated by this molecule.

PD-1 has been recognized as a complementary checkpoint protein to CTLA-4 and is expressed on activated CD4+ and CD8+ T cells, B cells, monocytes, natural killer T (NKT) cells, and dendritic cells (DCs) *[Agata 1996]*. PD- 1 signaling in T cells regulates immune responses by minimizing damage to bystander tissue and preventing the development of autoimmunity by promoting self-tolerance to self-antigens *[Sznol 2013]*. Its major ligand PD-L1 (B7-H1) is typically expressed on a subset of macrophages but can be induced by inflammatory cytokines in a variety of tissue types *[Dong 1999; Mazanet 2002]*. PD-L1 is also found on T cells, B cell, DCs, and mast cells *[Agata 1996]*. When activated T-cells expressing PD-1 encounter PD-L1, T-cell effector functions are subsequently diminished. The effector T cell functions including cytokine production, proliferation, and cell survival are inhibited as a result of the engagement of PD-1 to PD- L1. Tumor regression and prolonged host survival has been seen in preclinical studies of PD-1:PD-L1 blockade in murine tumor models. These promising results were noted in several tumor models including ovarian carcinoma, squamous cell carcinoma, melanoma, mastocytoma, hepatoma, and acute myeloid leukemia *[Iwai 2002; Strome 2003; Hirano 2005]*. Tumor regression was accompanied by increased effector T-cell function and cytokine production.

The therapeutic benefit of nivolumab has been well established in NSCLC, melanoma, clear-cell renal cell carcinoma (RCC), classical Hodgkin Lymphoma (cHL), urothelial carcinoma (UC), squamous cell carcinoma of the head and neck (SCCHN), in addition to other tumor types. In a phase I study, single doses of nivolumab were found to induce rapid and durable responses in patients with solid tumors including melanoma, colorectal cancer, and renal cell carcinoma *[Brahmer 2010]*. Recent clinical trials have demonstrated activity of single-agent nivolumab in metastatic melanoma with a tolerable safety profile. In NSCLC, the phase III CheckMate (CM) 017 and 057 studies evaluated the role of nivolumab 3 mg/kg every 2 weeks in previously treated squamous and nonsquamous advanced NSCLC, respectively *[Borghaei 2015; Brahmer 2015]*. Both studies demonstrated statistically significant improvements in OS: 9.2 months for nivolumab compared to 6.0 months for docetaxel in CM 017 (HR 0.59, $p<0.001$) and 12.2 months for nivolumab compared to 9.4 months for docetaxel in CM 057 (HR 0.73, $p=0.002$). A recent publication reported very few grade 3 or 4 adverse events with nivolumab monotherapy at the same dose and schedule even in patients with prior ipilimumab treatment *[Webe 2013]*. This trial also demonstrated objective responses to single-agent nivolumab in patients who were either ipilimumab refractory (20%-30%) or ipilimumab naïve (~30%). They also found a correlation of response to tumor cell staining for PD-L1, but there were responses (20%-25%) even in patients without PD-L1 staining in tumor by immunohistochemistry. The promising clinical data noted above for PD-1 blockade as an immunotherapy target suggests its potential for use across solid tumors.

2.5 Ipilimumab

Ipilimumab, a human IgG1 monoclonal antibody to CTLA-4, activates T cells by blocking the inhibitory action of CTLA-4. The immune response to tumors is a complex, multistage process that begins with tumor-associated antigen recognition and T-cell activation *[Croft 1994]*. Full activation of naïve T cells requires not only stimulation of the antigen receptor by peptide/major histocompatibility complexes, but also by co-stimulatory signals. These signals are provided by the binding of CD28, a constitutively expressed T-cell surface receptor, to CD80 (B7.1) and CD86 (B7.2), molecules that are present on antigen presenting cells. CD28-B7 co-stimulatory signals are critical for induction of T-cell proliferation, cytokine secretion, and effector functions, which ultimately translate into clinical effects.

CTLA-4 is an activation-induced T-cell surface molecule that binds CD80 and CD86 but with greater avidity than CD28. CTLA-4 ligation down-regulates T-cell responses which results in an abrogation of the clinical effects provided by T-cell activation *[Hodi 2007]*. Conversely, the blockade of CTLA-4 interactions with CD28 results in an increase of T cell activation. Several in vitro studies have demonstrated that monoclonal antibodies against CTLA-4 enhance T-cell responses, whereas direct cross-linking of CTLA-4 with B7.1 and B7.2 results in a blockade of cell cycle progression, diminished cytokine expression, and decreased T-cell proliferation.

In vivo, ipilimumab blockade of CLTA-4 promotes generation of short-lived effector CD8+ T cells and a more persistent central memory CD4+ T cell response *[Hokey 2008; Di Giacomo]* resulting in a significant inhibition of tumor growth *[vanElsas 1999]*.

Clinically, the therapeutic potential of ipilimumab has been clearly established. The OS of patients with advanced malignant melanoma was prolonged in 2 randomized, double-blind multinational phase III trials of ipilimumab as monotherapy *[Hodi 2010]* and in combination with dacarbazine chemotherapy *[Robert 2011]*. This OS benefit was provided with an acceptable safety profile. Based on a positive risk-benefit ratio, ipilimumab has been approved by the U.S. FDA for use in patients with malignant melanoma. Convincing activity has also been seen in other solid tumors. For example, in a randomized phase II trial in both NSCLC and SCLC *[Lynch 2012]*, the addition of ipilimumab to paclitaxel and platinum resulted in statistically significant prolonged immune-related progression-free survival, the primary endpoint, suggesting ipilimumab will have activity in multiple solid tumor types.

2.6 Nivolumab Combined with Ipilimumab

Though both CTLA-4 and PD-1 inhibit T-cell function, they work through different mechanisms. Agents blocking one pathway may lead to upregulation of other immune mediators. Pre-clinical studies illustrate stronger antitumor responses with combined CTLA-4 and PD-1 inhibition. In mouse models, single agent therapy with either anti-CTLA-4 or anti-PD-1 enhanced T-cell activation to tumor tissue, but these T-cells acquired high levels of co-inhibitory molecules that ultimately diminished the immune response *[Curran, 2010]*. Combined blockade allowed re-expansion of T-cell subsets consequently reducing adaptive tumor immune responses and promoting regression of tumors. In clinical studies, combinations of immunotherapy agents directed against co-inhibitory pathways (e.g. anti- CTLA-4 and anti-PD-1/L1 therapy) have demonstrated efficacy in patients with advanced melanoma and lung cancer *[Antonia 2015; Larkin 2015; Patnaik 2015]*. In particular, data from a phase I trial of combination ipilimumab and nivolumab in patients with advanced melanoma demonstrated that 31% of the patients who responded had tumor regression of 80% or more, a finding that was uncommon in prior immunotherapy studies evaluating either agent individually *[Wolchok 2013]*. This small phase 1 dose-escalation trial was designed to test the safety of the combination of ipilimumab at a dose of 3 mg/kg in combination with nivolumab at doses ranging from 0.3 to 3 mg/kg (cohorts 1–3). In larger, phase III trials in melanoma, the combination of PD-1/CTLA-4 blockade translated to numerical improvements in survival *[Larkin 2015]*.

In CM-012, a multi-cohort phase Ib trial evaluating the safety and tolerability of nivolumab in chemotherapy-naive NSCLC either as monotherapy or in combination with other agents including ipilimumab, combination therapy was characterized by high response rates and tolerable safety profile *[Hellmann 2017]*. The primary endpoint of the trial was safety with secondary endpoints of ORR and 24-week PFS. Exploratory endpoints included OS and efficacy by PD-L1 expression. In the trial, patients were randomly assigned (1:1:1) to receive nivolumab 1 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 12 weeks, or nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks until disease progression, unacceptable toxicities, or withdrawal of consent. The confirmed ORR was 47% (N3 q2w + I1 q12w) and 39% (N3 q2w + I1q6w). The median duration of response (DOR) was not reached. The rate of treatment-related adverse events in the Q12W (82%) and Q6W (72%) arms were comparable to monotherapy (72%). In the trial, Grade 3/4 adverse events were 37%, 33%, and 19% for the Q12W, Q6W and nivolumab monotherapy arms, respectively. Treatment-related Grade 3-4 AEs lead to discontinuation in 5% and 8% of patients in the Q12W and Q6W cohorts, respectively and were similar to nivolumab monotherapy. There were no treatment-related deaths. The treatment-related select AEs in patients administered the optimized dosing scheduled (3 mg/kg of nivolumab every two weeks plus 1 mg/kg of ipilimumab every six weeks) were skin related (36%), gastrointestinal (23%), endocrine (20%), and pulmonary (5%) and there were $\leq$ 5% treatment related grade 3/4 AEs per category.

The above data suggests combined CTLA-4 and PD-1 inhibition may drive deeper, more robust anti-tumor responses than single agent therapy. Supporting this in data from CM-142, a multi-cohort phase II trial of nivolumab with or without ipilimumab in advanced MSI-H CRC, presented at ASCO in 2017 demonstrated a 31% ORR for nivolumab alone compared to 55% for combination therapy with a median duration of response that was not reached for either arm *[Andre 2017]*.

2.7 Trial Rationale

2.7.1 *Screening for POLE and POLD1 Mutations*

POLE and POLD1 encode components of the exonuclease, proofreading subunits of polymerase ε and polymerase δ complexes, respectively. These domains exhibit substantial homology (residues 268-471 for POLE and 304-517 for POLD1) and mutations affecting exonuclease function are most frequently reported to cause genomic instability and increased mutagenesis *[Konstantinopoulos 2015]*. It is unclear whether mutations outside of these regions have a similar impact or act more as "passenger" mutations *[Bourdais 2017]*. Importantly, TCGA and other studies generally employ whole exome sequencing to capture rates of nonsynonymous mutations. Given the cost and resources needed for this method, it is challenging to gauge mutational burden in routine clinical practice. Instead, an assessment of POLE and POLD1 mutations via commercially available comprehensive genomic sequencing platforms including cfDNA testing represents a rapid and attractive strategy.

2.7.2 *Randomized to Nivolumab and Nivolumab in Combination with Ipilimumab*

The above data suggest that combination immunotherapy with anti-PD-1 therapy in conjunction with anti-CTLA-4 blockade drives deep, durable responses in hypermutated MSI-H tumors - we hypothesize that a similar activity will occur in tumors with mutations in POLE and POLD1. To directly address this hypothesis, we propose a phase II non-comparative trial of nivolumab ± ipilimumab in patients with advanced solid tumors that demonstrate mutations in POLE or POLD1 with primary efficacy analysis for clinically relevant ORR.

2.7.3 *Possible Future Trial Expansion*

The current study protocol includes patients with solid tumors that have detectable POLE or POLD1 mutations. The study protocol may be modified to include additional cohorts if new blood or plasma based assays for other hypermutation phenotypes that may correlate with activity of immunotherapies become available.

3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 [redacted]

[redacted]

[redacted]

3.1.8 [redacted]

3.2.5 [redacted]

4.0 STUDY POPULATION

The trial population will consist of patients with advanced tumors (metastatic or unresectable) with detectable POLE or POLD1 mutations.

This study is designed to include women and minorities as appropriate, but is not designed to measure differences in intervention effects.

This study has two steps:

1. Registration for screening for the presence of POLE/POLD1 mutations (hereafter referred to as registration).
2. Enrollment and randomized in the trial (if eligible based on the results of screening).

The inclusion criteria for this study have been carefully considered. Inclusion criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that NO EXCEPTIONS be made to these criteria for admission to the study. Questions about inclusion criteria should be addressed prior to registration / randomization.

4.1 Inclusion Criteria

The following criteria will be required prior to registration:

4.1.1 Patients must have histologically confirmed advanced (metastatic or unresectable) solid tumors. Patients with primary CNS tumors are ineligible.

4.1.2 *Prior Therapy*

- Patients must have received at least 1 standard cancer therapy for their tumor type and progressed on their most recent regimen; patients may be treatment naïve if they refuse standard treatment or there is no standard treatment for their cancer.
- Prior adjuvant/neoadjuvant therapy with curative intent is considered a prior therapy if disease recurrence occurs within at least 6 months.
- Patients may not have received prior immunotherapy.

4.1.3 Patients must consent to blood collection for testing after registration by a central reference laboratory (see Section 12.0).

4.1.4 Patients must have clinically and/or radiologically documented disease with at least one lesion measurable as defined by RECIST 1.1.

4.1.5 Patients must be $\geq$ 18 years of age.

4.1.6 ECOG performance status 0 or 1.

4.1.7 Patients must have adequate hematology and organ function. Please refer to 4.2.3 below, Laboratory Requirements, these lab results may be ascertained based on patient chart review. It is not necessary to repeat these labs prior to registration for the purposes of screening for this study, if the results are available within the previous 28 days.

4.1.8 Patient consent for screening must be appropriately obtained in accordance with applicable local and regulatory requirements.

Review the exclusion criteria to ensure patient does not meet any of these criteria (4.3).

4.2 Additional Criteria To Be Met Prior To Study Enrollment

All patients must fulfil all of the following criteria to be eligible for randomization to the study.

4.2.1 Patients must have solid tumors that demonstrate POLE or POLD1 mutations identified at study entry via plasma cfDNA testing or tumor tissue testing for POLE and POLD1 mutations. A CLIA-certified testing of tumor tissue demonstrating POLE or POLD1 mutation can qualify for eligibility and randomization, however plasma will be submitted for central cfDNA testing. In the event of discordance between tissue and central laboratory testing, the patient will continue in study but will not be included in the primary analysis. These patients will however be included in the secondary analysis.

4.2.2 *Prior Therapy*

- Patients must have recovered to ≤ grade 1 from all reversible toxicity related prior systemic or radiation therapy and have a 2 weeks washout.
- Previous major surgery is permitted provided that it has been at least 28 days prior to patient registration and that wound healing has occurred.

4.2.3 *Laboratory Requirements*
(must be done within 14 days prior to enrollment).

Hematology	White Blood Cells	≥ 2.0 x 10^9/L (2000/µL)
	Absolute neutrophils	≥ 1.5 x 10^9/L (1500/µL)
	Platelets	≥ 100 x 10^9/L (100 x 10^3/µL)
	Hemoglobin	≥80 g/L* (8.0 g/dL)
Chemistry	Bilirubin	≤ 1.5 x ULN (upper limit of normal)**
	AST and/or ALT	≤ 3 x ULN
	Serum creatinine *or:* Creatinine clearance***	≤ 1.5 x ULN ≥40 mL/min

* Contact CCTG if hemoglobin is < 80 g/L and the patient is not decompensated, is asymptomatic and transfusion is not indicated.
** If confirmed Gilbert's, eligible providing ≤ 3 x ULN.
*** Creatinine clearance to be measured directly by 24 hour urine sampling or as calculated by Cockcroft and Gault equation below:

Females: GFR = $\frac{1.04 \times (140\text{-age}) \times \text{weight in kg}}{\text{serum creatinine in µmol/L}}$

Males: GFR = $\frac{1.23 \times (140\text{-age}) \times \text{weight in kg}}{\text{serum creatinine in µmol/L}}$

4.2.4 Patients must be willing to consent to provision of archival tissue (tumor block or minimum of 20 slides cut at a minimum of 4 micron thickness - fewer slides may be accepted if discussed with CCTG) or fresh biopsy (optional) for correlative analyses and the center/pathologist must have agreed to the submission of the specimen(s). Patients will not be excluded if they have POLE/POLD1 mutations in tumor detected by testing outside of this protocol, and additional archival tissue is not available and/or optional fresh biopsy is not possible.

4.2.5 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrollment in the trial to document their willingness to participate.

Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

4.2.6 Patients must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the trial.

4.2.7 In accordance with CCTG policy, protocol treatment is to begin within 2 working days of patient randomization.

4.2.8 Women of childbearing potential (WOCBP) and men who are sexually active with WOCBP must have agreed to use a highly effective contraceptive method as indicated in Section 9.3. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or vasectomy/vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

Female patients of childbearing potential who are sexually active with a non sterilized male partner must use at least one highly effective method of contraception (failure rate of < 1% per year) while on study and for 23 weeks after the last dose of nivolumab and or ipilimumab. Male partners of a female patient and non-sterilized male patients who are sexually active with a female partner of childbearing potential must use any contraceptive method with a failure rate of < 1% per year for 31 weeks after the last dose of nivolumab and or ipilimumab. Female partners of a male subject must use a highly effective method of contraception throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. See Section 9.3 for additional details.

WOCBP will have a pregnancy test to determine eligibility as part of the Pre-Study Evaluation (see Section 5.0); this may include an ultrasound to rule-out pregnancy if a false-positive is suspected. For example, when beta-human chorionic gonadotropin is high and partner is vasectomized, it may be associated with tumor production of hCG, as seen with some cancers. Patient will be considered eligible if an ultrasound is negative for pregnancy.

Women must not breastfeed while on study and for 23 weeks after the last dose of nivolumab and/or ipilimumab.

4.3 Exclusion Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

4.3.1 Patients with a history of other untreated malignancies or malignancies, which required therapy within the past 2 years. 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 may be eligible after consultation with the CCTG.

4.3.2 Patients with primary CNS tumors are not eligible.

4.3.3 Patients with active brain metastases or leptomeningeal metastases are not eligible. Patients with brain metastases are eligible if these have been treated and clinically stable. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents).

4.3.4 History of primary immunodeficiency, history of allogeneic organ transplant that requires therapeutic immunosuppression and the use of immunosuppressive agents within 14 days of study drug administration*.

** NOTE: Intranasal/inhaled corticosteroids or systemic steroids that do not to exceed 10 mg/day of prednisone or equivalent dose of an alternative corticosteroid are permissible in the absence of active autoimmune disease.*

4.3.5 Active or prior documented autoimmune or inflammatory disorders. Including, inflammatory bowel disease (e.g. colitis or Crohn's disease), diverticulitis with the exception of diverticulosis, celiac disease or other serious gastrointestinal chronic conditions associated with diarrhea), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis), rheumatoid arthritis, hypophysitis, uveitis, etc., within the past 3 years prior to the start of treatment.

Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions considered to be of low risk for recurrence are permitted to enroll.

4.3.6 History of hypersensitivity to nivolumab or ipilimumab or any excipient.

4.3.7 Any previous treatment with a PD-1 or anti-PD-L1, anti-PD-L2 inhibitor, including nivolumab or an anti-CTLA4, including ipilimumab, or drug specifically targeting T-cell stimulation or immune checkpoint pathways.

4.3.8 Patients with serious illnesses or medical conditions which would not permit the patient to be managed according to the protocol (including corticosteroid administration), or would put the patient at risk. This includes but is not limited to:

- History of significant neurologic or psychiatric disorder which would impair the ability to obtain consent or limit compliance with study requirements.

- Active infection requiring systemic therapy; (including any patient known to have active hepatitis B, hepatitis C or human immunodeficiency virus (HIV) or tuberculosis or any infection requiring systemic therapy).
- Active peptic ulcer disease or gastritis.
- Active pneumonitis.

4.3.9 Patients receiving concurrent treatment with other anti-cancer therapy or other investigational anti-cancer agents.

4.3.10 Patients who have experienced untreated and/or uncontrolled cardiovascular conditions and/or have symptomatic cardiac dysfunction (unstable angina, congestive heart failure, myocardial infarction within the previous year or cardiac ventricular arrhythmias requiring medication, history of 2nd or 3rd degree atrioventricular conduction defects).

4.3.11 Pregnant or lactating women.

4.3.12 Men who are sexually active with women of childbearing potential and women of childbearing potential must agree to use adequate contraception as described in Section 4.2.8.

5.0 PATIENT EVALUATION FLOWSHEET: PRE-TREATMENT, ON STUDY, AND AFTER TREATMENT

All patients entered on study must be evaluated according to the schedule outlined below with documentation submitted according to the schedule in Appendix IV.

Required Investigations	Prior to Screening	Prior to Enrollment (Day -14 to -1)	Cycle 1 and all cycles beyond (Cycle = 6 weeks)			At disease progression	4 weeks after completion of protocol therapy	Q3 month follow-up
			Day 1 each cycle	Cycle 1, Day 15 Only	Cycle 1, Day 29 Only			
History and Physical Exam								
Including: height, weight, ECOG performance status, documentation of all measureable and non-measurable disease, clinical tumor measurements (if applicable)	ECOG only within 28 days	X	X	X	X		X	
Blood pressure, heart rate, temperature (after baseline to be taken as per institutional standard of care prior to, during and after study drug administration)		X						
Laboratory Procedures/Assessments[1]								
CBC's with differential	X[2]	X	X	X	X		X	X[5]
Serum creatinine, electrolytes (calcium, magnesium, sodium, potassium, chloride), LDH, AST and/or ALT, bilirubin, ALP, glucose, amylase[3], lipase[3], TSH[4], BUN or serum urea level	X[2]	X	X	X	X		X	X[5]
PTT, PT/INR		X	As clinically indicated					
Hep B/C (HBV, sAG, HCV antibody)		X						
Pregnancy Test[6]		X						
Tumor Markers[7]		X	X				X[8]	
Radiology								
Tumor Imaging (Chest, abdomen, and pelvis; other scans as necessary to document disease)[9]		within 28 days prior to randomization or 35 if negative	Every 12 weeks ± 1 week[10]				X[9]	X[9]
MRI brain (if clinically indicated)		within 28 days prior to randomization or 35 if negative				X		
Other Investigations								
EKG (if clinically indicated)		X						
Adverse events		X	Continuously			X	X	X[11]
Survival status								X
Correlative Studies								
Tissue (archival tissue at baseline; optional biopsy at PD)		X				X[8]		
Correlative Blood[12]	X	X	X[13]	X (cycle 1 only)		X[8]		

Footnotes are on next page ...

1	Bloodwork Timing: Pre-treatment blood draws may be done the day prior to treatment if necessary, and when treatment is to begin on a Monday, may be done on the previous Friday (maximum 72 hours prior to treatment). In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol.
2	Confirmation that the patient would meet the requirements for randomization (CBC with differential, serum creatinine, bilirubin, and AST&/or ALT only). These lab results may be ascertained based on patient chart review. It is not necessary to repeat these labs prior to the screening step for the purposes of this study, if results already available within the previous 28 days.
3	It is preferable that both amylase and lipase are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.
4	Free T3 and free T4 will be measured if TSH is abnormal.
5	To be done additionally every 3 months thereafter to follow abnormal lab results felt related until resolved to ≤ Grade 2.
6	Women of child-bearing potential only (urine or serum test). Must be performed within 72 hours prior to administration of study drug. To be done every 4 weeks when on-study.
7	Tumor markers including CEA, CA-125, CA-19-9, etc., as indicated per standard of care testing for primary tumor. If elevated at baseline, will be monitor serially. If not elevated at baseline, will not be monitored serially.
8	Studies at time of progression at the discretion of patients and treating physician if feasible (optional).
9	To be done every 12 weeks until relapse or progression (iCPD) for up to 2 years, for patients with CR/iCR, PR/iPR, SD/iSD response as defined in Section 8.0. For patients with iUPD, confirmatory scans must be performed at least 4 weeks, but no longer than 8 weeks, after iUPD was identified.
10	First tumor assessment should be performed 12 weeks (± 1 week) following randomization. To ensure comparability, baseline scans and subsequent scans to assess response must be performed using identical technique (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). Maintain schedule every 12 weeks even if cycles are delayed.
11	Every three months thereafter to follow adverse events felt related until resolved to ≤ Grade 2. Adverse Events to be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTCAE v.5.0) (see Appendix V).
12	See Section 12.0 for details. Documentation of POLE or POLD1 mutation in tumor OR by cfDNA in plasma required prior to randomization. Please refer to Section 12.1.3 and the Correlative Studies Manual for details regarding collection.
13	To be done day 1 of each cycle (excluding cycle 1) for first 4 cycles.

5.1 Follow-up for Patients

The follow-up requirements for ineligible randomized patients who have received no protocol therapy include submission of the Baseline Report and an End of Treatment Report. Data submission for ineligible participants who have received at least one dose of protocol therapy should be according to the protocol to allow for treatment and adverse event assessment. For patients without detectable POLE or POLD1 mutations on cfDNA screening, no follow-up is required.

6.0 ENTRY/RANDOMIZATION PROCEDURES

6.1 Entry Procedures

All registrations and randomizations will be done through the CCTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and registering/randomizing patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the CRI-CCTG-0001 trial specific web-site. If sites experience difficulties accessing the system and/or registering/randomizing patients, please contact the help desk (link in EDC) or the CRI-CCTG-0001 Study Coordinator.

All patients who are registered by the participating treatment center will be assigned a serial number which must be used on all documentation and correspondence with CCTG.

Registration for Screening

All consenting patients who are believed to be eligible will be registered prior to the collection and submission of a cfDNA screening sample for POLE/POLD1. The completion of an abbreviated eligibility check will be required and a serial number assigned which must be used to identify the patient on the samples sent for testing. Details of the central laboratory including sample collection and shipment are provided in the CRI-CCTG-0001 Screening Manual.

The following information will be required for screening and enrollment:

- trial code (CRI-CCTG-0001)
- patient's initials (may be coded)
- screening informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- confirmation of the requirements listed in Section 4.0

Randomization

Following receipt of the screening results, eligible patients will be randomized to one of two study arms.

The following additional information will be required:

- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- tissue banking/optional consent version date
- confirmation of the requirements listed in Section 4.0, including dates of essential tests and actual laboratory values
- height and weight
- stratification factors

6.2 Stratification

Subjects will be stratified at the time of randomization by:

- ECOG performance status (0, 1)
- Number of prior treatments (0, 1-2, 3 or more)

6.3 Registration and Randomization

Registration and Randomization will be provided electronically.

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All eligible patients admitted to the trial will be followed by the coordinating center. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting registration.

All randomized patients are to be followed until death or until sites are informed by CCTG that further follow-up is no longer required. The follow-up requirements for ineligible patients are outlined in Section 5.1.

7.0 TREATMENT PLAN

Although the Canadian Cancer Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with CCTG policy, protocol treatment is to begin within 2 working days of patient randomization.

7.1 Treatment Plan

7.1.1 *Drug Administration*

When nivolumab is given with ipilimumab, nivolumab will be administered first. Prior to the ipilimumab infusion, the patient's line should be flushed and filter changed. The ipilimumab infusion should not be started until 30 minutes after the end of the nivolumab infusion.

One cycle will be defined as 6 weeks.

Arm	Agent(s)	Dose	Route	Duration	Schedule
1 & 2	Nivolumab	240 mg	IV	30 min	Day 1, then every 2 weeks
2	Ipilimumab	1 mg/kg	IV	30 min	Day 1, then every 6 weeks

7.1.2 *Premedication*

Premedication (e.g. for nausea) or hypersensitivity prophylaxis is not required. Management of symptoms should take place as necessary (see Section 7.1.6 below). Details of any premedication or concomitant medication given to manage or prevent adverse events should be recorded on the electronic case report form (eCRF).

7.1.3 *Patient Monitoring*

Vital signs should be taken as per institutional standard of care prior to, during and after drug administration.

All patients should be closely monitored according to guidelines in Section 5.0 and be advised to contact the treating center in the case of significant toxicities.

7.1.4 *Dose Modifications*

The major toxic effects of nivolumab or ipilimumab which are anticipated to limit dosing are hypersensitivity/ infusion related reactions and possible class related immune related AEs, based on the mechanism of action of nivolumab and ipilimumab leading to T-cell activation and proliferation. Potential immune related AEs include pneumonitis, enterocolitis, dermatitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, pancreatitis, nephritis and endocrinopathy. Patients should be monitored for signs and symptoms of immune related AEs. In the absence of an alternate etiology (e.g. infection or relapse), signs or symptoms of pneumonitis, enterocolitis, dermatitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, pancreatitis, nephritis and endocrinopathy should be considered to be immune-related.

The guidelines which follow outline dose adjustments for several of these toxic effects. If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that requires the greatest dose hold or discontinuation. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix V).

Dose adjustments (slowing/interruption of infusion rate, omission of a dose, or permanent discontinuation) will be made for adverse events. There will be no dose reductions.

If the infusion cannot be administered, it should be omitted until the next planned infusion. When nivolumab is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay either the combination treatment or nivolumab alone can be resumed based on evaluation of the individual patient.

Treatment should not be given (including day 1 cycle 1) until the laboratory criteria in Section 4.2.3 are met and resolution of all drug related toxicity to $\leq$ grade 2. Discuss with CCTG if asymptomatic/not felt to be clinically significant.

7.1.4.1 *Dose Delays*

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both). Refer to Appendix II for full details of toxicity management. Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade $\geq$ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay.
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for AST, ALT, or total bilirubin:
  - If a patient has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade $\geq$ 2 toxicity.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

7.1.4.2 *Discontinuation (Unacceptable Toxicity)*

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - AST or ALT > 8 x ULN
      - Total bilirubin > 5 x ULN
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are improved with supplementation/appropriate management within 72 hours of their onset.
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a patient with a dosing interruption lasting > 6 weeks, the CCTG must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by CCTG. Prior to re-initiating treatment in a patient with a dosing interruption lasting > 6 weeks, CCTG must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued nivolumab or ipilimumab dosing.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a participant in the nivolumab/ipilimumab combination arm meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the trial.

7.1.5 *Management of Toxicity*

See Appendix II for full details of toxicity management.

For adverse events (AEs) that are considered at least partly due to administration of nivolumab and/or ipilimumab the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the agents suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing nivolumab or ipilimumab along with appropriate continuing supportive care. If medically appropriate, dose delays are permitted for nivolumab and/or ipilimumab (see Appendix II).
- All dose delays should be documented with clear reasoning and documentation of the approach taken.
- In addition, there are certain circumstances in which nivolumab or ipilimumab should be permanently discontinued.

7.1.6 *Management of Infusion Reaction*

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, urticaria, angioedema, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE version 5.0 guidelines

For Grade 1 symptoms:
(Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor patient until recovery from symptoms. Infusion rate may be slowed. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely.

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab or ipilimumab administrations, slowing infusion rate as above.

For Grade 2 symptoms:
(Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g. antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; close observation for recurrence and treatment medications may need to be continued for 24-48 hours)

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and acetaminophen (or paracetamol) 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

Grade 3 symptoms:
(Severe reaction; prolonged [i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g. renal impairment, pulmonary infiltrates])

Grade 4 symptoms:
(life threatening; pressor or ventilatory support indicated)

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the patient as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1: 1,000 solutions for subcutaneous administration or 0.1 to 0.25 mg of a 1: 10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur; nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g. appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g. oral antihistamine, or corticosteroids).

Please note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation. Please evaluate accordingly.

7.2 Duration of Therapy

Patients should continue on trial treatment until RECIST 1.1/iRECIST defined progression or unacceptable toxicity or other treatment discontinuation criterion is met (see below).

An individual patient will not receive any further investigational product if any of the following occur in the patient in question:

- Patient request.

- Lost to follow-up.
- Patient is determined to have met one or more of the exclusion criterion for the trial.
- Participation at trial entry and continuing investigational therapy might constitute a safety risk.
- Pregnancy or intent to become pregnant.
- Initiation of alternative anti-cancer therapy including another investigational agent.

There is no maximum duration of treatment as patients may continue to receive investigational product beyond RECIST 1.1/iRECIST defined progression as long as they are continuing to show clinical benefit. In such cases, patients may continue to receive treatment following objective progression at Investigator's discretion and as agreed with the patient.

7.3 Concomitant Therapy

Details of any concomitant medications (prescription, non-prescription, or over-the-counter medications) taken by the patient at study entry and during protocol therapy must be recorded on the appropriate electronic case report forms (eCRFs).

7.3.1 *Permitted*

- Supportive care for disease-related symptoms may be offered to all patients on the trial.
- Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

7.3.2 *Not Permitted*

- Immunosuppressive agents (except to treat a drug-related adverse event)
- Systemic corticosteroids > 10 mg daily prednisone equivalent (except as stated in Section 7.1 and 7.3.1 to treat a drug-related adverse event).
- Any concurrent antineoplastic therapy (i.e. chemotherapy, hormonal therapy, immunotherapy, radiation therapy) except for palliative radiation therapy or standard or investigational agents for treatment of cancer.

8.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

8.1 Definitions

8.1.1 *Evaluable for Adverse Events*

All patients will be evaluable for adverse event evaluation from the time of their first treatment.

8.1.2 *Evaluable for Response*

All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below *[Seymour 2017]*.

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumors) committee as well as the modified iRECIST guidelines *[Seymour 2017]*. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria.

8.2 Response and Evaluation Endpoints

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumors) committee as well as the Immune-Related modified RECIST. Investigators should continue treatment, as appropriate, in the absence of unacceptable toxicity, until unequivocal disease progression. This is particularly important for patients in whom pseudoprogression may have occurred. Follow up response assessments must be continued until unequivocal disease progression has occurred.

8.2.1 *Measurable Disease*

Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$ 20 mm with chest x-ray and as $\geq$ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component $\geq$ 10 mm by CT scan). *Malignant lymph nodes* must be $\geq$ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

8.2.2 *Non-measurable Disease*

All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

8.2.3 *Target Lesions*

When more than one measurable tumor lesion is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be 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*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 8.2.4). At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

8.2.4 *Non-target Lesions*

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

8.2.5 *Response*

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of *target* and *non-target* lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases *[Seymour 2017]*) before CR can be accepted. Confirmation of response is only required in non-randomized studies.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is only required in non-randomized studies.

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

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Patients that are clinically well may continue on therapy following RECIST progression with new lesions or increase in target lesions if the increase in disease burden does not meet the definition of PD by immune response criteria *[Seymour 2017]*. In this situation, patients do not have unequivocal progression until immune response criteria are met (see Table 1 below).

Table 1: Integration of Target, non-Target and New Lesions into Response Assessment:

Target Lesions	Non-Target Lesions	New Lesions*	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 9 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes*	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes*	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

* Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments – see table 2.

8.3 Immune-Related Response Assessment

Overall response will also be assessed using iRECIST *[Seymour 2017]*. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum :
  - Continued unequivocal progression in non-target disease with an increase in tumor burden
  - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in table 2, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

New Lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of NLT should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Table 2: Time-point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: - further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: - previously identified T lesion iUPD SOM ≥5 mm and / or - NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: - previously identified T lesion iUPD ≥5 mm and / or - previously identified NT lesion iUPD (need not be unequivocal) and /or - size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on - increase in size or number of new lesions previously identified

* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same.
** In any lesion category.
*** Previously identified in assessment immediately prior to this TP.

Table 3: iRECIST Best Overall Response (iBOR)

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

- Table assumes a randomized study where confirmation of CR or PR is not required.
- NE = not evaluable that cycle.
- Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

8.4 Response Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

8.5 Stable Disease Duration

Stable disease duration will be measured from the time of randomization until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

8.6 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

8.6.1 *Clinical Lesions*

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

8.6.2 *Chest X-ray*

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

8.6.3 *CT, MRI*

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When 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). Other specialized imaging or other techniques may also be appropriate for individual case *[Eisenhauer 2009]*. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

8.6.4 *Ultrasound*

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

8.6.5 *Endoscopy, Laparoscopy*

The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

8.6.6 *Tumor Markers*

Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

8.6.7 *Cytology, Histology*

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

9.0 SERIOUS ADVERSE EVENT REPORTING

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix IV). All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the CCTG SAE form. The term 'reportable SAE' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to CCTG.

9.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events, which are unexpected and related to protocol treatment, occurring during the treatment period and within 100 days after the last protocol treatment administration, must be reported in an expedited manner. (See Section 9.2 for reporting instructions.) Any late serious adverse event occurring after this 100 day period which is unexpected and related to protocol treatment must also be reported in an expedited manner (see Section 9.2 for reporting instructions).
- Unexpected adverse events are those which are not consistent in either nature or severity with information contained in the investigator brochure.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol agent cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

9.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CCTG Generic Data Management Guidebook for EDC Studies posted on the CRI-CCTG-0001 section of the CCTG website (www.ctg.queensu.ca).

Within 24 hours: Complete preliminary Serious Adverse Event Report and submit to CCTG via EDC system.

Within 7 days: Update Serious Adverse Event Report as much as possible and submit report to CCTG via EDC system.

EDC SAE web application interruption:
In the rare event that internet connectivity to the EDC SAE system is disrupted, please print and complete a paper copy of the SAE Report, available from the trial specific website.

FAX paper SAE Report to:

CRI-CCTG-0001 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2411

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the CRI-CCTG-0001 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

In cases of prolonged internet interruptions, please contact the CCTG Safety Desk for further instructions (613-533-6430).

9.3 Other Protocol Reportable Events – Pregnancy Reporting and Exposure Reporting

9.3.1 *Pregnancy Prevention*

Women of Childbearing Potential (WOCBP) and males who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criterion 4.2.8. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

9.3.2 *Pregnancy Reporting*

If a patient becomes pregnant during the course of the study, the investigational agent should be discontinued immediately.

Pregnancy itself - occurring in female participants, and female partners of male participants - is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

The investigator is required to report to CCTG any pregnancy occurring in female participants, and female partners of male participants. Pregnancies occurring up to 6 months after the last dose of study treatment and pregnancies in female partners of male participants occurring up to 8 months after the last dose of study treatment must also be reported.

The investigator should report the pregnancy within 24 hours of learning of the pregnancy using the CCTG Pregnancy Reporting Form available from the trial webpage.

Once informed consent has been obtained, the form should be updated to provide further pregnancy information and to reflect the outcome of the pregnancy. All follow-up reports must be submitted to CCTG in a timely manner. For pregnant partner of trial participant (and pregnant participants, if required by local policy), a copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812/ safety-desk@ctg.queensu.ca).

If the pregnancy results in death (e.g. spontaneous abortion, stillbirth); is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above. Please note, hospitalization for labour/delivery alone does not constitute an 'inpatient hospitalization' for the purposes of pregnancy reporting.

9.3.3 *Exposure Reporting (Non-study Participants)*

The investigator is required to report to CCTG any incidence of exposure to study agent(s). Exposure is defined as significant, direct, contact/inhalation/consumption of agent(s) by non- study participant (an individual who is not otherwise participating in this clinical trial). An example of an exposure includes a non-study participant receiving study medication. The investigator is responsible for determining significance, based on the agent to which the individual is exposed.

The investigator should report the exposure in a timely manner, within 24 hours of learning of the exposure using the CCTG Exposure Reporting Form available from the trial webpage.

Once informed consent has been obtained, the form should be updated to provide further exposure information and to reflect the outcome of the exposure as the information becomes available upon appropriate follow-up of the exposed individual within 100 days of exposure. All follow-up reports must be submitted to CCTG in a timely manner. A copy of the signed exposure follow-up consent signature page must also be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812/ safety-desk@ctg.queensu.ca).

If the exposure results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above.

9.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada

The CCTG will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials) for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected (as determined by reference to the Investigator Brochure), AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

9.5 CCTG Reporting Responsibility to Bristol Myers Squibb

Bristol Myers Squibb will be notified of all reportable serious adverse events (as defined in Section 9.1) within 4 working day(s) of receipt of report at CCTG. CCTG, as sponsor will determine regulatory reportability in Canada. Bristol Myers Squibb will be notified of all pregnancies and outcomes within 4 working days of receipt of report at CCTG.

9.6 CCTG and Bristol Myers Squibb Reporting Responsibilities

Bristol Myers Squibb will report all regulatory reportable serious adverse events from non-CCTG trials (Safety Updates) with nivolumab and ipilimumab to CCTG within 7 - 15 days. CCTG will review these events to determine which meet the criteria (serious, unexpected, drug related) for reporting to CRI-CCTG-0001 investigators. Bristol Myers Squibb will report these events to Health Canada. In addition Bristol Myers Squibb will provide 6 monthly line listings to CCTG for all other reports.

9.7 Reporting Safety Reports to Investigators

CCTG will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities in Canada as reported to the CCTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the CCTG trial CRI-CCTG-0001 web-based safety monitoring utility.

Investigators must notify their Research Ethics Boards/Institutional Review Boards (REBs/IRBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes. The date of REB/IRB Submission for these SAEs and SUs will need to be entered into the CCTG trial CRI-CCTG-0001 web based safety monitoring utility and documentation of REB/IRB submission must be retained in the study binder on site. The REB/IRB submission template provided by CCTG can be used to assist with tracking, submission, filing and monitoring.

The submission of events to your ethics board should be done as soon as possible (we suggest within 30 days). REB/IRB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.

10.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

10.1 Criteria for Discontinuing Protocol Treatment

Patients who are clinically stable but meet the criteria for iUPD should be continued on treatment until the next disease assessment at least 4 weeks later. It is recommended that the next imaging assessment be no longer than 8 weeks later in order to ensure patients remain fit for salvage therapies. Clinical stability is defined as:

- Stability or improvement in performance status.
- No clinically relevant increase in disease related symptoms such as pain or dyspnea (generally understood to mean a requirement for increased palliative intervention as below).
- No requirement for increased management of disease related symptoms including increased analgesia, radiation or other palliative care.

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 7.0.
- Tumor progression or disease recurrence as defined in Section 8.0.
- Request by the patient.

Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

10.2 Duration of Protocol Treatment

(see Section 8.0 for response definition)

- For complete responders, therapy will continue until progression (refer to Section 8.2)
- For partial responders, therapy will continue until progression.
- For stable patients, therapy will continue until progression (refer to Section 7.2).
- Patients who progress (treatment failure) will go off study at the time unequivocal progression is documented clinically and/or radiographically.

10.3 Therapy After Protocol Treatment is Stopped

At the discretion of the investigator.

10.4 Follow-up Off Protocol Treatment

All patients will be seen at 4 weeks after completion of protocol therapy. Continued follow-up required for all patients every 3 months to collect information on ongoing toxicities, late toxicities (including second malignancies) and survival data. This follow-up will continue until death or conclusion of the trial.

For patients who go off protocol treatment with CR/iCR, PR/iPR, SD/iSD or iUPD ongoing, tumor assessments will be required every 3 months until relapse (see Section 5.0 for investigations to be performed). Please note for patients who go off protocol treatment with iUPD, confirmatory scans should be performed at least 4 weeks, but no longer 8 weeks, after iUPD was documented.

A Death report will be required on all patients. Due within 2 weeks of knowledge of death (see Appendix IV- Documentation for Study).

11.0 CENTRAL REVIEW PROCEDURES

11.1 Central Radiology Review

As part of the trial, copies of x-rays and/or scans may be collected to evaluate cancer response to treatment. There will be no central radiology review for this study.

11.2 Central Pathology Review

There will be no central pathology review for this study.

12.0 CORRELATIVE STUDIES

A detailed Correlative Studies Manual will be provided on the CRI-CCTG-0001 trial specific website, which will include details regarding sample preparation, handling and shipping.

Specimens collected may be used by researchers now or in the future to better understand the nature of cancer and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of randomization to the trial the surgical/histology number and/or patient initials. Material issued to researchers will be anonymized and only identified by a coded number.

Testing for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the patient).

All patients on whom a diagnostic tumor block is collected will be aware of this retrieval and will have given their consent.

Genetic Testing

In the course of genetic testing for this study, there is a chance that "clinically relevant incidental findings" may occur; these refer to unanticipated discoveries made in the course of research but that are outside of the scope of the research *[TCPS2 2014]* being conducted. These findings could be inherited changes that might predispose a person to particular cancers or other diseases, and may be passed on in families.

The plasma cfDNA testing performed at screening and on-study will be done in a Clinical Laboratory Improvement Amendments (CLIA) laboratory. The panel is designed to identify somatic mutations and is not intended to detect the presence or absence of germline mutations. While common germline variants have been removed, the test may detect rare germline mutations.

During the informed consent process, participants will be told about the remote possibility of clinically relevant incidental findings being discovered, and given the opportunity to make informed choices about whether they wish to receive this information.

If a clinically relevant incidental finding is discovered during the testing for this study and a participant consented to learning about the results. These results will be included in the report provided directly to the study QI/AI. The QI/AI at the enrolling institution will be responsible for following local SOPs with regard to confirming the result, ensuring of genetic counseling is available, obtaining REB approval (if required) and contacting the study participant.

Germline testing may be performed on normal tissue as part of secondary and exploratory analyses. These analyses will be performed at study completion in the context of research in a non-CLIA certified laboratory. Therefore, these results will not be disclosed to the patient.

12.1 Protocol-Mandated Correlative Studies

12.1.1 *POLE and POLD1 Screening –Tumor Tissue and Blood Specimen (Mandatory for All Patients)*

Patients must have solid tumors that demonstrate POLE or POLD1 mutations identified at study entry via plasma cfDNA testing (PGDx) or tissue testing for POLE and POLD1 mutations (any CLIA-certified tissue assay).

- Patients enrolled onto the study via CLIA-certified tissue assay must also submit plasma for cfDNA testing (PGDx).
- Patients enrolled onto the study via plasma cfDNA testing (PGDx) must have tissue samples available (archival or fresh) for analysis, either a tumor block or two cores and a minimum of 20 slides of 4 micron thickness- less can be accepted if discussed with CCTG. Patients must be willing to consent to provision of archival tissue or fresh biopsy (optional).

Pre-treatment tumor tissue specimens that have been previously tested for POLE and POLD1 mutation testing using comprehensive genomic profiling will be allowed for trial entry and randomization. All patients must sign the pre-screening consent prior blood samples being sent.

A mandatory central testing for plasma cfDNA will be required for the primary endpoint. As such, two 10 ml tubes of peripheral whole blood will be collected from patients prior to randomization and sent for circulating tumor DNA (cfDNA) testing for identification of POLE and POLD1 mutations (PGDx). All patients will have POLE and POLD1 mutation testing centrally – patients randomized on the basis of archival tumor testing will have cfDNA testing of peripheral whole blood performed retrospectively.

Patients who do not have POLE/POLD1 mutations will not be eligible.

Diagnostic pathology reports are received as part of the supporting documentation required for this trial. A copy must be submitted at the time of Baseline Folder completion.

Please refer to the CRI-CCTG-0001 Correlative Studies and Screening Manuals for details.

12.1.2 *Tumor Tissue Collection*

The submission of a representative block of the diagnostic tumor tissue is mandatory for participation in this trial. Requests for this tissue will not be issued as these samples are expected to be submitted upon randomization for all patients. One tumor block and one adjacent normal tissue block are requested from any of the biopsies or resections of the tumor or solitary lesions following an initial response or biopsy samples collected upon progression. If no primary cancer blocks are available, one block of metastatic tissue can be sent instead.

Blocks are the preferred material to collect, as it is well known that tissue materials (including protein and nucleic acid integrity) on unstained sections deteriorate rapidly within 3-6 months after preparation. This will optimize the amount of tissue available to investigators and permit the preservation of the block submitted. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

Where local center regulations prohibit submission of blocks of tumor tissue, the approval of the CCTG must be sought prior to randomization of the first patient to allow cores (two 2 mm cores of tumor from the block) or a minimum of 20 slides cut at 4 microns obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen to be substituted in response to the Central Tumor Bank request. If 20 slides are not possible, please contact CCTG to discuss.

Diagnostic pathology and genomic testing reports are received as part of the supporting documentation required for this trial. Receipt of these will initiate a request directly from the Queen's Department of Pathology to pathology departments for a representative tumor block.

Planned priority assays on tumor tissue include but are not limited to:

- POLE and POLD1 mutations,
- Whole-exome sequencing,
- RNA sequencing.

Where archival tissue is not available, patients will not be excluded if prior tumor testing identified POLE or POLD1 mutation and additional blocks/slides are not available.

12.1.3 *Blood Collection*

The CCTG is interested in exploring the use of surrogate tissues such as blood, serum and plasma in evaluating potential prognostic or predictive biomarkers, or as evidence of pharmacodynamics effects. Some of the research blood collected will be tested for the following:

- T-cell subsets,
- Peripheral Blood Mononuclear Cells (PBMCs),
- HLA typing.

Detailed instructions for timepoints, sample acquisition, preparation, and shipping are found in the *CRI-CCTG-0001 Correlative Studies Manual*.

12.2 Optional Fresh Tumor Biopsy

Banking of Tumor Tissue
Mandatory submission of tumor tissue has been described above. The subsequent banking of collected diagnostic tissue is not mandatory for participation in the study, but the participation of all centers is strongly encouraged. Blocks will be carefully banked as part of the CCTG tissue/tumor bank at Queen's University in Kingston, Ontario.

Patients will be required to sign an optional tissue consent. All patients who consent to the fresh tumor biopsy will have the biopsy performed at progression at the discretion of the treating investigator if feasible. Patients who consent to this procedure but a fresh biopsy is not possible will not be excluded from the study.

Planned priority assays on tumor tissue include but are not limited to:

- POLE and POLD1 mutations
- Whole-exome sequencing
- RNA sequencing

Proposals to use the banked specimens for the purposes of assessing markers involved in predicting treatment response and outcomes may be submitted to the bank. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval.

12.3 Statistical Analyses

A variety of factors that could potentially predict clinical response to nivolumab and/or nivolumab in combination with ipilimumab will be investigated in peripheral blood (serum, plasma, and peripheral blood mononuclear cells (PBMCs)) and in tumor specimens taken from all patients prior to treatment, on study, and at progression and as outlined in Section 5.0. Data from these investigations will be evaluated for associations with response, survival (overall survival, progression free survival) and/or safety (adverse event) data. In addition, analyses of markers between the treatment arms will provide the necessary data to identify and validate biomarkers with predictive vs prognostic value. All samples collected may also be used for future exploratory analyses (unless restricted by local requirements) to assess biomarkers associated with immunotherapy treatment.

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Design

The primary objective for this randomized phase II open label and non-comparative trial is to evaluate efficacy as measured by objective response rate (ORR) by RECIST 1.1 of nivolumab monotherapy and of nivolumab combined with ipilimumab in randomized patients with advanced solid tumors with detectable POLE and POLD1 mutations as determined by plasma cfDNA. Secondary objectives include evaluating efficacy by ORR of nivolumab ± ipilimumab, duration of response (DOR), safety and toxicity in patients receiving nivolumab ± ipilimumab, and assess correlation between POLE/POLD1 mutations in tumor and POLE/POLD1 mutations in blood. Patients will be stratified by ECOG status (0 or 1) and number of prior treatments (0, 1-2, and ≥ 3), and randomized in 1:1 ratio to receive nivolumab alone or in combination with ipilimumab. The study will accrue up to 50 eligible and evaluable patients per treatment arm (100 total).

13.2 Endpoints and Analysis

The primary endpoint is ORR by RECIST 1.1 in immunotherapy naïve patients with advanced solid tumors with detectable mutations as determined by central blood-based assay (cfDNA for POLE/D1 mutations). Patients with detectable mutations in tissue but with no detectable mutations based on plasma cfDNA will be excluded from this analysis.

Response rates will be reported using percentages over all randomized patients with 90% exact confidence intervals (CI) of each arm in a non-comparative analysis. In addition, exact logistic regression models will be used to assess the effect of treatment on objective response probability, adjusting for mutational load values and trial site.

Secondary endpoints include: ORR of nivolumab monotherapy and of nivolumab combined with ipilimumab in all treated patients. Response rates will be reported using percentages over all patients who have received at least one dose of treatment with 90% exact CI of each arm in a non-comparative analysis. In addition, exact logistic regression models will be used to assess the effect of treatment on objective response probability, adjusting for mutational load values and trial site.

Duration of response (DOR) will be calculated from time of response to documentation of progression or death or censored at last time of disease assessment among all patients who have responded. Kaplan-Meier method will be used to estimate median duration of response and 90% confidence interval in each arm.

The responses assessed by iRECIST will be analyzed similarly as that by RECIST 1.1.

To assess the safety and characterize toxicities of nivolumab combined with ipilimumab and nivolumab monotherapy in all patients, estimation of the adverse event profile associated with treatment will be performed. All toxicities regardless of attribution will be reported using the CTCAE version 5.0 criteria. Adverse events rates will be reported using percentages with 90% exact CI.

Correlation between detectable mutations in tumor and detectable mutations in blood will be assessed by Fischer's exact test in each arm.

Detectable mutations in the initial study population are POLE/POLD1 mutations based on plasma cfDNA.

PFS and OS of nivolumab monotherapy and of nivolumab combined with ipilimumab in patients with advanced solid tumors with detectable mutations as determined by plasma cfDNA, and in all treated patients (detectable mutations in tissue or cfDNA) will be evaluated as exploratory endpoints.

Kaplan-Meier method will be used to estimate probabilities of OS and PFS for each arm. Patients alive at the time of trial analysis will be censored as of the date of their last disease assessment. Medians and 90% CI will be provided, if available. No formal comparisons will be made between the two arms. Adjusted analyses will be also consider mutational load as one of the covariates.

Tumors will undergo whole exome and RNA sequencing to evaluate the genetic landscape of mutated tumors in responders versus non-responders to immune checkpoint blockade.

Detectable mutations in the initial study population are POLE/POLD1 mutations based on plasma cfDNA.

13.3 Sample Size and Duration of Study

Approximately 100 immunotherapy-naïve patients with *POLE* or *POLD1* mutations identified at study entry via either circulating tumor DNA (cfDNA) central testing or prior local tumor assessment (to be confirmed retrospectively in such patients via central cfDNA testing) will be enrolled to this open-label, randomized, non-comparative trial.

We hypothesize that for this analysis treatment with immunotherapy will show a clinically relevant ORR of > 30% with single agent nivolumab or > 50% with combination nivolumab + ipilimumab in patients with advanced solid tumors with detectable POLE or POLD1 mutations.

A sample size of 50 evaluable patients in each arm will achieve 90% power to show a clinically meaningful ORR. These calculations assume a single agent $p0 < 13\%$, $p1 > 30\%$ and combination therapy $p0 < 30\%$, $p1 > 50\%$. Both assume a two-sided α and β of 0.10.

Additional enrollment of up to 20% will be permitted as needed to replace patients found to not demonstrate POLE or POLD1 mutations on central cfDNA.

As additional blood-based assays become available, the study may be amended to include additional cohorts.

Patients will be accrued from approximately four cancer treatment centers in the United States and four cancer treatment centers across Canada over a period of approximately 24 months.

13.4 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported bi-annually at investigators' meetings.

The trial may be discontinued if the trial is terminated by the data and safety monitoring committee (if applicable), the Food and Drug Administration (FDA), or other regulatory authorities.

Any unforeseen deaths or serious adverse events may, after a discussion between the Sponsor, principal investigator and investigators at other sites, prompt an interruption to trial accrual pending a full investigation into the circumstances surrounding the event.

13.5 Screening Monitoring

The estimated mutation rate in the screened population is 7-15% based on prior publications. The frequency of POL mutations detected in blood will be assessed after every 50 patients screened. If the frequency is < 5%, the screening approach will be reviewed by the trial committee to determine whether modifications to the protocol are required to improve the efficiency of screening by, for example, targeting specific tumor histologies or other approaches.

14.0 PUBLICATION POLICY

14.1 Authorship of Papers, Meeting Abstracts, Etc.

14.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will be based on overall enrollment and scientific contribution.
- A limited number of the members of the Canadian Cancer Trials Group, Cancer Research Institute, BMS, PDGx and additional investigators from participating centers, may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.

14.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the Canadian Cancer Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

14.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following study closure the manuscript has not been submitted, the central office reserves the right to make other arrangements to ensure timely publication.

Dissemination of Trial Results
CCTG will inform participating investigators of the primary publication of this trial. The complete journal reference and, if where publicly available, the direct link to the article will be posted on the Clinical Trial Results public site of the CCTG web site (http://www.ctg.queensu.ca).

14.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by the Cancer Research Institute, Columbia University and, the CCTG Senior Investigator, Senior Biostatistician, Study Coordinator, and approval of the Study Chair. Individual participating centers may not present outcome results from their own centers separately. Supporting groups and agencies will be acknowledged.

15.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

15.1 Regulatory Considerations

All institutions must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result, the conduct of this trial must comply with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act).

This trial is being conducted under an IND or related arrangement in other countries and all applicable Laws, Regulations and Policies must be followed.

15.2 Inclusivity in Research

CCTG does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, color, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of CCTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB/IRB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REB/IRBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centers are expected to ensure compliance with local REB/IRB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a CCTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. US sites should follow all applicable policies and regulations. It is the center's responsibility to ensure compliance with all local SOPs.

It is CCTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into CCTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB/IRB (if applicable).

Subjects who were competent at the time of enrollment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. CCTG will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

15.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in a CCTG trial, in accordance with ICH-GCP section 4.8. The center is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, CCTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. CCTG recognizes that in many centers other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

CCTG requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. CCTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

CCTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local center. Centers should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject.

15.3.1 *Obtaining Consent for Pregnancy/Exposure Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner, exposed individual) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them. If the main consent form adequately addresses the collection of information regarding the outcome of a pregnancy of a trial participant, a "Pregnancy Follow-up consent form will not be required by CCTG.

Trial-specific consent forms for "Pregnancy Follow-up" and "Exposure Follow-up" can be found on the trial webpage. The appropriate consent form must be used to obtain consent from any non-trial participant (such as the pregnant partner or exposed individual).

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy/exposure. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

Obtaining Consent for Research on Children

In the case of collecting information about a child (i.e. the child resulting from a pregnant participant/partner or an exposed child), consent must be obtained from the parent/guardian.

For reporting an exposure, the parent/guardian is required to sign an "Exposure Follow-up" consent form (even if they are a participant in the main study) prior to collecting information about the child.

15.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the CCTG all centers will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the CCTG will provide this information to centers as well.

If this trial is discontinued at any time by the center (prior to closure of the trial by the CCTG), it is the responsibility of the qualified investigator to notify the CCTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the CCTG or locally by the center, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

15.5 Retention of Patient Records and Study Files

All essential documents must be maintained as per C.05.012 and in accordance with ICH-GCP.

The Qualified Investigator must ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site.

For Canadian centers essential documents must be retained for 25 years following the completion of the trial at the center (25 years post final analysis, last data collected, or closure notification to REB/IRB, whichever is later), or until notified by CCTG that documents no longer need to be retained.

For international participating regions, local regulatory guidance should be followed with respect to duration of records retention, unless otherwise contractually dictated.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB/IRB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CCTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

15.6 Centre Performance Monitoring

Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

This study is eligible for inclusion in the Centre Performance Index (CPI).

15.7 On-Site Monitoring/Auditing

CCTG site monitoring/auditing will be conducted at participating centers in the course of the study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Canada Inspectorate.

CRI and Biopharma Partners have reserved the right to audit participating centers. Audits may only be conducted after consultation with CCTG.

16.0 REFERENCES

Agata, Y., et al., Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes. Int Immunol, 1996. 8(5): p. 765-72.

Albertson, T.M., et al., DNA polymerase epsilon and delta proofreading suppress discrete mutator and cancer phenotypes in mice. Proc Natl Acad Sci U S A, 2009. 106(40): p. 17101-4.

Andre, T., et al., Combination of nivolumab (nivo) + ipilimumab (ipi) in the treatment of patients (pts) with deficient DNA mismatch repair (dMMR)/high microsatellite instability (MSI-H) metastatic colorectal cancer (mCRC): CheckMate 142 study. Journal of Clinical Oncology, 2017. 35(4-suppl): p. abstr 3531.

Antonia S, G.S., Chow L, Nivolumab and ipilimumab in first-line NSCLC: interim phase I results. American Society of Clinical Oncology Annual Meeting; 2015; Chicago, USA.

Atlas, C.G., Comprehensive molecular characterization of human colon and rectal cancer. Nature, 2012. 487(7407): p. 330-337.

Borghaei, H., et al., Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. New England Journal of Medicine, 2015. 373(17): p. 1627-1639.

Bourdais, R., et al., Polymerase proofreading domain mutations: New opportunities for immunotherapy in hypermutated colorectal cancer beyond MMR deficiency. Crit Rev Oncol Hematol, 2017. 113: p. 242-248.

Brahmer, J.R., et al., Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol, 2010. 28(19): p. 3167-75.

Brahmer, J., et al., Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med, 2015. 373(2): p. 123-35.

Briggs, S. and I. Tomlinson, Germline and somatic polymerase ε and δ mutations define a new class of hypermutated colorectal and endomestudy cancers. J Pathol., 2013. 230.

Canadian Institute of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, December 2014.

Cancer Genome Atlas, N., Integrated genomic characterization of endomestudy carcinoma. Nature, 2013. 497(7447): p. 67-73.

Castellucci, E., et al., DNA Polymerase varepsilon Deficiency Leading to an Ultramutator Phenotype: A Novel Clinically Relevant Entity. Oncologist, 2017. 22(5): p. 497-502.

Chalmers, Z.R., et al., Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Medicine, 2017. 9(1): p. 34.

Chen, D.S. and I. Mellman, Elements of cancer immunity and the cancer-immune set point. Nature, 2017. 541(7637): p. 321-330.

Croft, M., L.M. Bradley, and S.L. Swain, Naive versus memory CD4 T cell response to antigen. Memory cells are less dependent on accessory cell costimulation and can respond to many antigen-presenting cell types including resting B cells. J Immunol, 1994. 152(6): p. 2675-85.

Curran, M.A., et al., PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci U S A, 2010. 107(9): p. 4275-80.

Dexheimer, T.S., DNA Repair Pathways and Mechanisms, in DNA Repair of Cancer Stem Cells, L.A. Mathews, S.M. Cabarcas, and E.M. Hurt, Editors. 2013, Springer Netherlands: Dordrecht. p. 19-32.

Di Giacomo, A.M., et al., Therapeutic efficacy of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with metastatic melanoma unresponsive to prior systemic treatments: clinical and immunological evidence from three patient cases. Cancer Immunology, Immunotherapy, 2009. 58(8): p. 1297-1306.

Domingo, E., et al., Somatic POLE proofreading domain mutation, immune response, and prognosis in colorectal cancer: a retrospective, pooled biomarker study. The Lancet Gastroenterology & Hepatology, 2016. 1(3): p. 207-216.

Dong, H., et al., B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nat Med, 1999. 5(12): p. 1365-9.

Eisenhauer E, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: Revised RECIST guideline version 1.1. Eur J Can 45: 228-47, 2009.

Hellmann, M.D., et al., Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. The Lancet Oncology, 2017. 18(1): p. 31-41.

Hirano, F., et al., Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res, 2005. 65(3): p. 1089-96.

Hodi, F.S., Cytotoxic T-lymphocyte-associated antigen-4. Clin Cancer Res, 2007. 13(18 Pt 1): p. 5238-42.

Hodi, F.S., et al., Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. New England Journal of Medicine, 2010. 363(8): p. 711-723.Robert, C., et al., Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med, 2011. 364(26): p. 2517-26.

Hokey, D.A., et al., CLTA-4 blockade in vivo promotes the generation of short-lived effector CD8 T cells and a more persistent central memory CD4 T cell response. J Med Primatol, 2008. 37 Suppl 2: p. 62-8.

Iwai, Y., et al., Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A, 2002. 99(19): p. 12293-7.

Konstantinopoulos, P.A. and U.A. Matulonis, POLE mutations as an alternative pathway for microsatellite instability in endomestudy cancer: Implications for Lynch syndrome testing. Cancer, 2015. 121(3): p. 331-334.

Lange, S.S., K. Takata, and R.D. Wood, DNA polymerases and cancer. Nat Rev Cancer., 2011. 11.

Larkin, J., et al., Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med, 2015. 373(1): p. 23-34.

Le, D.T., et al., PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. New England Journal of Medicine, 2015. 372(26): p. 2509-2520.

Le, D.T., et al., Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade. Science, 2017.

Lynch, T.J., et al., Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol, 2012. 30(17): p. 2046-54.

Mazanet, M.M. and C.C.W. Hughes, B7-H1 Is Expressed by Human Endothelial Cells and Suppresses T Cell Cytokine Synthesis. The Journal of Immunology, 2002. 169(7): p. 3581-3588.

McCulloch, S.D. and T.A. Kunkel, The fidelity of DNA synthesis by eukaryotic replicative and translesion synthesis polymerases. Cell Res, 2008. 18(1): p. 148-61.

Mehnert, J.M., et al., Immune activation and response to pembrolizumab in POLE-mutant endomestudy cancer. J Clin Invest, 2016. 126(6): p. 2334-40.

Overman, M.J., et al., Nivolumab in patients with DNA mismatch repair deficient/microsatellite instability high metastatic colorectal cancer: Update from CheckMate 142. Journal of Clinical Oncology, 2017. 35(4_suppl): p. 519-519.

Palles, C., et al., Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet, 2013. 45(2): p. 136-44.

Patnaik A, S.M., Gubens M., Phase I study of pembrolizumab plus ipilimumab as second-line therapy for advanced NSCLC: KEYNOTE-021 cohort D. American Society of Clinical Oncology Annual Meeting; 2015; Chicago, USA.

Rayner, E., et al., A panoply of errors: polymerase proofreading domain mutations in cancer. Nat Rev Cancer, 2016. 16(2): p. 71-81.

Rizvi, N.A., et al., Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science, 2015. 348.

Schumacher, T.N. and R.D. Schreiber, Neoantigens in cancer immunotherapy. Science, 2015. 348(6230): p. 69-74.

Seymour L, Bogaerts J, Perrone A et al. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18:143-52.

Shlien, A., et al., Combined hereditary and somatic mutations of replication error repair genes result in rapid onset of ultra-hypermutated cancers. Nat Genet, 2015. 47(3): p. 257-262.

Snyder, A., et al., Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med., 2014. 371.

Strome, S.E., et al., B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res, 2003. 63(19): p. 6501-5.

Sznol, M. and L. Chen, Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. Clin Cancer Res, 2013. 19(5): p. 1021-34.

van Elsas, A., A.A. Hurwitz, and J.P. Allison, Combination immunotherapy of B16 melanoma using anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and granulocyte/macrophage colony-stimulating factor (GM-CSF)-producing vaccines induces rejection of subcutaneous and metastatic tumors accompanied by autoimmune depigmentation. J Exp Med, 1999. 190(3): p. 355-66.

Weber, J.S., et al., Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. J Clin Oncol, 2013. 31(34): p. 4311-8.

Wolchok, J.D., et al., Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med, 2013. 369(2): p. 122-33.

Zehir, A., et al., Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med, 2017. advance online publication.

APPENDIX I - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

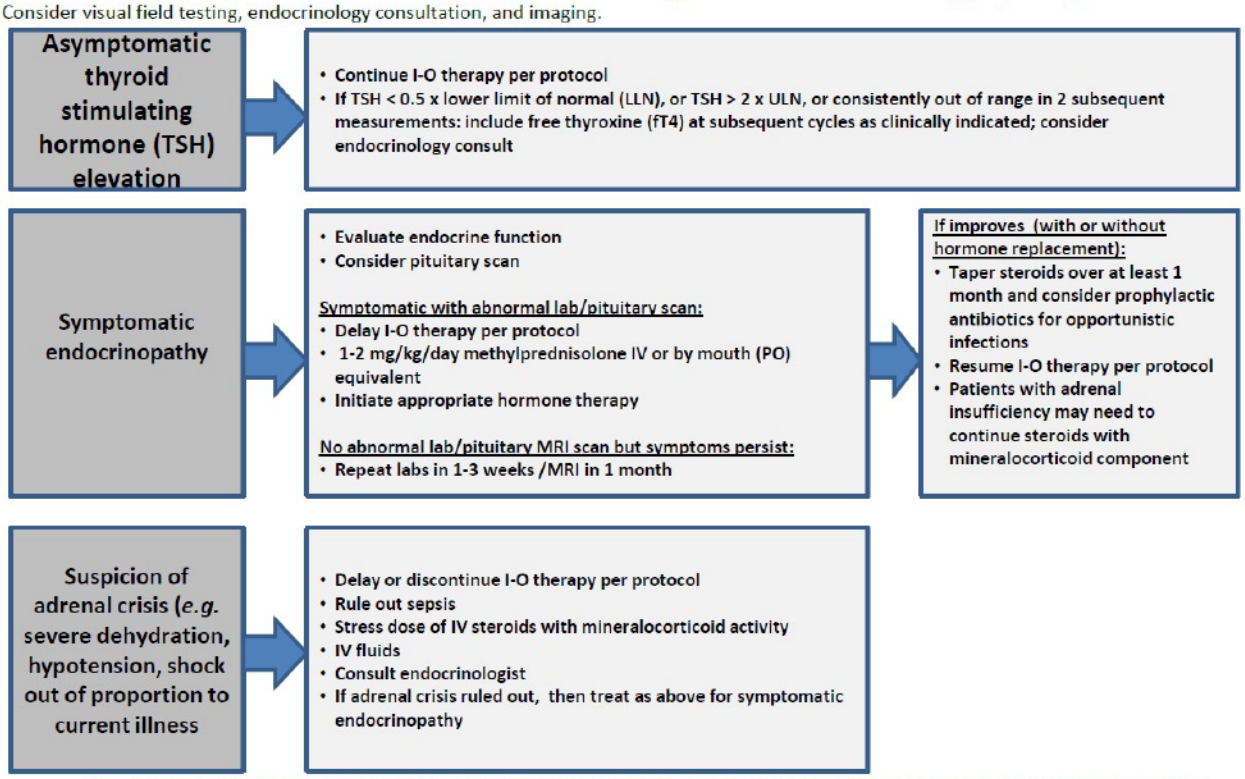
ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX II - MANAGEMENT ALGORITHMS FOR ENDOCRINOPATHY, GASTROINTESTINAL, HEPATIC, NEUROLOGICAL, PULMONARY AND SKIN ADVERSE EVENTS

Endocrinopathy Management Algorithm

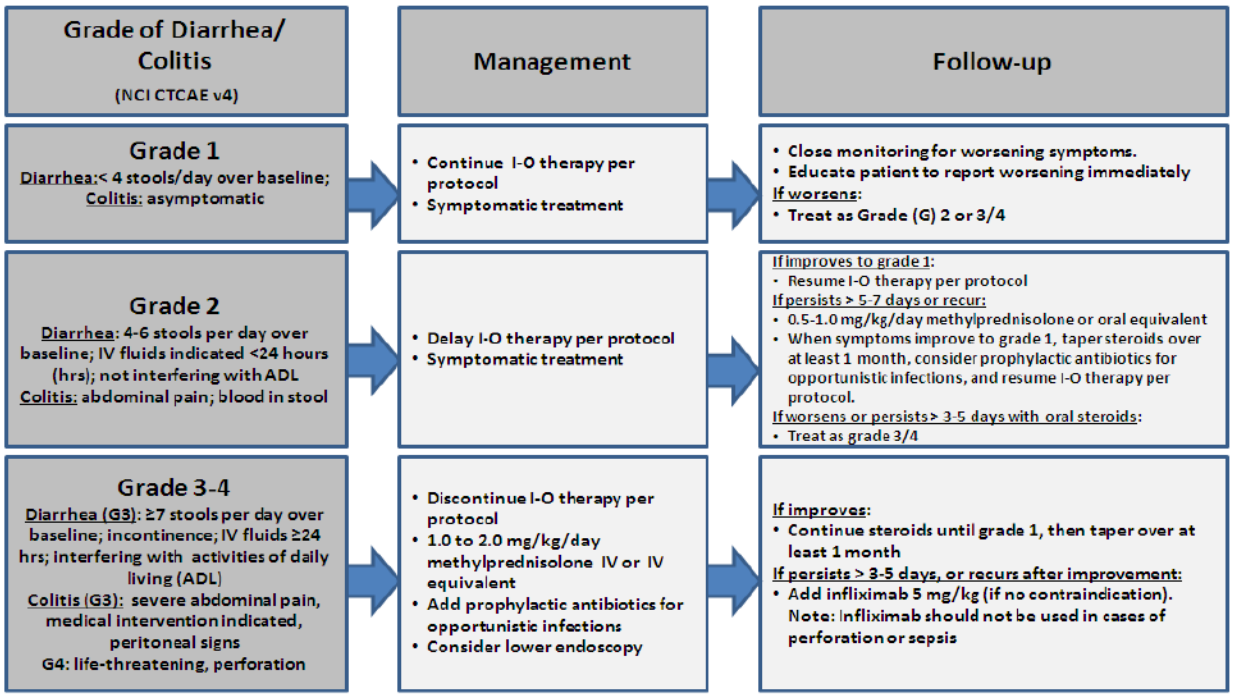
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy.
Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

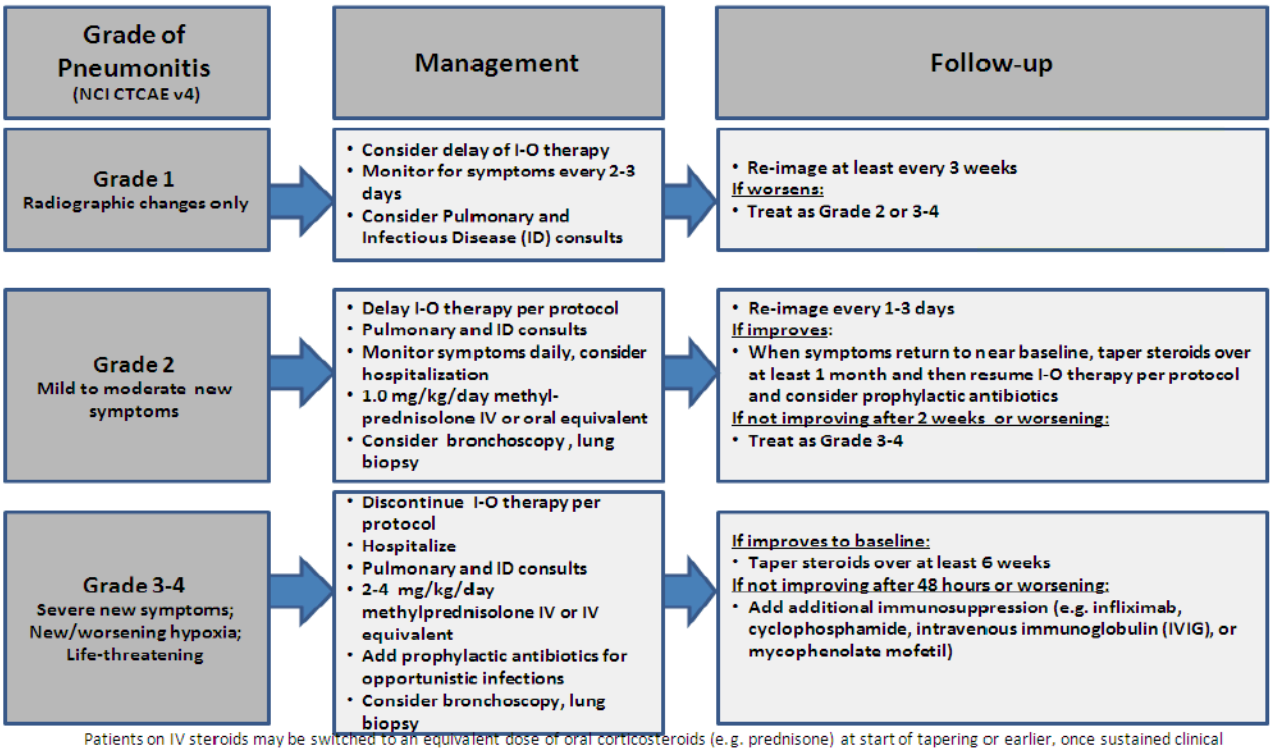
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > upper limit of normal (ULN) and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy	<u>If returns to Grade 1</u>: •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u>: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

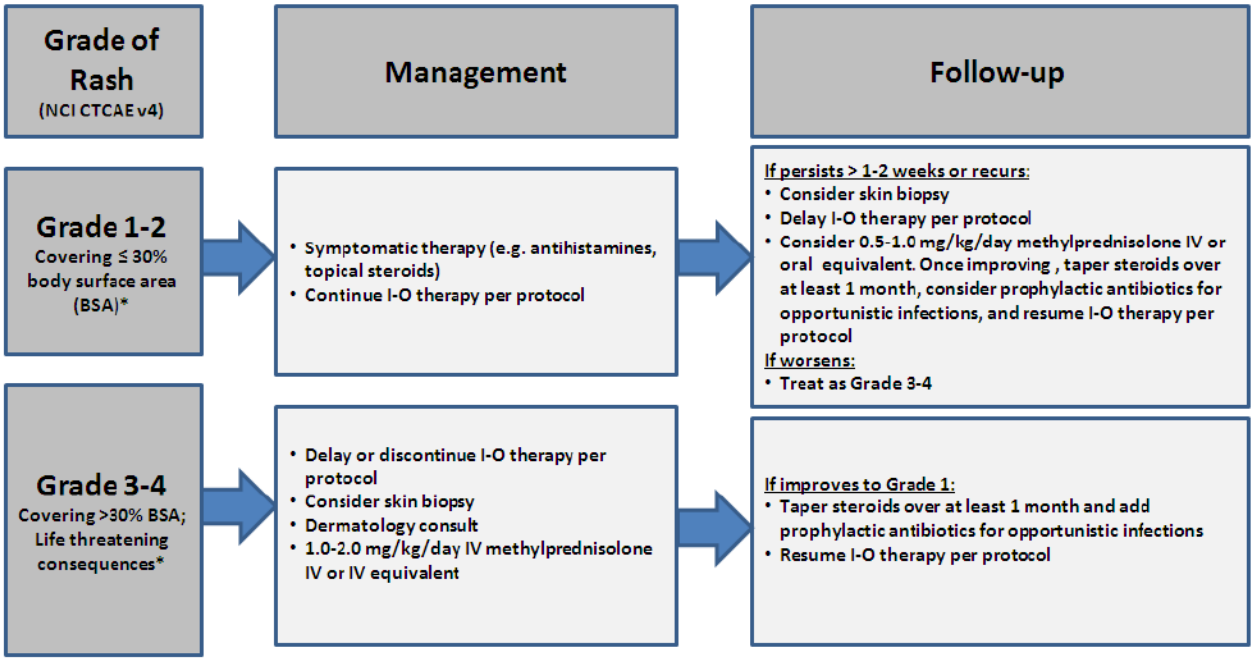
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin (T. bili) > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue liver function tests (LFT) monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN and /or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 gram (g) twice daily (BID) • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Distribution

Nivolumab and ipilimumab for the US will be supplied by Bristol Myers Squibb and distributed directly by the company to participating American centers. For Canada, nivolumab and ipilimumab will be supplied by Bristol Myers Squibb and distributed by a Canadian depot directly to Canadian centers.

Investigational product should be stored in a secure area according to local regulations and under the storage conditions stipulated on the investigational product label

Initial Drug Supply

Once a center is locally activated (following receipt and review of all required documentation), CCTG will authorize a start-up supply of nivolumab and ipilimumab to be shipped directly to the center. Drug will be shipped to the center within 10 working days of local activation.

Note: shipment will not be made on Mondays and weekends for American sites and they will not be made on Thursdays, Fridays and weekends for Canadian sites.

Drug accountability and drug re-order forms will be available on the CRI-CCTG-001 trial website.

Drug Ordering Resupply

For re-supply of nivolumab and ipilimumab, sites should print off and submit a Drug Re-Supply Form available on the CRI-CCTG-0001 website. This form should be submitted directly to the distributor. Once received, Bristol Myers Squibb and the Canadian drug vendor will process the request and initiate shipment of re-supply.

Please allow sufficient time for shipment of drug (up to 10 working days). Note: shipment will not be made on Mondays and weekends for American sites and they will not be made on Thursdays, Fridays and weekends for Canadian sites.

Drug Accountability

The investigational products are to be prescribed only by the Qualified Investigator or Sub-investigators having this delegated duty on the participants list. Under no circumstances will the investigator allow the drug to be used other than as directed by the protocol. Accurate records must be maintained, accounting for the receipt, dispensation, return and/or destruction of the investigational product utilizing the Drug Accountability Log, available on the CRI-CCTG-0001 trial website. At the end of the study, it must be possible to reconcile shipment records with records of usage/returned stock by completion of the study drug accountability form. Any discrepancies must be accounted for and documented.

Drug Destruction

Drug Destruction of Expired Medication

The CCTG Study Coordinator must be contacted prior to destruction of expired medication to ensure an extension of expiry date is not expected. Expired trial medication may be destroyed per local policy, AFTER accountability and reconciliation has been completed and documented by the site. Documentation of destruction must be kept on file in the site pharmacy and is subject to on site monitoring/audit.

Drug Destruction of Unused Medication (End of Trial)
Instructions for return or destruction of unused drug will be supplied at the time of expiry and at trial closure.

** PLEASE NOTE **
DRUG FROM THIS SUPPLY IS TO BE USED
ONLY FOR PATIENTS REGISTERED ON THIS STUDY

Study drug shipped to participating centers may be transferred from the main hospital pharmacy to a satellite pharmacy, provided separate drug accountability records are maintained in each pharmacy and appropriate storage is available. Investigational agent may NOT however, be transferred to pharmacies or physicians outside the participating center.

APPENDIX IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of registration and will apply to all eligible and ineligible patients. This trial will use a web-based Electronic Data Capture (EDC) system for all data collection including SAE reporting (see Section 9.0 for details regarding SAE reporting). For details about accessing the EDC system and completing the on-line Case Report Forms, please refer to the Data Management Guidebook posted on the CRI-CCTG-0001 area of the CCTG web-site (www.ctg.queensu.ca).

The ELECTRONIC CRFs to be used in this trial are:

Electronic Case Report Form	To be Completed/Submitted Electronically:	Supporting Documentation to be sent using Supporting Document Upload Tool*
PATIENT REGISTRATION AND ENROLLMENT	At the time of patient registration and enrollment (see ENTRY/REGISTRATION PROCEDURES).	Copy of the screening consent form signature page, if enrolled based on POLE/POLD1 mutation by tumor tissue testing, copy of report with results, copy of report from plasma cfDNA testing performed at screening.
BASELINE REPORT	Due within 2 weeks of patient registration.	Copies of signature pages of main, and optional consent forms; relevant pathology & radiology reports.
TREATMENT REPORT	To be completed every 6 weeks (i.e. after each cycle). Due within 2 weeks of end of course. This report documents treatment, adverse events, investigations and response assessment for each course.	Relevant radiology reports.
CORRELATIVE STUDIES	See Section 12.0.	
END OF TREATMENT REPORT	To be completed when patient goes off protocol treatment. Due within 2 weeks of end of protocol treatment.	
4 WEEK POST TREATMENT REPORT	To be completed once on all patients, 4 weeks after going off protocol treatment. Due within 2 weeks after contact with patient.	Relevant radiology reports.
FOLLOW-UP REPORT	Follow-up Report to be completed every 3 months until death or conclusion of trial. Due within 2 weeks after contact with patient.	Relevant radiology reports.
RELAPSE/ PROGRESSION REPORT	To be completed at the time of disease relapse or progression. Due within 2 weeks after contact with patient.	Relevant radiology reports.
DEATH REPORT**	Required for all patients while study is open. Due within 2 weeks of knowledge of death.	Autopsy report, if done.
SERIOUS ADVERSE EVENT (SAE) REPORT	All reportable serious adverse events must be reported as described in Section 9.0. Preliminary CCTG Serious Adverse Event Report due within 24 hours. Updated CCTG Serious Adverse Event Report due within 7 days.	All relevant test reports, admission, discharge summaries/notes and other documentation, as requested.

* Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. Supporting documents should be uploaded immediately after the report they refer to has been submitted electronically.

** NB It is the investigator's responsibility to investigate & report the date/cause of death of any patient who dies during this period. Any death that occurs during this protocol therapy or within 30 days after last dose must also be reported as a Serious Adverse Event as described in Section 9.0.

APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for Adverse Event (AE) reporting. 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/protocolDevelopment/electronic_applications/ctc.htm.

APPENDIX VI - THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

The 7th Edition of the TNM Classification of Malignant Tumours has recently been released. To facilitate this process, educational resources have been made available to promote the use of staging (visit http://www.cancerstaging.org). These staging criteria should be used for new trials.

LIST OF CONTACTS

PATIENT REGISTRATION
All patients must be registered with CCTG before any treatment is given.

	Contact	Tel. #	Fax #
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Caitlin Burns Study Coordinator, CCTG Email: cburns@ctg.queensu.ca *or* Dr. Janet Dancey Senior Investigator, CCTG Email: jdancey@ctg.queensu.ca *or* Dr. Martin Smoragiewicz Senior Investigator, CCTG Email: msmoragiewicz@ctg.queensu.ca	613-533-6430	613-533-2411
STUDY CO-CHAIRS	Dr. Naiyer Rizvi Study Chair Email: nar2144@cumc.columbia.edu	646-371-3141	212-305-3035
	or Dr. Patricia Tang Canadian Co-Chair Email: patricia.tang@albertahealthservices.ca	403-521-3688	403-283-1651
SERIOUS ADVERSE EVENT REPORTING See protocol Section 9.0 for details of reportable events.	Dr. Janet Dancey, Senior Investigator, CCTG *or* Dr. Martin Smoragiewicz, Senior Investigator, CCTG *or* Caitlin Burns Study Coordinator, CCTG	613-533-6430	613-533-2411
DRUG ORDERING See Appendix III for full details.	See Appendix III and trial website : https://www.ctg.queensu.ca/trials/ind/i235-cri-cctg-0001 For details and contact information		
ELECTRONIC DATA CAPTURE (EDC) AND RIPPLE (technical support)	CCTG Home Page (Toolbox): https://scooby.ctg.queensu.ca Email Support Staff at: support@ctg.queensu.ca		