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Clinical Trial Protocol (CA209-7LA)

A Phase I trial of Regorafenib, Ipilimumab, and Nivolumab (RIN) in Patients with Microsatellite Stable (MSS) Metastatic Colorectal Cancer Who Progressed on Prior Chemotherapy

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159 ABBREVIATIONS

Abbreviation	Meaning
AE	Adverse Event
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Coordinator
CRF	Case Report Form
CSFR1	Colony Stimulating Factor 1 Receptor
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DLT	Dose Limiting Toxicity
DSMC	Data & Safety Monitoring Committee
EHR	Electronic Health Record
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HFSR	Hand-foot skin reaction
IB	Investigator's Brochure
IDS	Investigational Drug Services
IND	Investigational New Drug
irAE	Immune Related Adverse Event
IRB	Institutional Review Board
MDSC	Myeloid Derived Suppressor Cells
MSI-H	Microsatellite Instability High
MSS	Microsatellite Stable
NCI	National Cancer Institute
OIDRA	Office of IND Development and Regulatory Affairs
OS	Overall Survival
ORR	Objective Response Rate
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death Ligand 1
PFS	Progression Free Survival
PI	Principal Investigator
PMT	Protocol Management Team
PR	Partial Response
RECIST	Response Evaluation Criteria In Solid Tumors
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SD	Stable disease
Treg	Regulatory T cell
TILs	Tumor Infiltrating Lymphocytes

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase I trial of Regorafenib, Ipilimumab, and Nivolumab (RIN) in Patients with Microsatellite stable (MSS) Metastatic Colorectal Cancer (CRC) Who Progressed on Prior Chemotherapy

Short Title: Regorafenib, Ipilimumab and Nivolumab in Refractory MSS CRC

Rationale:

Anti-programmed cell death protein-1 (anti-PD-1) antibodies, nivolumab or pembrolizumab as monotherapy are not effective in pMMR/MSS CRC. The combination of durvalumab plus tremelimumab in MSS colorectal cancer with progression on standard chemotherapy has been associated with an improvement in the median OS from 4.1 months (best supportive care) to 6.6 months. These improvements were not deemed of significant clinical magnitude to support the routine implementation of this regimen in metastatic colorectal cancer. However, it does support PD-1/CTLA-4 targeting as a regimen to build on in MSS colorectal cancer. Similarly, the combination therapy of Ipilimumab and Nivolumab achieved very little in improving overall survival and very few patients (<5%) responded to this combination. Regorafenib is approved for the treatment of metastatic colorectal cancer (mCRC) patients in 3rd or later line of therapy based on overall survival benefit. In a Phase Ib trial of Japanese patients with advanced pMMR/MSS CRC, the combination of regorafenib and nivolumab was safe and demonstrated significant activity with a confirmed objective response rate (ORR) of 33%.

The purpose of this study is to investigate the combination of regorafenib, ipilimumab and nivolumab (RIN) in MSS metastatic colorectal patients who progressed on standard systemic therapy in order to determine the safety and feasibility of this regimen and describe its clinical activity in an expanded safety cohort. We hypothesize that the combination of regorafenib, ipilimumab and nivolumab may result in improved efficacy and the ORR would be around 33% or higher, estimated from the Japanese study using the combination of Regorafenib and Nivolumab.

Objectives: objectives are listed in section 2.0

Number of Centers: Single Center Study

Number of Subjects: 26~32 evaluable patients will be enrolled on this study

Study Population: Patients participating on this study should have a diagnosis of MSS metastatic colorectal cancer and should have progressed on standard chemotherapy

Study Design:

Nivolumab and ipilimumab will be given at fixed doses of 240mg IV Q 2 weeks and 1mg/kg IV every 6 weeks, respectively. Regorafenib will start at 80mg orally once daily x 21 days every 28 days. A cycle will be defined as 28-day cycle. A cohort of 3 patients will be enrolled at the first dose level of regorafenib of 80mg, if 1 or less patients experience a Dose Limiting Toxicity (DLT), an addition 3 patients will be enrolled on cohort. When there is at most 1 patient have a DLT out of 6 patients, this dose will be considered the recommended expansion dose. If 2 or more patients have a DLT when treated with first dose level, an alternative dose of regorafenib of 40 mg x 21 days every 28 days will be investigated for safety with the same 3 + 3 design. If the lower dose is deemed non-tolerable the study will be suspended.

RP2D will be selected to enroll additional 20 patients for dose-expansion. PI may choose a lower dose safer than the dose level with 1/6 toxicity in the dose-selection stage. If DLT satisfying toxicities are noted in > 33% of patients at the RP2D level (with a minimum of 9 treated patients), then the study will evaluate a dose level -1 as the expansion dose (if RP2D is Dose Level 1) or will consider termination/ change treatment schedule and dose (if RP2D is Dose Level -1). A minimum of 10 patients should be treated in the expansion phase of the reduced dose.

Upon the completion of the enrollment of the intended cohort, we have noted significant clinical benefits that support the investigation of this regimen. In the first 13 patients enrolled on this study, only 3 patients had progressive disease on the first imaging study (2 months), one of whom has subsequent

disease regression at the 4-month mark (initial pseudoprogression). Therefore, the disease control rate in the treatment evaluable patients has been 11/13 patients. These results are highly promising in a refractory patient population where the disease control rate with other alternative therapies (trifluridine or regorafenib) are only 40% at 2 months. Seven patients had a radiographic assessment at 4 months so far, only 1 of whom had progressive. All 6/7 patients that were evaluable at the 4-month mark has disease regression, two of whom satisfied PR definition. In contrast, available FDA approved agents for our patient population (trifluridine or regorafenib monotherapy) have a response rate of 1%. Based on these initial exciting data, we are confident that our regimen will be explored further in patients with refractory colorectal cancer.

As we prepare to investigate this regimen in larger studies, it will be important to further refine toxicity management, especially as to what applies to regorafenib and immunotherapy related toxicity. Particularly, a transient grade 3 rash has been noted in our study and other combinations of regorafenib and nivolumab studies. This rash was non-DLT defining, occurred in the first cycle of treatment, responded promptly with complete resolution within 1 week to a short course of steroids, and did not recur with resumption of study treatment after rash resolution. We hypothesize that this rash is related to an initial "flare" associated with study treatment and should not lead to permanent dose reductions or modification is subsequent study dose treatment. While the current starting dose and regimen is feasible and appears on preliminary analysis to be associated with significant activity, it will be important to explore variant schedules that can reduce its incidence. Particularly, it will be important to assess if a lower dose of regorafenib of 40 mg daily on cycle 1, followed by escalation to 80 mg daily can result in better tolerance as far as skin related side effects. We are therefore proposing an additional 10 patient cohort to investigate this variant dosing.

Data and Statistical Plan:

A 3+3 design will be used to evaluate the safety of regorafenib given at 80mg (orally once daily x 21 days every 28 days or 40 mg once daily x 21 days every 28 days if the 80 mg dose level is not tolerated) when combined with nivolumab and ipilimumab at the fixed doses. Additional 20 patients will be enrolled for the dose-expansion part of the study at the selected RP2D. The dose-expansion study aims to estimate the ORR for the 3-drug combination and we anticipate the combination therapy will achieve ORR similar or higher than regorafenib combined with nivolumab at 33%. Exact binomial 95% confidence interval will be provided for the estimated ORR with Person-Klopper method. In addition, we will test the hypothesis ORR>=33% against historical data for nivolumab and ipilimumab alone with ORR <5%. With 26 patients treated at RP2D, a single arm Binomial test is able to reject the null hypothesis with type I error 0.05 and 99% power. For a more conservative estimate of the ORR at 21%, the test still has 82% power. The null hypothesis of 5% will be rejected when at least 4 out 26 patients respond with ORR>= 15.4%. When 5 out of 26 patients respond, the ORR is estimated 19.3% and the 95% C.I. by Person-Kleopper method rules out the true ORR less than 6.6%. When further reduction is made from the RP2D at dose level -1, with the minimum 10 patients, we will have 79% power to test the ORR at 33% against the null of <5% and the null will be rejected when >=3 patients respond.

An additional 10-patient cohort will be enrolled on study with a starting dose of regorafenib of 40 mg/day on cycle 1, to be escalated to 80 mg per day on cycle 2 if no dose limiting toxicities are noted on cycle 1. Transient G3 skin toxicity (non-DLT) has occurred so far in approximately ~40% (9/23) of patients and has been transient without recurrence. The expanded cohort will explore if this variant dosing results in better tolerance and eliminates the occurrence of this transient skin toxicity.

1.2 Study Calendar

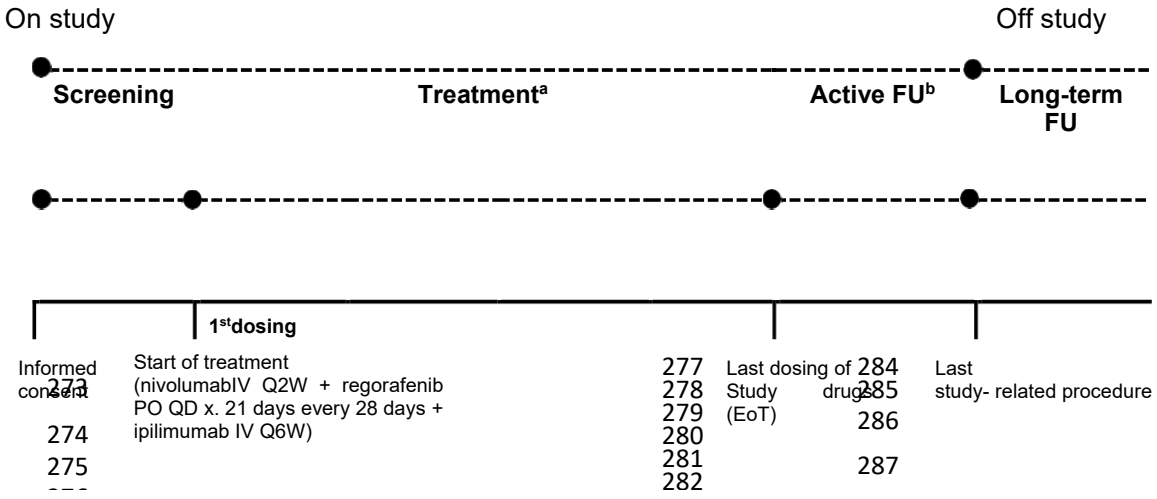
Schedule of activities are listed in Section 10.0

1.3 Schema

This study is composed of the following periods: Screening, treatment, active follow-up (FU), and long-term follow-up. Participants will be considered "on study" during screening, treatment and active FU periods. During the long-term FU period the participants will be considered "off study" (i.e.

no study-related procedures with the participant). An overview of the study schema is presented in Figure 1–1.

Figure 1–1: Study Schema



Abbreviations: C = cycle; D = day; EoT = End of treatment; FU = follow-up; i.v. = intra venous; LD = last dose; min = minute; q.d. = quaque die (once daily); Q4W = every 4 weeks; Q6W = every 6 weeks

a. Nivolumab 240 mg, IV fusion, every 2 weeks (Q2W). Regorafenib starting dose 80 mg orally every day (QD.) for 21 days of every 28 days. Ipilimumab, 1 mg/kg, IV infusion, every 6 weeks. If starting dose is not tolerated, regorafenib dose should be de-escalated to 40 mg orally daily.

b. Mandatory safety FU visit (at least 30 d after LD of regorafenib/ipilimumab/nivolumab and 100 d after LD of immunotherapy) and other active FU visits to collect safety and efficacy information for participants who discontinue study treatment without disease progression, if applicable.

2.0 OBJECTIVES

2.1 Primary Objectives

- The primary endpoint of this study is to determine the recommended dose level of the combination of regorafenib, nivolumab and ipilimumab in patients with advanced metastatic colorectal cancer

2.2 Secondary Objectives

- Assess the objective overall response rate per RECIST v1.1
- Estimate the duration of response, duration of stable disease (SD), progression free survival (PFS), and overall survival (OS)
- Describe the safety of this regimen as determined by frequency and severity of associated adverse events
- Describe the safety of a variant dosing strategy in 10 patients with an initial dose of regorafenib 40mg/ day on cycle 1 followed by escalation to 80 mg/day on cycle 2 and beyond

2.3 Exploratory Objectives

- Correlate the presence of colony stimulating factor 1 receptor (CSF1R)+ macrophages, regulatory T cells (Tregs), TILs (tumor infiltrating lymphocytes) and tumor PD-L1, CTLA-4 and PD-1 expression (at baseline and post treatment) on tumor biopsies with response rate
- Characterize the systemic immune alteration through evaluation of mandatory pre and post cycle 1, and cycle 2, and at progression blood draws

3.0 BACKGROUND

3.1 Standard Treatment of Metastatic Colorectal Cancer

Metastatic colorectal cancer remains the second cause of cancer death in the US, with an estimated 51,000 deaths in 2019 (American Cancer Society, www.cancer.org). While systemic chemotherapy and targeted therapy has evolved significantly over the last 20 years[1, 2], cures with systemic treatment remain elusive and 5-year overall survival rates remain dismal (14% for patients diagnosed between 2008 and 2014).

Systemic 5-fluorouracil (5-FU) based chemotherapy remains the mainstay of management for mCRC. The addition of irinotecan and oxaliplatin to 5-FU has improved the OS to a median of 21 months [3, 4]. With the addition of VEGF or EGFR targeting, the median OS in patients with mCRC has now reached to more than 30 months [5]. Therefore, the current standard of care for first-line treatment is combination cytotoxic chemotherapy using the fluoropyrimidine backbone (5-FU or capecitabine) with either oxaliplatin (FOLFOX or XELOX) or irinotecan (FOLFIRI or XELIRI) in combination with the anti-VEGF agent bevacizumab or anti-EGFR agents (cetuximab or panitumumab) for patients with left-sided, wild-type *RAS* and *BRAF*. Even as the disease progresses through initial lines of therapy, many patients maintain an adequate performance status to tolerate further therapy.

3.2 Third- or Later-line Therapy for Metastatic Colorectal Cancer

Limited treatment options are available for patients with metastatic colorectal cancer beyond 2 lines of therapies [6]. Based on OS benefit of the Phase III CORRECT trial, regorafenib was approved by the US Food and Drug Administration (FDA) for the treatment of mCRC patients who progressed following a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and an anti-EGFR when appropriate [7]. TAS-102, an oral agent that combines trifluridine and tipiracil hydrochloride, was approved by FDA in similar settings based on the improvement in overall survival compared to placebo (7.1 months vs 5.3 months, HR=0.68, 95% CI, 0.58 to 0.81; P<0.001) [8]. The limited added benefit in OS with these two agents calls for more efficacious treatment options in this patient population.

3.3 Immunotherapy for Colorectal Cancer

Colorectal tumors with MSI-H are associated with high mutation load, increased tumor infiltrating lymphocytes, and high expression of checkpoints such as PD-1, Lag 3, and CTLA-4 [9].Indeed, the targeting of PD-1 in patients with MSI-H has been associated with robust clinical responses, while little to no activity has been reported in tumors with microsatellite stability [10]. In preclinical and clinical settings, the combination of PD-1 inhibition and CTLA-4 inhibition has provided enhanced activity over anti-PD-1 monotherapy [11, 12]. Indirect comparisons suggest that nivolumab plus ipilimumab provides improved efficacy relative to nivolumab monotherapy alone in MSI-H mCRC (ORR 31% with nivolumab alone and 55% with nivolumab plus ipilimumab) [13, 14]. Such significant activity has led to a trial of combined PD-1/CTLA-4 targeting in the first line treatment of MSI-H colorectal cancer, where a 60% ORR was reported [15].

In MSS CRC tumors, PD-1 inhibition showed limited antitumor activity even after selecting for PD-L1 positive tumors [16]. The challenge of expanding the benefit of immunotherapy to patients with MSS colorectal cancer has been further demonstrated in IMblaze370 trial, where atezolimumab alone or in combination with cobimetinib did not improve the overall survival compared to regorafenib [17]. However, concurrent PD-1 and CTLA-4 targeting has been associated with an improved OS over best supportive care in patients with MSS advanced refractory colorectal cancer [18]. Although not significant enough to support clinical implementation, it does suggest that adding anti-CTLA-4 may improve the efficacy of PD-1 inhibition in an MSS population. Mechanistically, PD-1 inhibition and CTLA-4 inhibition act synergistically to promote T-cell antitumor immunity through complementary roles of action. Anti-CTLA-4 causes peripheral expansion of TCR clonotypes and PD-1 inhibition boosts this anti-tumor immune response by overcoming T cell exhaustion[19].

3.4 Immunomodulatory effects of Regorafenib

Regorafenib is a small molecular inhibitor targeting kinases involved in tumor angiogenesis and oncogenesis. The superior OS benefit in CORRECT trial (6.4 months vs 5.0 months, hazard ratio 0·77; 95% CI 0·64-0·94), has led to the approval of regorafenib for the treatment of mCRC patients in 3rd or later lines of therapy [7].Pre-clinical studies have demonstrated the enhanced concomitant anti-tumor activity of regorafenib and anti-PD-1 in in vivo CRC models [20]. Mechanistically, this effect may be mediated by a reduction of tumor associated macrophages (TAM) and reprogramming of TAMs toward M1 phenotype by the inhibition of CSF-1R by regorafenib[20], suppression of interferon gamma induced PD-L1 and IDO1 expression[21], and inhibition of VEGFR and its signaling pathway which may normalize tumor blood vessels and thereby improving cytotoxic T cell infiltration [22]. In addition, tumor biopsies from responding mCRC patients treated with regorafenib and nivolumab have shown a decrease in regulatory T-cells, therefore decreasing the immune suppressive processes in the tumor [23].

3.5 Rational for regimen development

There are limited treatment options for patients with mCRC after 2 lines of chemotherapy [6]. Significant interest has emerged in immunotherapy as a potential therapeutic strategy in mCRC. PD-1 inhibition, with or without CTLA-4 inhibitors, showed significant activity in patients with metastatic colorectal cancers in the setting of microsatellite instability (MSI-H), especially in patients with higher tumor mutation burdens [10, 13, 14, 24]. Such significant activity has led to the investigation of PD-1/CTLA-4 inhibitors in the first line treatment of MSI-H colorectal cancer. Indeed, recent data with the combination of the PD-1 inhibitor nivolumab and the CTLA-4 inhibitor ipilimumab showing promising response rates (RR) and progression free survivals (PFS) that surpasses historical data reported with chemotherapy [25]. However, microsatellite stable (MSS) tumors, have been proven resistant to anti-PD1 therapy, even when selecting for PD-L1 positivity [16]. There remains a significant unmet need to identify effective immunotherapy strategies for the 95% of metastatic colorectal cancers with MSS. One approach to improve on the activity of anti-PD-1/PDL-1 in MSS colorectal cancer is through concurrent CTLA-4 targeting. The combination of durvalumab plus tremelimumab in MSS colorectal cancer with progression on standard chemotherapy has been associated with an improvement in the median OS from 4.1 months (best supportive care) to 6.6 months (HR = 0.72) [18]. These improvements were not deemed of significant clinical magnitude to support the routine implementation of this regimen in metastatic colorectal cancer. However, it does support PD-1/CTLA-4 targeting as a regimen to build on in MSS colorectal cancer.

Regorafenib has immunomodulatory effects with pre-clinical studies showing beneficial combinatorial effects of regorafenib and anti-PD-1 in CRC in vivo models[20]. Recent clinical data has shown robust clinical activity with the combination of regorafenib and nivolumab in MSS chemotherapy-refractory colorectal cancers (RR 33%, median PFS 6.3 mo) [23]. We have treated 18 mCRC patients with this regimen, with 13 patients experiencing progressive disease (PD) on their first CT scan while 5 patients experienced stable disease (SD) and Carcinoembryonic Antigen (CEA) response (unpublished data). In addition, personal communication regarding the ongoing USA phase II trial of regorafenib + nivolumab suggest that the clinical benefits are considerably less than previously reported by the Japanese REGONIVO clinical study. Therefore, we hypothesize that the 33% RR reported on the Regorafenib plus Nivolumab trial is likely overrepresenting the efficacy of this regimen, and concurrent CTLA-4 inhibition may improve its efficacy. The purpose of this study is to investigate the combination of regorafenib, nivolumab, and ipilimumab (RIN) in MSS metastatic colorectal patients who progressed on standard systemic therapy to determine the safety and feasibility of this regimen and describe its clinical activity in an expanded safety cohort. We hypothesize that the combination of regorafenib, nivolumab and ipilimumab may result in improved efficacy.

Upon the completion of the enrollment of the intended cohort, we have noted significant clinical benefits that support the investigation of this regimen. In the first 13 patients enrolled on this study, only 3 patients had progressive disease on the first imaging study (2 months), one of whom had subsequent disease regression at the 4-month mark (pseudo-progression). Therefore, the disease control rate in the treatment evaluable patients has been 11/13 patients. These results are highly promising in a refractory patient population where the disease control rate with other alternative therapies (trifluridine or regorafenib) are only 40% at 2 months. Seven patients had a radiographic assessment at 4-month so far, only 1 of whom had

progressive. All 6/7 patients that were evaluable at the 4-month mark has disease regression, two of who satisfied PR definition. In contrast, available FDA approved agents for our patient population (trifluridine or regorafenib monotherapy) have a response rate of 1%. Based on these initial exciting data, we are confident that our regimen will be explored further in patients with refractory colorectal cancer.

As we prepare to investigate this regimen in larger studies, it will be important to further refine toxicity management, especially as to what applies to regorafenib and immunotherapy related toxicity. Particularly, a transient grade 3 rash has been noted in our study (39% (9 out of 23) of patients who completed 1+ months of treatment) and other combination of regorafenib and nivolumab studies. This rash was non-DLT defining, occurred in the first cycle of treatment, responds promptly (with complete resolution within 1 week) to a short course of steroids, and does not recur with resumption of study treatment after rash resolution. We hypothesize that this rash is related to an initial "flare" associated with study treatment and should not lead to permanent dose reductions or modification is subsequent study dose treatment. We are therefore proposing an additional 10-patient cohort with alternative dose modification to address the safety of re-escalation of regorafenib to the recommended dose in patients treated with RIN.

3.6 Overview of Study Design

This is a single-center safety and efficacy-assessment clinical trial [26]with regorafenib, nivolumab and ipilimumab for MSS metastatic colorectal patients who progressed on standard systemic therapy. The trial will follow a 3+3 design, followed by a treatment expansion cohort at the RP2D.

A cohort of 3 patients will be enrolled at the first dose level of regorafenib of 80mg orally once a day x 21 days every 28 days along with nivolumab 240 mg IV Q2weeks and ipilimumab 1mg/kg IV every 6 weeks. If 1 or less patients experience a DLT (defined in Section 11.1.), 3 additional patients will be enrolled on this cohort. If no more than 1 patient has a DLT out of 6 patients, this dose will be considered the recommended expansion dose. If 2 or more patients out of 6 or less patients at the first dose level have a DLT, an alternative dose of regorafenib of 40 mg x 21 days every 28 days will be investigated for safety in a similar 3 + 3 design. If the lower dose is deemed non-tolerable the study will be suspended.

An expansion cohort of 20 patients will be treated at the recommended dose of the combination of regorafenib, ipilimumab, and nivolumab (RIN). This cohort will provide additional data on the safety and tolerability of the recommended dose level of RIN while providing some additional efficacy information that will guide further the development of this study.

Now that we have completed enrollment on the expansion cohort, an additional 10-patient cohort will be enrolled on study and will interrogate regorafenib starting dose of 40mg per day on cycle 1, followed by 80 mg daily staring cycle 2 (in the event no dose limiting toxicities related to regorafenib are noted on cycle 1). This cohort will provide additional clinical safety to support re-escalation of regorafenib.

3.7 Justification for Dose

The starting dose and schedule of regorafenib and nivolumab is based on the phase 1 clinical trial presented by Shitara et al. at ASCO 2019[27]. A fixed dose of nivolumab will be used instead of 3mg/kg for the purpose of convenience. Such substitution (240 mg dosing) has become a standard approach for 3mg/kg dosing. This dose level was deemed tolerable and was associated with significant efficacy in patients with metastatic colorectal cancer who are resistant to standard therapies. In addition, ipilimumab will be dosed at 1mg/kg every 6weeks. This combination is based on the safety of this dose in combination with nivolumab at 3mg/kg Q2 weeks in a large metastatic MSI-H colorectal cancer cohort [25]. We do not expect intolerance to the combination of triple regimen given the excellent tolerance of the doublets regorafenib + nivolumab and nivolumab + ipilimumab at the proposed doses and therefore the propose start at the recommended doses of these doublet combinations. We have built in a dose de-escalation path in the event unexpected toxicity is noted at the first dose level.

4.0 STUDY POPULATION

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

4.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. A signed informed consent must be obtained prior to conducting any study-specific procedures.
2. Male and female adult participants 18 years of age or older on day of signing informed consent.
3. Histological or cytological confirmed advanced, metastatic, or progressive pMMR/MSS adenocarcinoma of colon or rectum.
    a) Microsatellite status should be performed per local standard of practice (e.g., IHC and/or PCR, or next-generation sequencing). Only participants with pMMR/MSS mCRC are eligible.
4. Known extended RAS and BRAF status as per local standard of practice.
5. Participant must have progressed following exposure of all the following agents or below:
    - Prior exposure to the following:
        a) Fluoropyrimidines (capecitabine or 5-FU)
        b) Irinotecan
        c) Oxaliplatin
        d) Anti-EGFR therapy if RAS and BRAF wild type with left colon primary
    - Patient must have evidence of progression on or after the last treatment regimen received and within 6 months prior to study enrollment
    - Patients who were intolerant to prior systemic chemotherapy regimens are eligible if there is documented evidence of clinically significant intolerance despite adequate supportive measures.
    - Adjuvant/neoadjuvant chemotherapy can be considered as one line of chemotherapy for advanced/metastatic disease if the participant had disease recurrence within 6 months of completion
6. ECOG Performance Status of 0 to1 (Appendix A).
7. Adequate hematologic and organ function as assessed by the following laboratory tests performed within 7 days before treatment initiation:
    - Total bilirubin ≤1.5 x the upper limit of normal (ULN)
    - Alanine transaminase (ALT) and aspartate aminotransferase (AST) ≤3 x ULN if no liver metastases; ALT or AST ≤5 x ULN allowed for patients with liver involvement
    - Platelet count ≥100,000 /mm3, Hemoglobin (Hb) ≥9 g/dL, WBC ≥2000/µL and absolute neutrophil count (ANC) ≥1500/mm3
    - Serum creatinine ≤1.5 x ULN or creatinine clearance ≥40 mL/min (measured or calculated using the Cockroft-Gault formula)
8. Measurable disease as determined by RECISTv1.1
9. Provision of recent tumor tissue (as defined below) is mandatory for all participants at screening (Formalin-fixed paraffin-embedded block or minimum of 20slides).
    - Tumor tissue obtained within 180 days of enrollment and after the last dose of most

recent anti-cancer therapy

- Or a new biopsy

Exceptions for patients with no recent baseline tumor tissues or biopsies may be considered after documented discussion and approval with the PI of the study

10. Anticipated life expectancy greater than 3months
11. Be able to swallow and absorb oral tablets.
12. Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study intervention and 120 days after last dose of regorafenib and 5 months after the last dose of nivolumab. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study intervention and 120 days after last dose of regorafenib and 7 months after the last dose of nivolumab. In addition, male participants must be willing to refrain from sperm donation during this time.

    Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Please refer to Appendix B for more information.

4.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Participants with MSI-H colorectal cancer
2. Prior therapy with regorafenib, anti-PD-1, PD-L1, or CTLA-4 inhibitors
3. Systemic anti-cancer treatment within 14 days or less than 5 half-lives (whichever is shorter) of the first dose of study treatment
4. Has unresolved clinically significant toxicity of greater than or equal to National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE, v5.0) Grade 2 attributed to any prior therapies (excluding anemia, lymphopenia, alopecia, skin pigmentation, and platinum-induced neurotoxicity)
5. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 3 months before the start of study medication (except for adequately treated catheter-related venous thrombosis occurring more than one month before the start of study medication)
6. Congestive heart failure ≥ New York Heart Association (NYHA) class 2 (Appendix G)
7. Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months), myocardial infarction less than 6 months before start of study drug
8. Uncontrolled cardiac arrhythmias
9. Poorly controlled hypertension, defined as a blood pressure consistently above 150/90 mmHg despite optimal medical management
10. Persistent proteinuria of NCI-CTCAE Grade 3. Urine dipstick result of 3+ or abnormal, based on type of urine test strip used, is allowed if protein excretion (estimated by urine protein/creatinine ratio on a random urine sample) is <3.5 g/24 hr
11. Major surgical procedure or significant traumatic injury within 28 days before start of study medication. Note: If participants received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy
12. Non-healing wound, non-healing ulcer, or non-healing bone fracture
13. Participants with evidence or history of any bleeding diathesis, irrespective of severity

14. Any hemorrhage or bleeding event ≥ NCI-CTCAE Grade 3 within 28 days prior to the start of study medication
15. Significant acute gastrointestinal disorders with diarrhea as a major symptom e.g., Crohn's disease, malabsorption, or ≥ NCI-CTCAE Grade 2 diarrhea of any etiology.
16. Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus (T1DM), hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
17. Participants with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
18. History of (non-infectious) pneumonitis that required steroids or current pneumonitis
19. History of interstitial lung disease
20. Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission prior to study entry and no additional therapy is required or anticipated to be required during the study period.
21. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy.
22. Presence of symptomatic central nervous system (CNS) metastases, or CNS metastases that require local CNS-directed treatment (such as radiotherapy or surgery). Participants with stable CNS disease or previously treated lesions are eligible for study entry. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of 10 mg daily prednisone (or equivalent).
23. Ongoing infection > Grade 2 NCI-CTCAE requiring systemic therapy.
24. Known history of human immunodeficiency virus (HIV) infection (HIV 1/2 antibodies).
25. Any positive test result for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating presence of virus, e.g. Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).
26. Pregnancy or breast feeding.
27. Psychological, familial, or sociological condition potentially hampering compliance with the study protocol and FU schedule.
28. Previous treatment with live vaccine within 30 days of planned start of study drugs (seasonal flu vaccines that do not contain a live virus are permitted).
29. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation.

5.0 PARTICIPANT ENROLLMENT

5.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained. The informed consent process is to be fully documented (see Section 17.4), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in Section 10.0.

5.2 Participant Enrollment

Eligible participants will be registered on the study centrally by the DCC at City of Hope. DCC staffs are available between the hours of 8:00 a.m. and 5:00 p.m. PST, Monday through Friday (except holidays).

- Phone: (626) 256-4673 ext. 83968
- E-mail: DCC@coh.org

5.3 Slot verification and reservation

Designated study staff should call the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject. Slots can only be held for a limited time.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

5.4 Registration Process

To register a participant, the subsequent procedure is to be followed.

1. The participating site's data manager/coordinator/research nurse should contact the DCC via telephone or email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The data manager/coordinator/research nurse should then e-mail copies to DCC@coh.org of the following documents to the DCC:
   - Completed Eligibility Criteria List (Section 4.0 of the protocol)
   - Source documentation to support eligibility criteria**
   - Signed subject's bill of rights and informed consent document
   - Signed HIPAA authorization form (if separate from the informed consent document)

   **Provide copies of source documentation only if not readily available as a finalized record in a COH Electronic Health Record (EHR).
3. After having received all transferred documentation, the DCC will complete their review of the documents to verify eligibility, working with the participating site as needed to resolve any missing required source elements. A participant failing to meet all protocol eligibility requirements will not be registered.
4. Once eligibility has been confirmed, DCC staff will register the participant by: assigning a subject accession number, registering the subject on study centrally into the COH clinical trials management system for non-COH participants, and enter the subject into the eCRF system.
5. Once registration has been completed, DCC staff will send a Confirmation of Registration Form within 24 hours, including the participant study number to:
   - The study team: treating investigator, protocol nurse, biostatistician, CRC and pharmacy
   - The COH sponsor team designees, including Study PI

5.5 Screen Failures and Registered Participants Who Do Not begin Study Treatment

Issues that would cause treatment delays should be discussed with the Principal Investigator.

The DCC is to be notified of all participants who sign consent but do not meet eligibility criteria or do not initiate protocol therapy.

5.6 Dose Level Assignment

Dose escalation/de-escalation will be assigned to a dose level per Section 6.3. Expansion cohort participants will be assigned to the tolerable dose level defined during the dose escalation/de-escalation process.

6.0 TREATMENT PROGRAM

6.1 Treatment Program Overview

This is a single-center safety and efficacy-assessment clinical trial with regorafenib, nivolumab and ipilimumab for MSS metastatic colorectal cancer patients who progressed on standard systemic therapy.

The study consists of 2 stages:

- **Dose Escalation/de-escalation Stage** (Section 6.3) to define the recommended dose and evaluate safety/tolerability of the combination regimen and
- **Expansion Stage** (Section 6.5) to preliminary evaluate activity or futility of the combination regimen

Protocol therapy will be administered in an outpatient basis until unacceptable toxicities or progression or treatment completion, whichever comes first. Treatment cycles will be 28 days.

Participants who achieve complete response (CR) per RECIST v1.1 and discontinue initial combination therapy may enter the **Re-treatment Phase** per investigator discretion (Section 6.8).

If one agent is discontinued due to toxicity, then the participant may continue with the other one or two agents depending on the nature of the toxicity.

Follow-up will occur post-treatment (Section 6.7)

Windows for all assessments and treatments are detailed in Section 10.0.

6.2 Cycle Definition

Treatment cycle will be a fixed 28 days (i.e. cycle count continues despite a hold in study agent/regimen). A new cycle is defined by the start date of a new cycle of regorafenib.

6.3 Dose Escalation/de-escalation Treatment Plan

A slightly modified 3+3 design will be used for dose escalation/de-escalation, up to 6 evaluable participants per dose level will be enrolled (Dose Escalation/de-escalation Schema 6.4). Two dose levels may be tested. If Dose Level 1 is not tolerable, Dose Level -1 will be tested (Table 6.3).

Regorafenib will be given at 80mg orally once daily x 21 days every 28 days and will be combined with fixed doses of nivolumab and ipilimumab.

A cohort of 3 patients will be enrolled at the first dose level of regorafenib of 80mg, if 1 or less patients experience a DLT, an addition 3 patients will be enrolled on cohort. If no more than one patient has a DLT out of 6 patients, this dose will be recommended for the expansion dose. If 2 or more patients have a DLT when treated at the first dose level, an alternative dose of regorafenib of 40 mg x 21 days every 28 days will be investigated for safety in a similar 3 + 3 design. If the lower dose is deemed non-tolerable the study will be suspended.

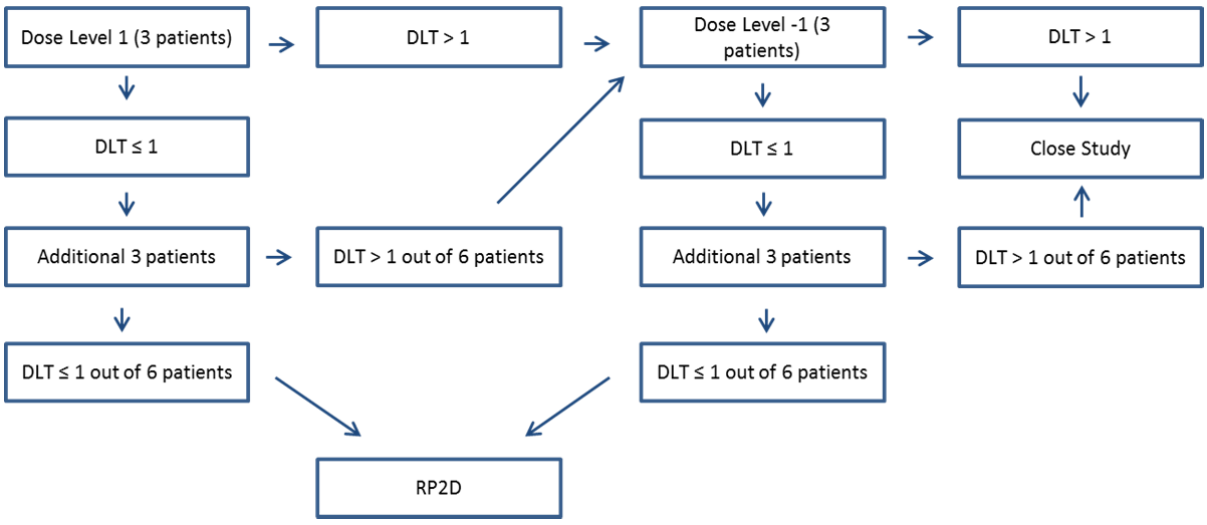
The determination of RP2D will be based on dose limiting toxicity observed from the time of first administration of RIN (cycle 1 day 1) until the planned administration of the third dose of nivolumab (cycle 2 day 1) that are attributable to any of the 3 agents or their combination.

Table 6.3 Dosing Regimen and Schedule

Dose Level	**Regorafenib** (Orally, once daily x 21 days every 28 days)	**Nivolumab** (IV, Q2weeks)	**Ipilimumab** (IV, every 6 weeks)
Dose Level -1	40 mg	240 mg	1 mg/kg

	Dose Level	Regorafenib (Orally, once daily x 21 days every 28 days)	Nivolumab (IV, Q2weeks)	Ipilimumab (IV, every 6 weeks)
Initial starting dose level	**Dose Level 1**	**80 mg**	**240 mg**	**1 mg/kg**

6.4 Dose Escalation/de-escalation Schema



6.5 Expansion Cohort Treatment Plan

Expansion cohort participants will be enrolled at the tolerable dose level defined by dose finding (Section 6.3). Accrual will continue until 20 evaluable participants at the recommended dose are treated. An additional 10-patient cohort will be added to the 20-patient expansion to investigate the possibility of lower starting dose of regorafenib of 40mg/day on cycle 1, followed by escalation to 80mg/day on cycle 2, as an alternative strategy to mitigate grade 3 and higher skin toxicities.

Patients enrolled during the dose escalation/de-escalation will be included along with the Expansion Stage for efficacy and safety analysis.

See Section 12.0 for details.

6.6 Duration of Therapy and Criteria for Removal from Protocol Therapy

Participants will receive protocol therapy with study agent(s) until one of the below criteria are met:

- Confirmed disease progression
  - **Note:** Participants with confirmed radiographic progression per RECIST v1.1 who are clinically stable but do not meet irRECIST (Appendix D) criteria for progression can continue to receive protocol therapy following consultation of the Study PI.
- The investigator determines that the participant does not require further therapy because the participant attained a **confirmed CR per RECIST v1.1AND** was treated for at least 8 cycles with combination therapy **AND** had at least 2 cycles of combination therapy beyond the date when the initial CR was declared
  - Refer to Section 6.8 for details regarding re-initiation of therapy for these participants.
- For CR participants who met criteria in Section 6.10 and re-initiated therapy: Received re-treatment for ~ 12 months
- Participant is deemed intolerant to protocol therapy because of toxicity, despite dose modification/ delay

- **Note:** If one agent is discontinued due to toxicity, then the participant may continue to receive the other study agent(s)as long as there is clinical benefit
- General or specific changes in the patient's condition which render the patient not candidate for further treatment in the judgment of the investigator
- Withdrawal of consent for further protocol therapy (Section 17.5)

Once participants meet criteria for removal from protocol therapy, the participant should then proceed to End of Treatment assessments, and then to follow-up (Section 6.7).

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF. The COH DCC and the Study PI should be promptly notified of the change in participant status.

6.7 Follow-Up

Following completion of protocol therapy, all participants will enter follow-up after End of Treatment assessments.

The following assessments may occur concurrently.

- **Follow-up for safety**- **(i)**30 days post-last dose of study treatment AND**(ii)** 90 days post-last dose of immunotherapy OR until initiation of a new anticancer therapy (whichever occurs sooner)
  - **Note** the period for safety follow-up will be extended until stabilization or resolution for all serious AEs (per the agreement of the Study PI) and accompanying follow-up safety report.
- **Follow-up for response**- for those who have yet to progress
- **Follow-up for survival**- for those who progressed or ended response follow-up.

Assessment time points and windows are detailed in Section 10.0.

6.8 Re-Initiation of Treatment If Previously Achieved CR (Re-Treatment Phase)

Participants with radiographic disease progression may re-initiate treatment per investigator discretion if:

1. Participants stopped initial treatment with combination therapy after attaining an investigator-determined confirmed CR according to RECIST 1.1, **AND**
2. Was treated for at least 8 cycles with combination therapy before discontinuing therapy; **AND**
3. Received at least 2 cycles of combination therapy beyond the date when the initial CR was declared

If re-initiation of therapy is being considered, such **participants must meet criteria** in Section 6.10 to receive~12 month of re-treatment.

If criteria in Section 6.10are met, participants should be re-treated at the same dose as when they last received protocol therapy.

Participants will be monitored for unacceptable toxicity (Section 11.1).

Participants who meet criteria in Section 6.6 to discontinue therapy will enter follow-up per Section 6.7.

6.9 Duration of Study Participation

Study participation may conclude when any of the following occur:

- Completion of study activities (treatment/ re-treatment and 5 years of follow-up)
- Withdrawal of consent (Section 17.5)
- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- At the discretion of the investigator for safety, behavioral, or administrative reasons
- Study closure with the IRB

Documentation of the reason for discontinuing study participation and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF. The COH DCC should be promptly notified of the change in participant status.

6.10 Criteria to Initiate Re-Treatment with combination therapy

Participants who achieved CR previously **must meet re-treatment criteria** below (Table 6.10) to receive re-treatment with regorafenib, ipilimumab and nivolumab.

Table 6.10 Criteria to Initiate Re-treatment with Combination Therapy

Criteria to be met in order to initiate Re-Treatment	Action if ALL criteria to the LEFT are NOT met
1. Participants stopped initial treatment with combination therapy after attaining an investigator-determined confirmed CR according to RECIST 1.1, **AND** Was treated for at least 8 cycles with combination therapy before discontinuing therapy; **AND** Received at least 2 cycles of combination therapy beyond the date when the initial CR was declared	Participant **can not** receive re-treatment with combination therapy
2. Confirmed radiographic progression	
3. Investigator determines re-treatment is in the best interest of the participant	
4. No anti-cancer treatment was administered since last dose of RIN protocol therapy	
5. ECOG ≤1	
6. Patient should satisfy all prior inclusion criteria with the exception of prior immunotherapy and regorafenib exposure (Section 4.1)	
7. The trial is open (closure of study treatment on this trial is anticipated once last patient has progressed or discontinued because of toxicities)	

7.0 STUDY INTERVENTION

Study intervention is defined as any investigational intervention intended to be administered to a study participant according to the study protocol.

7.1 Agent Administration

Each treatment cycle will be 28 days in duration. Regorafenib will be administered as two 40 mg tablets q.d. for 21 days of every 28 days as a starting dose of 80 mg. If the starting dose of 80 mg daily is not tolerated, dose should be de-escalated to 40 mg orally daily starting with C2D1 as detailed above.

When combined with nivolumab and ipilimumab, regorafenib will be administered prior to the nivolumab and ipilimumab infusion.

If a participant misses a dose and > 6 hours have passed since the scheduled dose time, the missed dose will be skipped and will not be made up. Doses that are vomited will not be made up.

Participants will be given a drug diary to document each dose of regorafenib that is taken or missed (Appendix E).

Nivolumab (240 mg, Q2W) will be administered as a 30-minute IV infusion per standard institution practice.

The ipilimumab dose is fixed at 1 mg/kg intravenously over 30 minutes once every 6 weeks, as per standard institution practice, immediately following nivolumab administration.

7.2 Preparation/Handling/Storage/Accountability

The Investigator (or designee) must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Study intervention should be stored in a secure locked location and at the recommended label temperature for the regorafenib 40 mg tablets in bottles, the nivolumab 100 mg/10 ml vials and the ipilimumab 200 mg/ 40 ml vials.

Note: The regorafenib bottle contains a desiccant. Once the drug has been received it has to be kept in a secure, dry location. The tablets must be stored in the original bottle according to the labeled storage advice. Regorafenib will be used as a commercial supply and be delivered to patient through a specialty pharmacy as is the standard process at City of Hope.

The personnel will use the study intervention only within the framework of this clinical study and in accordance with this protocol. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in a separate document.

7.3 Measures to Minimize Bias: Randomization and Blinding

Randomization and blinding are not applicable for this study.

This is an open-label study and all open label intervention at all visits must be assigned by the IxRS for tracking and accountability purpose.

- **Participant identification**

  After a participant has signed the PI/ICF, the participant will be assigned an identification number.

7.4 Study Intervention Compliance

The administration of intravenous nivolumab and ipilimumab will be performed in the clinical research unit at COH. The date and time of each infusion administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). Reasons for dose delay or infusion interruption will also be recorded in the source data and in the eCRF. The number of vials used will be recorded on the appropriate treatment dispensing form.

Participants will self-administer regorafenib at home, compliance with regorafenib will be assessed at each study visit. Compliance will be assessed by counting returned tablets. A record of the number of regorafenib tablets dispensed to and returned by each participant must be maintained and reconciled with regorafenib start and stop dates, including dates for dose delays and/or dose reductions which will also be recorded in the eCRF. Any discrepancies between actual and expected amount of returned study medication must be discussed with the participant at the time of the visit, and any explanation must be documented in the source records. An adequate record of receipt, distribution, and return/destruction of all study intervention must be kept.

7.5 Concomitant Therapy

7.5.1 Drug-Drug Interactions Relevant for Regorafenib

- **Inhibitors / Inducers of CYP3A4**

Concomitant use of strong inhibitors of CYP3A4 activity (Appendix F) are not permitted as their influence on the steady state exposure of regorafenib and its metabolites has not been studied.

Inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered

Appendix F provides an overview of the most commonly used strong CYP3A4 inhibitors and CYP3A4 inducers) that should be avoided during the study.

7.5.2 Permitted Concomitant Therapies

All concomitant medications (including start / stop dates, total daily dose, and indication) must be recorded in the patient's source documentation and in the eCRF.

Patients who are therapeutically treated with low molecular weight heparin or novel oral anticoagulants (NOACs) such as dabigatran or rivaroxaban will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists.

Patients may receive palliative or supportive care for any underlying illness (e.g.: anti-emetics, anti-diarrheal, IV fluids).

Bisphosphonates and/or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor therapies (such as denosumab) for bone metastases may be continued if treatment with an agent from one of these two classes was initiated prior to signing informed consent. Bisphosphonates and/or RANKL Bisphosphonates and/or RANKL inhibitor therapies cannot be initiated after informed consent has been signed, unless in the opinion of the investigator, the patient does not have PD.

Hematopoietic colony stimulating growth factors such as granulocyte colony stimulating factor (G-CSF) and other hematopoietic growth factors may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the Investigator; however they may not be substituted for a required dose reduction or used prophylactically. Patients taking chronic erythropoietin are permitted.

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses >10 mg daily prednisone are permitted. A brief (less than 3 weeks) 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 a contact allergen) is permitted

Radiotherapy:

- Palliative radiotherapy during the study is allowed for local pain control after individual benefit-risk assessment provided that:
  - In the opinion of the Investigator, the patient does not have PD,
  - No more than 25% of the patient's bone marrow is irradiated
  - The radiation treatment field may not include a target lesion by RECIST v1.1.
- Nivolumab and ipilimumab should be withheld for at least 1 week before, during and 1 week after radiation. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AE should resolve to Grade ≤1 prior to resuming therapy. Regorafenib may only be continued during palliative radiotherapy after an individual benefit-risk assessment. The Investigator should consult the Sponsor.

Major surgery for any reason different than symptom management or tumor control should only be performed during the study period if, in the opinion of the Investigator and after careful individual benefit/risk assessment (taking into account the potential wound healing complications that have been described with all anti-VEGF drugs), the surgery will be beneficial for the patient. It is recommended to stop study treatment two weeks before surgery. The decision to resume study treatment after surgery should be based on clinical judgment of adequate wound healing. Patients should be placed back on study therapy within 4 weeks of the scheduled interruption of regorafenib.

Patients may receive other medications that the Investigator deems to be medically necessary.

7.5.3 Prohibited Prior and Concomitant Therapies

Patients are prohibited from receiving the following therapies during the course of the study:

- Disease-specific anti-neoplastic therapies, including kinase inhibitors, immunotherapy, chemotherapy, hormonal therapy, non-palliative radiation therapy or experimental therapies other than regorafenib ipilimumab and nivolumab are not allowed.
- Any botanical preparation (e.g., herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- Surgery for symptom management or tumor control.
- Concomitant use of strong inhibitors of CYP3A4 and strong inducers of CYP3A4 (listed in Section Appendix F) are not permitted for 2 weeks prior to start of study intervention or during the study.
- Grapefruit and grapefruit juice (CYP3A4 inhibitor) consumption is not permitted during the study.
- Any live/attenuated vaccine (e.g., varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post LD of nivolumab. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
- Immunosuppressive agents and immunosuppressive doses of systemic corticosteroids (Exceptions: (i) Inhaled/topical steroids; (ii) systemic steroids at doses ≤ 10 mg/day prednisone/ equivalent, unless medically necessary to address toxicities related to auto-immune disease, or for other medical conditions that arise where no other suitable alternatives are present)

7.5.4 Documentation of Prior and New Concomitant Therapies

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

7.5.5 Rescue Medicine

Not applicable for this study intervention.

7.6 Dose Modification and Toxicity Management

Based on the known toxicity profiles of regorafenib, nivolumab and ipilimumab, certain AEs are likely to be associated with one drug versus the other. For example, treatment emergent hypertension and hand-foot skin reaction (HFSR) are likely to be associated with regorafenib rather than nivolumab and ipilimumab; similarly, immune-related AEs (irAEs) are likely to be associated with nivolumab and/or ipilimumab rather than regorafenib. However, some drug-related AEs such as diarrhea, abnormal thyroid function, and fatigue are overlapping. Therefore, it is important to evaluate each AE to confirm etiology or exclude other causes in order to determine proper management of the adverse reaction and action regarding study treatment. A careful decision should be made by Investigators based on all clinical information, e.g., relatedness to study medications.

Dose modifications must be based on the maximum toxicity experienced during a cycle. If appropriate, the Investigator may attribute each toxicity event to regorafenib or ipilimumab or nivolumab alone or to the combination. In situations where clear attribution cannot be made to individual drugs, more conservative dose modification approach should be used for all the drugs. In case of dose

modifications, any efforts should be made to restart study intervention as per original schedules for regorafenib nivolumab and ipilimumab.

7.6.1 Regorafenib

Section 6.3 outlines different regorafenib dose levels for the purpose of dose modification. In case dose de-escalation for regorafenib is necessary, the study intervention will be administered as outlined in Table 7-1 to Table 7-4.

Table 7-1: Regorafenib Dose Modification/Dose Interruption Guide:

(except HFSR, Hypertension, and Liver Function Test Abnormalities)

CTCAE Grade	Occurrences	Dose Interruption	Dose modification (when resuming treatment)
Grade 0-2	Any	No change	No change
Grade 3	1st and 2nd occurrence	Hold until recovery to <G2 or baseline[a]	Restart at same dose level or reduce 1 dose level (at the investigator's discretion)[b]
	3rd occurrence	Hold until recovery to <G2 or baseline[a]	Reduce 1 dose level or consider permanent discontinuation[b]
Grade 4	1st occurrence	Hold until recovery to <G2 or baseline[a]	Reduce 1 dose level or consider permanent discontinuation[b]
	2nd occurrence	Hold until recovery to <G2 or baseline[a]	Discontinue

Abbreviations: CTCAE = common terminology criteria for adverse events; G = Grade; HFSR = hand-foot skin reaction

a) Excludes: alopecia,non-refractory nausea/vomiting ,lymphopenia and asymptomatic laboratory abnormalities. Treatment can be resumed with grade 2 fatigue or hypothyroidism

b) If reductions are required resulting in regorafenib daily dose of less than 80 mg every other day, the regorafenib will be permanently discontinued. Subjects requiring a delay of >4 weeks should discontinue regorafenib treatment. However, continuation of regorafenib may be considered if, in the investigator's opinion, the patient may continue to benefit from the regorafenib treatment, and after consultation with the PI. Transient G3 skin rash toxicities that recover within 1 week to Grade 1 or less do not require dose reduction in regorafenib.

Table 7-2: Regorafenib Dose Modification Guidance: HFSR/ Palmar-Plantar Erythrodysesthesia Syndrome

Skin toxicity grade (CTCAE) Specific to HFSR	Occurrence	Dose Interruption	Dose modification (when resuming treatment)
G1	Any	Maintain dose level and institute supportive measures immediately for symptomatic relief	No Change
G2	1st occurrence	Interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade0–1	Institute supportive measures and continue same dose or consider decrease by 1 dose level
	No improvement within 7 d or 2nd occurrence	Interrupt until toxicity resolves or improves to G1.	When resuming treatment, treat at reduced dose level or consider discontinuation[a]
	3rd occurrence	Discontinue	
G3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for ≥ 7 d until toxicity resolves or improves to G1.	When resuming treatment, decrease by 1 dose level
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for ≥ 7 d until toxicity resolves or improves to G1.	When resuming treatment, decrease by 1 additional dose level or consider discontinuation[a]
	3rd occurrence	Discontinue	

Abbreviations: CTCAE = common terminology criteria for adverse events; G = Grade; HFSR = hand-foot skin reaction

a) If reductions are required resulting in regorafenib daily dose of less than 40 mg every day, the regorafenib will be

permanently discontinued. If toxicity returns to Grade 0-1 after dose reduction, dose reescalation is permitted in the subsequent cycle at the Investigator's discretion. Subjects requiring a delay of >4 weeks should discontinue regorafenib treatment. However, continuation of regorafenib may be considered if, in the investigator's opinion, the patient may continue to benefit from the regorafenib treatment, and after consultation with study PI.

Table 7-3: Regorafenib Dose Modification Guidance, Non-Immune Toxicities: Hypertension

CTCAE Grade	Suggested regorafenib dose interruption	Suggested regorafenib dose modification
Specific guidance for HYPERTESION		
G1	No change.	Consider increased BP monitoring
G2	If symptomatic, hold until symptoms resolve AND diastolic BP ≤ 90 mmHg. Treat with anti-hypertensive medications	At restart, continue at the same dose level
G3	Hold until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve. Treat with additional anti-hypertensive medications	At restart, continue at the same dose level.
	If BP is not controlled with the addition of new or more intensive therapy.	Reduce by 1 dose level
	If G3 hypertension recurs despite dose reduction and optimal antihypertensive therapy	Reduce another dose level or consider discontinuation[a]
G4	Discontinue	

Abbreviations: BP = blood pressure; CTCAE = common terminology criteria for adverse events; G = Grade; Hg = mercury

a) If reductions are required resulting in regorafenib daily dose of less than 40 mg every day, the regorafenib will be permanently discontinued. If toxicity returns to Grade 0-1 after dose reduction, dose reescalation is permitted in the subsequent cycle at the investigator's discretion. Subjects requiring a delay of >4 weeks should discontinue regorafenib treatment. However, continuation of regorafenib may be considered if, in the investigator's opinion, the patient may continue to benefit from the regorafenib treatment, and after consultation with the Study PI.

Table 7-4: Regorafenib Dose Modifications for Liver Function Test Abnormalities[a]

Increases in AST/ALT/Bilirubin[a,b]	Occurrence	Dose Interruption	Dose Modification (when resuming treatment)
(from baseline within normal limits) AST and/or ALT < 3 times ULN or total bilirubin < 1.5 times ULN	Any	**Continue dosing**	No Change
(from baseline AST/ALT more than 1 and up to 3 times ULN) AST or ALT more than 3 and up to 5 times the ULN	Any	**Continue dosing**	No Change
(from baseline within normal limits) AST or ALT more than 3 and up to 5 times the ULN or total bilirubin more than 1.5 and up to 3 times the ULN	1st occurrence	**Delay dosing until return to Grade ≤ 1 or baseline**	Reduce 1 dose level[c]
	Re-occurrence	**Discontinue**	
(from baseline any grade) AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN	1st occurrence	**Delay dosing until return to Grade ≤ 1 or baseline**	If the potential to reinitiate regorafenib is considered to outweigh the risk of hepatotoxicity: reduce 1 dose level
	Re-occurrence	**Discontinue**	
(from baseline any grade) AST and/or ALT > 20 x ULN	Any	**Discontinue**	
AST and/or ALT > 3 x ULN with concurrent bilirubin > 2 x ULN	Any	**Discontinue**[c]	

Abbreviations: ALT=alanineaminotransferase; AST=aspartateaminotransferase; ULN=upperlimitofnormal

a) In the event hepatic toxicity is attributed to the immunotherapy, and not to regorafenib, and resolves with steroids, regorafenib may be resumed at the dose level prior to hepatic toxicity.
b) For any of the events listed above (dose interruption or modification): monitor liver function tests weekly or more frequently until recovery to baseline or stabilization
c) If all values remain stable for 2 full cycles, dose re-escalation may be considered at the discretion of the Investigator. After re-escalation AST, ALT, bilirubin should be checked 2×/week for 2 weeks, followed by weekly assessments for at least 4weeks.
Exception: participants with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.

The dose modification can occur independently for the 3 drugs used if toxicity can be clearly attributed to one of the drugs. Resumption of regorafenib dosing is not required to receive further nivolumab and ipilimumab dosing and vice versa. Treatment with individual drugs (regorafenib or ipilimumab or nivolumab) may continue on schedule even if other drug is interrupted or permanently discontinued due to toxicity.

7.6.2 Nivolumab

There will be no dose reductions for nivolumab. If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. There are no recommended dose modifications for hypothyroidism or hyperthyroidism. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions.

Table 7-5: Recommended Dose Modifications for nivolumab

Adverse Reaction	Severity*	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	Withhold dose[a] in the case of diarrhea without suspected colitis. Discontinue in the setting of G3 colitis.
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis/non-HCC[b]	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal (ULN) or total bilirubin more than 1.5 and up to 3 times the ULN	Withhold dose[a]
	AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN	Permanently discontinue
Hepatitis/ HCC[b]	• If AST/ALT is within normal limits at baseline and increases to more than 3 and up to 5 times the ULN • If AST/ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times the ULN • If AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times the ULN	Withhold dose[c]
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue

Table 7-5: Recommended Dose Modifications for nivolumab

Adverse Reaction	Severity*	Dose Modification
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue[d]
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the ULN	Withhold dose[a]
	Serum creatinine more than 6 times the ULN	Permanently discontinue[d]
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue[d]
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reactions	 Withhold dose[a] Permanently discontinue[d]
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue[d]
	Grade 3 myocarditis	Permanently discontinue[d]
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue[d]
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue[d]

*Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCI CTCAE V5)

[a] Resume treatment when adverse reaction improves to Grade 0 or 1.

[b] HCC: hepatocellular carcinoma.

[c] Resume treatment when AST/ALT returns to baseline.

[d] In the event patients develop severe immunotherapy related toxicities that lead to nivolumab and ipilimumab withholding and in a setting where the patient is clearly deriving clinical benefit and has no other viable treatment options, the patient may be restarted on nivolumab only (without ipilimumab) after discussion with the Principal Investigator and only if the immune toxicities have resolved to G1 or less. In that setting, resumption of ipilimumab will not be allowed.

7.6.3 Ipilimumab

When ipilimumab is administered in combination with nivolumab, if ipilimumab is withheld, nivolumab should also be withheld. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Discontinue in patients with severe or life-threatening infusion reactions.

Table 7-6: Recommended Dose Modifications for Ipilimumab

Target/Organ System	Adverse Reaction (CTCAE v5)	Treatment Modification
Endocrine	Symptomatic endocrinopathy	Withhold ipilimumab Resume ipilimumab in patients with complete or partial resolution of adverse reactions (Grade 0 to 1) and who are receiving less than 7.5 mg prednisone or equivalent per day.
	• Symptomatic reactions lasting 6 weeks or longer • Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day	Permanently discontinue ipilimumab
Ophthalmologic	Grade 2 through 4 reactions • not improving to Grade 1 within 2 weeks while receiving topical therapy or • requiring systemic treatment	Permanently discontinue ipilimumab
All Other[a]	Grade 2	Withhold ipilimumab Resume ipilimumab in patients with complete or partial resolution of adverse reactions (Grade 0 to 1) and who are receiving less than 7.5 mg prednisone or equivalent per day.
	• Grade 2 reactions lasting 6 weeks or longer • Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day • Grade 3 or4	Permanently discontinue ipilimumab

[a]Does not apply to grade 3 skin toxicities which will be managed in a similar fashion as dictated in the nivolumab dose modification table

7.6.4 Management of Immune-Mediated AEs

Immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of nivolumab and/or ipilimumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of I-O reagents, administration of corticosteroids and/or other supportive care. To ensure early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and renal toxicity. These adverse event management algorithms are included in Appendix H.

These general guidelines constitute guidance to the Investigator. A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated. Corticosteroids are a primary therapy for immune related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

7.6.5 Treatment of Nivolumab and or Ipilimumab Related Infusion Reactions

All Grade 3 or 4 infusion reactions should be reported within 24 hours to the Sponsor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE, v5.0 guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms:

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab and/or ipilimumab administrations.

For Grade 2 symptoms:

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 25-50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/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 participant closely. If symptoms recur, then no further study medication will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: Diphenhydramine 25-50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab and/or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms:

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution 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. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

In 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).

Additional details on the immune mediated AEs of nivolumab and/or ipilimumab, including results from other clinical studies, are also available in the nivolumab and ipilimumab IB.

7.7 Intervention after the End of the Study

At the EOS intervention for each individual participant, further therapeutic options with drugs other than regorafenib and/or nivolumab are at the discretion of the Investigator.

8.0 AGENT INFORMATION

8.1 Nivolumab

Nivolumab is FDA approved for

- patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab.
- patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.
- patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.
- patients with metastatic small cell lung cancer with progression after platinum-based chemotherapy and at least one other line of therapy.
- patients with advanced renal cell carcinoma who have received prior antiangiogenic therapy.
- patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab.
- adult patients with classical Hodgkin lymphoma that has relapsed or progressed after:
    - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
    - 3 or more lines of systemic therapy that includes autologous HSCT.
- patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.
- patients with locally advanced or metastatic urothelial carcinoma who:
    - have disease progression during or following platinum-containing chemotherapy
    - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
    - adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab
    - patients with hepatocellular carcinoma who have been previously treated with sorafenib.

Please refer to the IB for a detailed description.

8.1.1 Other Names

OPDIVO

8.1.2 Description and Molecular Weight

Type	IgG4 kappa monoclonal
Source:	Humanized (from mouse)
Target:	PD-1 receptor
Molecular weight:	146kDa

8.1.3 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling

through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

8.1.4 Pharmacokinetics

Half-life elimination: 25 days

8.1.5 Formulation

Nivolumab is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. Nivolumab injection for intravenous infusion is supplied in single-dose vials. Each mL of nivolumab solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

8.1.6 Storage and Stability

The product does not contain a preservative. Store in a refrigerator (2°C to 8°C).

Store in the original package in order to protect from light.

The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

After preparation, store the nivolumab infusion either:

- at room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.

Do not freeze.

8.1.7 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the agent.

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

8.1.8 Dose Calculation

240 mg fixed dose= 3 vials (100 mg/10 ml) will be used to prepare the 240mg dose

8.1.9 Preparation

- Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

- Withdraw the required volume of nivolumab and transfer into an intravenous container.
- Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not exceed 160 mL.
- For adult and pediatric patients with body weights less than 40 kg, the total volume of infusion must not exceed 4 mL/kg of body weight.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of nivolumab

8.1.10 Administration

See Section 7.1.

8.1.11 Supplier

The agent will be supplied free of charge by BMS.

8.1.12 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using a drug accountability log.

8.1.13 Destruction and Return

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

Any unused agent at the end of the study, expired agent, and damaged agent will be destroyed according to applicable federal, state, local and institutional guidelines and procedures. **Prior** to the destruction, the DCC should be notified and an acknowledgement to proceed from the DCC should be received. Destruction will be documented in a drug accountability log.

8.2 Ipilimumab

Ipilimumab is FDA approved for

- Treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older)
- Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.
- Treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with nivolumab.

Please refer to the IB for a detailed description.

8.2.1 Other Names

YERVOY

8.2.2 Description and Molecular Weight

Type	IgG1 kappa monoclonal
Source:	Humanized (from mouse)
Target:	CTLA-4
Molecular weight:	148kDa

8.2.3 Mechanism of Action

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.

8.2.4 Pharmacokinetics

Half-life elimination: 15.4 days

8.2.5 Formulation

Ipilimumab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution for intravenous infusion, which may contain a small amount of visible translucent-to white, amorphous ipilimumab particulates. It is supplied in single-use vials of 200 mg/40 mL. Each milliliter contains 5 mg of ipilimumab and the following inactive ingredients: diethylenetriaminepentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), tris hydrochloride (3.15 mg), and Water for Injection, USP at a pH of 7.

8.2.6 Storage and Stability

- Store ipilimumab under refrigeration at 2°C to 8°C (36°F to 46°F).
- Protect ipilimumab from light by storing in the original carton until time of use.
- Do not freeze or shake.

8.2.7 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the agent.

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

8.2.8 Dose Calculation

8.2.9 Ipilimumab Injection is available via 200mg/40 ml single use vial.

8.2.10 Preparation

- Do not shake product.

- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter other than translucent-to white, amorphous particles.

Preparation of Solution

- Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of ipilimumab and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).
- Discard partially used vials or empty vials of YERVOY.

8.2.11 Administration

See Section 7.1.

8.2.12 Supplier

The agent will be supplied free of charge by BMS.

8.2.13 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using a drug accountability log.

8.2.14 Destruction and Return

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

Any unused agent at the end of the study, expired agent, and damaged agent will be destroyed according to applicable federal, state, local and institutional guidelines and procedures. **Prior** to the destruction, the DCC should be notified and an acknowledgement to proceed from the DCC should be received. Destruction will be documented in a drug accountability log.

8.3 Regorafenib

Regorafenib is FDA approved for

- Patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild- type, an anti-EGFR therapy
- Patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate
- Patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib

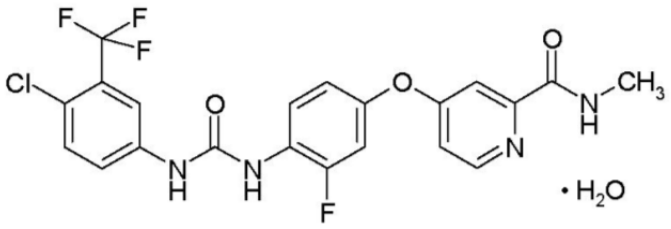
Please refer to the IB for a detailed description.

8.3.1 Other Names

STIVARGA

8.3.2 Description and Molecular Weight

Structural formula:



Empirical formula:	C21H15ClF4N4O3 • H2O
Molecular weight:	500.83
Chemical Name:	4-[4-({[4-chloro-3-(trifluoromethyl) phenyl] carbamoyl} amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide monohydrate

8.3.3 Mechanism of Action

Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, metastasis and tumor immunity. In in vitro biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, Abl and CSF1R at concentrations of regorafenib that have been achieved clinically. In in vivo models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model and inhibition of tumor growth in several mouse xenograft models including some for human colorectal carcinoma, gastrointestinal stromal and hepatocellular carcinoma. Regorafenib also demonstrated anti-metastatic activity in a mouse xenograft model and two mouse orthotopic models of human colorectal carcinoma.

8.3.4 Pharmacokinetics

Following a single 160 mg oral dose of STIVARGA, the geometric mean (minimum to maximum) elimination half-lives for regorafenib and the M-2 metabolite in plasma are 28 hours (14 to 58 hours) and 25 hours (14 to 32 hours), respectively. M-5 has a longer mean (minimum to maximum) elimination half-life of 51 hours (32 to 70 hours).

8.3.5 Formulation

Regorafenib tablet formulation will be used for this study.

8.3.6 Storage and Stability

Patients will be instructed to keep their pills at room temperature between 15 to 30°C (59 to 86°F).

Store tablets in the original bottle and do not remove the desiccant. Keep the bottle tightly closed after first opening.

8.3.7 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the unused agent.

8.3.8 Administration

See Section 7.1.

8.3.9 Supplier

The agent will be obtained as a standard of care prescription and will be obtained through a specialty pharmacy as is the standard approach at City of Hope.

8.3.10 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of patient compliance using a drug intake log.

8.3.11 Destruction and Return

Any unused agent, expired agent, and damaged agent will be destroyed according to applicable federal, state, local and institutional guidelines and procedures.

9.0 CORRELATIVE/ SPECIAL STUDIES

9.1 Correlative Research

Preclinical studies suggested that regorafenib treatment reduced tumor-infiltrating macrophages through inhibition of CSF1 receptor. A phase I clinical trial has demonstrated that response to the combination of regorafenib with nivolumab correlated with a decrease in effector Tregs. To study the immune alterations and identify biomarkers correlate to response RIN combination, we propose the following correlative studies to analyze the immune cells within tumors pre and post to treatment, as well as immune alterations in peripheral blood, before and after cycle 1 and cycle 2 and at progression. In addition, archival tissue will be requested, when available, all study patients. In addition, pre-treatment (within 2 weeks) before day 1 of cycle 1 and post-treatment (cycle 2, between day 14 and day 28), biopsies will be obtained from patients enrolled on the expansion arm when feasible (biopsy amenable).

1. Archived tumor samples and tumor biopsies (4 x 18 core needle biopsies when feasible) will be obtained and analyzed by multi-spectra IHC staining. Immune markers will be used include: CD163, CD68, CSF-1R, VEGFR-2, Foxp3, CD3, CD4, CD8, CD45RA, CD20, CD56, PD-1, CTLA-4 and PD-L1.
2. 15-color FACS analysis to phenotype immune cell subsets and functional readouts of biopsies and peripheral blood, including ex vivo cytokine production and signaling, markers include: CD3, CD8, CD4, FOXP3, CD45RA, CCR7, CD16, CD14, CD20, CD56, CD33, CD137, HLA-DR, PD-1, PD-L1, CTLA-4, IL-2, IFN-γ, TNF-α, T-bet, eomes, CD54, CD70, CD80, CD86
3. TCR repertoire analysis via deep sequencing of T cells in the peripheral blood. Expansion of the T cell repertoire after therapy may indicate epitope spread and suggest active immune response
4. 30-plex bead-based immunoassay on the Luminex platform to evaluate cytokines pre and post treatment involved in T cell activation, expansion, proliferation, differentiation as well as immunosuppressive cytokines

9.2 Correlative Tumor Study

An overview of collection, processing, and analysis details are shown in Table 9.2.

NOTE: Tumor correlative studies **do not** apply to participants undergoing re-treatment per Section 6.8.

Table 9.2 Tumor Tissue Studies Overview

Tissue Type & Timepoint of Collection	Receiving Lab	Downstream Analysis
If available/ feasible, FFPE archival tissue (Section 9.2.1)	Dr. Peter Lee's Laboratory Contact: Jian Ye(jiye@coh.org) or designee	Predictive markers of response or resistense
Research fresh tumor tissue(4 cores from 1 lesion/ timepoint; Section 9.2.2) • Within 21 days prior to Cycle 1 Day 1 • The 1st 3 weeks of cycle 2		• Immune cell profile in the tumor microenvironment • T cell evolution

9.2.1 Formalin fixed paraffin embedded (FFPE) archival tissue

- Tissue should precede prior RIN therapy
  - Upon notification to the Study PI that tissue is unavailable or cannot feasibly be obtained, **exceptions** may be granted by the Study PI.
  - If available and feasible, to be submitted anytime during screening/ during treatment.
- Ideally submit3 µm thick x 20 unstained slides and 3 µm thick X 1 H&E stained should to Dr. Lee's laboratory.
- Review of archival tissue and downstream analysis will be considered research.

9.2.2 Fresh tumor biopsies

- Provide **at least one day advance notice** to the Lee Laboratory of pending collection.
  - **Send calendar invite via e-mail** to Jian Ye(jiye@coh.org) or designee
- If feasible the same metastatic lesion should be sampled at both time points indicated above in Table 9.2.
- **Four cores** (each 4 x18 gauge needle biopsies) will be obtained **from the same lesion** at each time point for research purposes.

  NOTE: If it is not feasible/safe to obtain 3-4 cores / time point or obtain any cores, it will not be a deviation.

  1. Place 2 cores in saline **on ice** and promptly deliver to Dr. Lee's laboratory.
  2. Fix 2cores in formalin and embed in paraffin
     a. Send to COH Pathology for slide preparation.
     b. If feasible, per each core request 3 µm thick x 20 unstained slides and 3 µm thick X 1 H&E stained slide
     c. Send cut slides to Dr. Lee's laboratory.

9.3 Correlative Blood Study

Blood samples will be collected from an indwelling venous catheter or by venipuncture for the below stated analyses (see Table 9.3).

NOTE: Blood correlative studies **do not** apply to participants undergoing re-treatment per Section 6.8.

Table 9.3 Peripheral blood studies overview

Timepoint of collection	Volume per Timepoint	Tube Type	Processing/ Receiving Laboratory	Downstream Analysis
• Within 14 days prior to Cycle 1 Day 1 • End of Cycles 1-4 • Then end of every 3 cycles • At progression	30 mL	Green-top	Dr. Peter Lee's laboratory	• Circulating immune biomarker profile • Circulating ratio Tregs: effector T cells and ratio MDSC: effector T cells • Plasma cytokines

9.3.1 Notification of Pending Collection, Blood Collection and Labeling

Notification of Pending Collection to Lee Laboratory	Labeling and Collection Details	Post-collection Instructions
• Notify **at least one** day in advance) • **Send calendar invite via e-mail** to Jian Ye(jiye@coh.org) or designee	1. Label tubes with COH protocol #, subject ID, time of collection in 24-hour format, and timepoint of collection (e.g. D1C1 for Day1 of Cycle 1). 2. Timepoints of collection are stated in Table 9.2. 3. Invert tubes eight times after collection. 4. Place the tubes **on ice**.	• **Promptly** deliver the blood samples on ice to Dr. Lee's Laboratory**.**

9.3.2 Processing of samples by Lee laboratory

Samples will be processed for peripheral blood mononuclear cells (PBMC) and plasma.

10.0 STUDY CALENDAR

All assessments may increase in frequency as clinically indicated.

Re-treatment will follow the same assessments, tumor biopsy and blood correlative studies do not apply.

Table 10.0 Study Activity Calendar

	Screening	C1	C2	C3	C4	other cycles[i]	Off[j,m] treatment
Informed Consent[a]	X						
Demographics	X[c]						
Concurrent Meds	X[c]	X	X	X	X	X	X
Regorafenib D1-21 Nivolumab IV every 2 weeks Ipilimumuab IV every 6 weeks[b]		X	X	X	X	X	
Tumor Biopsy[d]	X		X			X	
Medical History and Height	X[c]						
Physical Exam and Toxicity Assessment	X[b]	X[f]	X	X	X	X	X
Vitals and Weight	X[b]	X	X	X	X	X	X
Performance Status	X[b]	X[f]	X	X	X	X	X
CBC, Diff, pls	X[b]	X[g]	X	X	X	X	X
Chemistry, amylase, lipase	X[b]	X[g]	X	X	X	X	X
CEA	X[b]	X[g]	X	X	X	X	
Urinalysis	X[b]	X	X	X	X	X	
B-HCG	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	
Tumor Assessment[k]	X[e]		X		X	X (every other cycle)	X[l]
EKG[n]	X						
Correlative Blood[o]	X	X	X	X	X	The end of every 3 cycles and at tumor progression	

C = cycle. Each cycle is comprised of 4 weeks. regorafenib will be given once daily PO x 21 days every 28 days; nivolumab will be given IV every 2 weeks, and ipilimumab will be

given IV every 6 weeks

a. The appropriate signed and dated ICF must be obtained before any study-specific procedures are performed
b. Procedures required ≤ 7 days before treatment; B-HCG pregnancy test should be performed in females who are still reproductive. A negative pregnancy test must be available within 24 hr before study drug administration
c. Procedures required ≤ 28 days before first treatment
d. Tumor biopsies will be performed within 2 weeks prior to study treatment and repeated in the last 2 weeks of cycle 2
e. CT scans (or MRI if indicated) will be performed every 8 weeks (2 cycles). CT scans can be done within +/- 14 days from the intended date.
f. Physical examination and toxicity assessment will be performed within 24 hours before weekly on cycle 1 and every other week on subsequent cycles. Physical examination and toxicity assessment do not have to be repeated on cycle 1 if already performed within 1 week before first treatment. Performance status should be documented every cycle of treatment. Physical exam will be performed on D1 and D15 of each cycle.
g. CBC, Diff, pls, chemistry (sodium, potassium, blood urea nitrogen (BUN), lactate dehydrogenase (LDH), magnesium, creatinine, total bilirubin, alkaline phosphatase, ALT, AST, calcium) will be performed on D1 and D15 of each cycle. CEA will be performed with the start of each cycle.
h. Urinalysis for the purpose of urine protein assessment will be performed every cycle
i. Patients without progressive disease will continue treatment until progression or until 2 years, whichever occurs earlier.
j. When a subject discontinues dosing for any reason, he/she will undergo a safety follow-up visit at 30 days (+ 7 days) after the last dose of all components of study treatment. After disease progression or unacceptable AEs, post-treatment follow-up will occur every 3 months (± 14 days) for survival- This can be performed through records review
k. CT scans of the abdomen, pelvis, and chest will be performed only for subjects who have withdrawn from the study for reasons other than progressive disease and have not had radiographic tumor assessments performed within the previous 6 weeks).
l. Disease assessment must be performed using modified RECIST criteria to assess tumor response (abdomen and pelvis ± chest). MRI is acceptable. Throughout the duration of the study, the subjects should be followed by the same scanning techniques and equipment as in the baseline scans.
m. Subjects who discontinue all components of study treatment due to unacceptable adverse events will also be assessed at each post-treatment follow-up visit for disease progression/survival and date of disease progression/death will be recorded
n. EKG is done within 4 weeks before starting on study. This is an important baseline for future comparison if needed and is recommended for patients on immunotherapy. The study may be repeated if clinically indicated.
o. Correlative research blood: Green-top tubes (30 mL per timepoint) should be placed **on ice**. **NOTE**: Refer to Section 9.3 regarding collection and advance notification of sample collection to Dr. Peter Lee's laboratory

11.0 ENDPOINT DEFINITIONS/MEASUREMENT OF EFFECT

11.1 Primary Endpoints

Primary Objectives	Endpoints/ Measurements
The primary objective of this study is to determine the recommended dose level of the combination of regorafenib, nivolumab and ipilimumab in patients with advanced MSS metastatic colorectal cancer	**Toxicities** will be graded per NCI CTCAE v5.0. • *During Cycle 1,* all grade toxicities with start and stop dates will be reported in the eCRFs. • *Cycle 2+ to end of Safety follow-up*, the highest grade for any toxicity plus Grade 3 or 4 event for the same toxicity (if not the highest grade) will be reported in the eCRFs. **Dose Limiting Toxicity:** per CTCAE v5.0, Any of the following adverse events occurring during the primary DLT observation period (4 weeks, from the time of first administration of RIN [Cycle 1 Day 1] until the planned administration of the second cycle of regorafenib [Cycle 2 Day 1] that are at least possibly attributable to any of the 3 agents or their combination will be classified as a DLT. Patients have to receive at least 75% of the intended doses of regorafenib on cycle 1 to be considered DLT evaluable. Patients who receive < 75% of the intended dose of regorafenib on the first cycle without satisfying the DLT criteria below will be replaced. • Any toxicity that would, in the opinion of the Study PI, prevent continued administration of protocol therapy • *Hematological* – Grade 4 anemia; – Grade 4 neutropenia lasting >7 days; – Febrile neutropenia, defined as absolute neutrophil count (ANC) <1000/mm3 with a single temperature of ≥ 38.3 degrees C (>101 degrees F) or a sustained temperature of 38 degrees C (100.4 degrees F) for more than 1 hour; – Grade ≥ 3 neutropenic infection; – Grade ≥ 3 thrombocytopenia with bleeding; – Grade 4 thrombocytopenia • *Non-hematological* - Non-hematologic Grade ≥3 laboratory abnormality if medical intervention is required to treat the patient, or if the abnormality leads to hospitalization. - Inability to administer the full intended dose of nivolumab/ ipilimumab or to receive at least 75% of the intended dosing of regorafenib in the DLT period (28-day cycle) due to toxicity - Any Grade ≥ 3 toxicity, except for any of the following: o Transient (≤6 hours) Grade 3 flu-like symptoms or fever, which is controlled o with medical management; o Transient (≤24 hours) Grade 3 fatigue, local reactions, or headache that o resolves to Grade ≤1; o Grade 3nausea and vomiting controlled by optimal medical therapy within 72 hours o Grade 3 hypertension controlled by medical therapy; o Grade 3 diarrhea or Grade 3 skin toxicity that resolves

Primary Objectives	Endpoints/ Measurements
	to Grade ≤1 in less than 7 days after medical management (eg, immunosuppressant treatment) has been initiated; o Any Grade ≥3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis; o Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor. . o Single laboratory values out of normal range that are unlikely related to trial treatment according to the investigator, do not have any clinical correlate, and resolve to Grade ≤1 within 7 days with adequate medical management are not considered DLTs. o o Laboratory values that are abnormal and without clinical significance and do not require medical intervention **NOTE:** AEs that would qualify as unacceptable toxicity by grade, were it not for attribution, must be probably or definitely attributed to another cause.

11.2 Secondary Endpoints

Secondary Objectives	Endpoints/ Measurements
1. Assess the objective overall response rate 2. Estimate the duration of response, duration of stable disease, PFS, and OS 3. Describe the safety of this regimen as determined by frequency and severity of associated adverse events	• RECIST v 1.1 (Appendix C) will be used to assess the following clinical outcomes: - **Progression-free survival**:Time to disease progression/ relapse or death as a result of any cause - **Duration of response**: Time to progression or death - **Overall survival**: Time to death as a result of any cause - **ORR**:the percentage of measurable disease participants who have achieved either complete response (CR) or partial response (PR) • **Incidence and severity of AEs** will be graded per NCI CTCAE v5

11.3 Exploratory Endpoints

Exploratory Objectives	Endpoints/ Measurements
1. Correlate the presence of CSF1R+ macrophages, Tregs, TILs (tumor infiltrating lymphocytes) and tumor PD-L1, CTLA-4 and PD-1 expression (at baseline and post treatment) on tumor samples with response rate 2. Characterize the systemic immune alteration through evaluation of mandatory pre and at the end of cycle 1-4, then end of every 3 cycles , and at progression blood draws	• **Archival tumor tissue** that preceded prior RIN therapy - *Predictive markers of response/resistense*: multispectral IHC analysis in 2 popuation (responders vs non-responders) • **Tumor tissue biopsies** obtained pre-treatment and post-treatment with combination therapy will be used to for the following: - *Immune profile in the tumor microenvironment*:Change in immune cell profileand correlation to treatment response via mass spectrometry immunohistochemistry and flow analysis - *T cell evolution*: Change in T cell clonality via deep-sequencing • **Serial blood samples** collected pre-treatment and during-treatment - *Circulating immune biomarker profile*: Changes in Immune biomarker profile in the peripheral blood mononuclear cells

Exploratory Objectives	Endpoints/ Measurements
	(PBMC) compartment via multi-color flow cytometry - *Circulating ratio Tregs: effector T cells and ratio MDSC*: *effector T cells*: Number of circulating immunosuppressive T regulatory cells (Tregs), myeloid derived suppressor cells (MDSC) and effector T cells - *Plasma cytokines*:Plasma cytokine level changes and profile

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design

This is a safety and activity trial[26], to evaluate RIN in MSS refractory metastatic CRC patients. Two dose levels may be evaluated (see Section 6.3).Dose level 1 will be deemed tolerable if ≤1/6 patients experience unacceptable toxicities during Cycle 1. If ≥ 2/6 patients experience unacceptable toxicities during Cycle 1, then Dose Level -1 will be tested. Dose level -1 will be deemed tolerable if ≤1/6 patients experience unacceptable toxicities during Cycle 1. If ≥ 2/6 patients experience unacceptable toxicities during Cycle 1, then Dose Level -1 the regimen will be deemed intolerable and the study will close. RP2D will be selected to enroll additional 20 patients for dose-expansion. If DLT satisfying toxicities are noted in > 33% of patients at the RP2D level (with a minimum of 9 treated patients), then the study will evaluate a dose level -1 as the expansion dose (if RP2D is Dose Level 1) or will consider termination/ change is treatment schedule and dose (if RP2D is Dose Level -1). A minimum of 10 patients should be treated in the expansion phase of the reduced dose.

An additional 10-patient cohort is added as an additional cohort to investigate the feasibility and safety of an alternative regimen of a lower starting dose of regorafenib at 40mg/day for cycle and then escalate to 80mg/day starting cycle 2 and beyond. This cohort will determine if such a strategy can reduce the incidence of grade 3 skin toxicities. An incidence of < 3 grade 3 skin toxicities in this 10-patient cohort would be considered favorable.

12.1.1 Primary Endpoints:

The primary end point is to determine the recommended dose level by measuring safety/tolerability. Tolerability is operationally defined as freedom from DLT, as defined in Section 11.1. Tolerability is monitored throughout the trial.

12.1.2 Secondary Endpoints:

The secondary endpoint is clinical activity using RECIST v 1.1 include ORR, PFS, DOR, and OS.

12.1.3 Exploratory Endpoints:

Correlative studies using serial tumor tissue and blood samples will assess immune response at pre-treatment and post-treatment.

12.2 Evaluable Participants and Participant Replacement

- ***Evaluable for toxicity*:** All patients who receive at least one dose of RIN will be evaluable for toxicity.
- ***Evaluable for DLT***:

Participants will be considered evaluable for DLT if:

1. They receive 1 ipilimumab, 1 nivolumab dose **AND** at least 75% of the planned regorafenib dose during Cycle 1;**OR**
2. They experience an DLT during Cycle 1 (Section 11.1).

Evaluable for Response: Participants will be considered evaluable for response if they are confirmed eligible, receive at least one dose of each of the study agent (Regorafenib, ipilimumab and nivolumab) and have had their disease re-evaluated by imaging at least once during treatment/follow-up, or are deemed to have clinical progression prior to imaging, or experience early death due to disease prior to imaging

12.3 Sample Size, Accrual Rate and Study Duration

- ***Total accrual*:** The total number of participants treated is expected to be 26 response-evaluable patients. If UT events were to require a reduction in regorafenib dose, a total of 32 patients

may be required. 29 patients have enrolled on the safety and expansion cohort. An additional 10-patient cohort will be added to investigate a lower starting dose of 40mg daily on cycle 1, followed by the identified recommended dose of 80 mg daily starting cycle 2 and beyond in order to reduce grade 3 and above skin toxicities. The total enrollment will be 39 patients.

- ***Accrual rate and Study Duration***: Assuming 2 patient enrolls each month, accrual is expected to be completed in 13-16 months. Study duration is planned for 3years.

12.4 Stopping Rules – Treatment-Related Death

A treatment-related death at any point will cause the trial to be halted, and a full review of the data by the COH Data Safety Monitoring Committee (DSMC) will be mandated. Patient accrual will not resume until approved by the regulatory committees, including DSMC.

12.5 Statistical Analysis Plan

Safety and tolerability will be addressed by summarizing the incidence of adverse events by MEDDRA term, and grade, with any unacceptable toxicities identified, and with aggregation by organ systems.

A 3+3 design will be used to evaluate the safety of regorafenib given at 80mg (orally once daily x 21 days every 28 days or 40 mg once daily x 21 days every 28 days if the 80 mg dose level is not tolerated) when combined with nivolumab and ipilimumab at the fixed doses. Additional 20 patients will be enrolled for the dose-expansion part of the study at the selected RP2D. The dose-expansion study aims to estimate the ORR (CR + PR) by RECIST v1.1 for the 3-drug combination and we anticipate the combination therapy will achieve ORR similar or higher than regorafenib combined with nivolumab at 33%. Exact binomial 95% confidence interval will be provided for the estimated ORR with Person-Klopper method. In addition, we will test the hypothesis ORR>=33% against historical data for nivolumab and ipilimumab alone with ORR <5%. With 26 patients treated at RP2D, a single arm Binomial test rejects the null hypothesis with type I error 0.05 and 99% power. For a more conservative estimate of the ORR at 21%, the test still has 82% power. The null hypothesis of 5% will be rejected when at least 4 out 26 patients respond with ORR>= 15.4%. When 5 out of 26 patients respond, the ORR is estimated 19.3% and the 95% C.I. by Person-Kleopper method rules out the true ORR less than 6.6%. When further reduction is made from the RP2D at dose level -1, with the minimum 10 patients, we will have 79% power to test the ORR at 33% against the null of <5% and the null will be rejected when >=3 patients respond.

Secondary endpoints of survival and PFS will be summarized using the Kaplan-Meier method. Duration of response (possibly censored) will be reported for each response.

The exploratory endpoints will be summarized using exploratory methods. Changes in tumor and blood measurements from pre-treatment to post-treatment will be displayed graphically and summarized with responding individuals identified. Academic standard statistical methods will be used for these exploratory analyses.

13.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

13.2 Data Capture Methods and Management

Data for this trial will be collected using City of Hope's electronic capture system that is compliant with 21 CFR Part 11.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

13.3 Case Report Forms/Data Submission Schedule

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

The investigator is responsible for all information collected on subjects enrolled in this study. All data collected during this study must be reviewed and verified for completeness and accuracy by the investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated in Section 13.2.

13.4 Regulatory Records

The investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

14.0 DATA & SAFETY MONITORING PLAN, ADVERSE EVENT AND UNANTICIPATED PROBLEM REPORTING

14.1 Definitions

14.1.1 Adverse Event (AE)

An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

14.1.2 Serious Adverse Event (SAE)

A serious adverse event is any expected or unexpected adverse events that result in any of the following outcomes:

- Death
- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary malignancy*
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

*Modified from 21 CFR 312.32

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

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

14.1.3 Unanticipated Problems Involving Risks to Subjects or Others

An unanticipated problem is any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol,

informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**

2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**

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

14.1.4 Pregnancy and Breastfeeding

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

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

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

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

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

14.1.5 Abnormal liver function tests

Liver function tests that meet the following criteria as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing must be reported expeditiously to BMS.

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

14.2 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, assessing the severity (i.e. grade), expectedness, and attribution of all adverse events.

14.2.1 Assessment of Adverse Event Name and Grade

Adverse events will be characterized using the descriptions and grading scales found in the most recent version of CTCAE. A copy of the scale can be found at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. The determination of severity for all other events not listed in the CTCAE should be made by the investigator based on medical judgment and the severity categories of Grade 1 to 5 as defined below:

- Grade 1 (mild) – An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Grade 2 (moderate) – An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- Grade 3 (severe) – An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
- Grade 4 (life threatening) – An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
- Grade 5 (fatal) – Death (loss of life) as a result of an event.

14.2.2 Assessment of Attribution

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely –** The event is doubtfully related to the investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions, or concomitant drugs.
- **Definite –** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs, AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

14.2.3 Assessment of Expectedness

The following definitions will be used to determine the expectedness of the event:

- **Unexpected** – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural

progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event. *Modified from 21 CFR 312.32 (a)

- **Expected –** An adverse event is expected if it does not meet the criteria for an unexpected event, OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

14.3 Reporting of Adverse Events

14.3.1 Routine Reporting of Non-Serious Adverse Events

Routine AE recording will occur via data entry into the study eCRF. Recording of adverse events will begin after the patient is given the study treatment or any study related procedures. Adverse events will be monitored by the Protocol Management Team (PMT). Adverse events that do not meet the criteria of serious OR are not unanticipated problems do not require expedited reporting. AEs reported through expedited processes (i.e. reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

14.3.2 Expediting Reporting Requirements of SAEs and UPs

Adverse events that meet the criteria of serious OR are unanticipated problems will be reported according to the approved City of Hope's Institutional policy via the AE/UP reporting form in iRIS. Reportable serious adverse events must be followed until the event is resolved, stabilized, or determined to be irreversible by the investigator. Follow-up SAE reports must be submitted for all events that require expedited reporting when the status of the event changes and until the resolution or stabilization of the event.

14.3.3 Additional AE Reporting Requirements

14.3.3.1 Reporting to the FDA

The study PI (or designee) will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope's Institutional policy.

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the Medwatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

In addition, the study PI will submit annually within 60 days (via COH OIDRA) of the anniversary date of when the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report of adverse drug experiences, and history of actions taken since the last report because of adverse drug experiences.

14.3.3.2 Reporting to BMS

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100days of discontinuation of dosing must be reported to BMS Worldwide Safety,

whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

An appropriate SAE form (e.g.ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS. If you prefer to use your own Institutional form, it must be reviewed by the BMS Protocol Manager prior to study initiation to ensure that at a minimum all of the data elements on the CIOMS form are present. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.

- ✓ The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
- ✓ The MedWatch form is available at: MedWatch 3500 Form

- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection.
- The Sponsor will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).
  - The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
  - GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
  - The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).
- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).
- In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.
  - ✓ Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.

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

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

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

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

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

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

All SAEs should be followed to resolution or stabilization.

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

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

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

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

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

NONSERIOUS ADVERSE EVENT

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

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin following the subject's written consent to participate in the study. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 90 days following the last dose of study treatment.

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

Laboratory Test Abnormalities

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

The following laboratory abnormalities should be documented and reported appropriately:

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

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

15.0 PROTOCOL DEVIATIONS &SINGLE SUBJECT EXCEPTIONS

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. Brief interruptions and delays may occasionally be required because of travel delays, airport closures, inclement weather, family responsibilities, security alerts, government holidays, and so forth. Delays can also extend to complications of disease or unrelated medical illnesses not related to disease progression. The PI has the discretion to deviate from the protocol when necessary so long as such a deviation does not threaten patient safety or protocol scientific integrity. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

15.1 Definitions

15.1.1 Deviation

A deviation is a divergence from a specific element of a protocol that occurred without prior IRB approval. Investigators may deviate from the protocol to eliminate immediate hazard(s) for the protection, safety, and well-being of the study subjects without prior IRB approval. Examples include, but are not limited to: a) dose adjustments based on excessive patient weight; b) alteration in treatment schedule due to non-availability of the research participant for treatment; and c) laboratory test results which are slightly outside the protocol requirements but at levels that do not affect participant safety.

15.1.2 Single Subject Exceptions (SSE)

An SSE is a planned deviation, meaning that it involves circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient. It is a deviation that is anticipated and receives **prior** approval by the Principal Investigator and the COH IRB.

15.2 Reporting of Deviations and Single Subject Exceptions

15.2.1 Reporting Deviations

For any deviation, the Investigator will notify the COH DSMC and IRB within 5 calendar days of its occurrence via iRIS in accordance with the Clinical Research Protocol Deviation policy.

15.2.2 Reporting Single Subject Exceptions as Planned Protocol Deviations

The SSE must be submitted as a "Single Subject Exception Amendment Request" via iRIS in accordance with IRB guidelines and the Clinical Research Protocol Deviation policy. An IRB approved SSE does not need to be submitted as a deviation to the DSMC.

In addition, if contractually obligated, the sponsor must also approve the deviation.

16.0 STUDY OVERSIGHT, QUALITY ASSURANCE, & DATA AND SAFETY MONITORING

16.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

All Investigators agree to:

- Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when necessary to protect the safety, rights or welfare of subjects.
- Personally conduct or supervise the study (or investigation).
- Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
- Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
- Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
- Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
- Seek IRB and Sponsor approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

16.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities as defined in § 21 CFR 312. Subpart D are executed in accordance with federal regulations.

16.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, collaborating investigators, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) at least monthly to review study status. This review will include, but not be limited to, reportable AEs and UPs, and an update of the ongoing study summary that describes study progress in terms of the study schema. The meeting will be a forum to discuss study related issues including accrual, SAE/AEs experienced, study response, deviations/violations and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed. It is recommended that minutes of these discussions be taken to document the date of these meetings, attendees and the issues that were discussed (in a general format).

16.4 Monitoring

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the City of Hope Office of Clinical Trials Auditing and Monitoring (OCTAM).

The Investigator will permit the study monitors and appropriate regulatory authorities direct access to the study data and to the corresponding source data and documents to verify the accuracy of this data. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Details of clinical site monitoring are documented in the OCTAM SOP. This document specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Staff from OCTAM will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SOP. Documentation of monitoring activities and findings will be provided to the study team, and the COH DSMC.

16.5 City of Hope Data and Safety Monitoring Committee

This is a risk level 4study as defined in the City of Hope Institutional Data and Safety Monitoring Plan. This determination was made because the study involves an investigator initiated safety clinical trial.

The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials that are sponsored by City of Hope. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. The committee reviews the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

The Study Principal Investigator is required to submit periodic status reports (the PMT report) according to the guidelines outlined in the City of Hope Institutional Data and Safety Monitoring Plan. The PMT report will be submitted to the COH DSMC quarterly from the date of activation.

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The DSMC will review up-to-date participant accrual; summary of all adverse events captured via routine and expedited reporting; a summary of deviations; any response information; monitoring reports, and summary comments provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request. For Phase I studies, a Phase I Tracking Log will be utilized and reviewed by the DSMC to monitor data and safety for dose escalation. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study. Information that raises any questions about participant safety will be addressed with the Principal Investigator, statistician and study team.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

17.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable, NIH policies and procedures
- Applicable institutional research policies and procedures

17.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.4 Informed Consent

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future

care or employment at City of Hope or any relationship they have with City of Hope. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

17.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies. The COH DCC should be promptly notified of the change in participant status.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and survival follow-up.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

Participants who agreed to the collection of research blood samples may withdraw consent to use their specimens, if they are not yet processed as detailed in the consent form. Once the PI and site PI is notified of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

17.6 Special and Vulnerable Populations

17.6.1 Women and Minorities

The study is open to anyone regardless of gender, race or ethnicity. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded because the study drugs may potentially affect the developing fetus.

17.6.2 Pediatric Population

Pediatric participants (< 18 years of age) are excluded from this study since safety and effectiveness of protocol therapy has not yet been defined for the study population. Additional studies may be performed in the pediatric population once safety and effectiveness of protocol therapy is defined in the adult study population.

17.6.3 HIV Positive Individuals

Participants with HIV are excluded due to concerns about inadvertent augmentation of infectious and/or inflammatory activity.

17.6.4 Vulnerable Populations

Per 45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, and economically or educationally disadvantaged persons as vulnerable populations.

Economically/educationally disadvantaged persons are not actively targeted for participation, nor are they excluded from participation. This study does not pose additional risks for economically/educationally disadvantaged persons than for the general population.

17.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, and the rights of a research participant to revoke their authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

The investigator/institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant specimens with a limited data set will be provided to collaborating laboratories. The specimens will be labeled with the study number, subject (accession) ID, date and time point of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

17.8 Use of Unused (Leftover) Specimens Collected for this Trial

Unused samples in existence at study completion (i.e. completion of all research activities under this study) will either be: (a) placed in a COH IRB approved biorepository with some clinical information and potentially PHI attached or (b) discarded.

17.9 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

17.10 Financial Obligations, Compensation, and Reimbursement of Participants

Regorafenib, ipilimumab and nivolumab will be provided free of charge to participants.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

Standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the participant were not in a research study.

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope to the injured participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

17.11 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement between City of Hope and BMS. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov. Results will be reported on ClinicalTrials.gov generally within 12 months after the completion date unless criteria to delay submission are met per the final rule.

18.0 REFERENCES

1. Fakih, M.G., *Metastatic colorectal cancer: current state and future directions.* J Clin Oncol, 2015. **33**(16): p. 1809-24.
2. Sandhu, J., V. Lavingia, and M. Fakih, *Systemic treatment for metastatic colorectal cancer in the era of precision medicine.* J Surg Oncol, 2019. **119**(5): p. 564-582.
3. Ciombor, K.K., C. Wu, and R.M. Goldberg, *Recent therapeutic advances in the treatment of colorectal cancer.* Annu Rev Med, 2015. **66**: p. 83-95.
4. Tournigand, C., et al., *FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study.* J Clin Oncol, 2004. **22**(2): p. 229-37.
5. Yoshino, T., et al., *Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS.* Ann Oncol, 2018. **29**(1): p. 44-70.
6. Bekaii-Saab, T., et al., *Third- or Later-line Therapy for Metastatic Colorectal Cancer: Reviewing Best Practice.* Clin Colorectal Cancer, 2019. **18**(1): p. e117-e129.
7. Grothey, A., et al., *Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial.* Lancet, 2013. **381**(9863): p. 303-12.
8. Mayer, R.J., et al., *Randomized trial of TAS-102 for refractory metastatic colorectal cancer.* N Engl J Med, 2015. **372**(20): p. 1909-19.
9. Llosa, N.J., et al., *The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints.* Cancer Discov, 2015. **5**(1): p. 43-51.
10. Le, D.T., et al., *PD-1 Blockade in Tumors with Mismatch-Repair Deficiency.* N Engl J Med, 2015. **372**(26): p. 2509-20.
11. 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.
12. Larkin, J., F.S. Hodi, and J.D. Wolchok, *Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma.* N Engl J Med, 2015. **373**(13): p. 1270-1.
13. Overman, M.J., et al., *Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study.* Lancet Oncol, 2017. **18**(9): p. 1182-1191.
14. Overman, M.J., et al., *Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer.* J Clin Oncol, 2018. **36**(8): p. 773-779.
15. Lenz, H.-J.J., et al., *LBA18_PRDurable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC).* Annals of Oncology, 2018. **29**(suppl_8).
16. O'Neil, B.H., et al., *Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma.* PLoS One, 2017. **12**(12): p. e0189848.
17. Eng, C., et al., *Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial.* Lancet Oncol, 2019. **20**(6): p. 849-861.
18. Chen, E.X., et al., *CCTG CO.26 trial: A phase II randomized study of durvalumab (D) plus tremelimumab (T) and best supportive care (BSC) versus BSC alone in patients (pts) with advanced refractory colorectal carcinoma (rCRC).* Journal of Clinical Oncology, 2019. **37**(4_suppl): p. 481-481.
19. Twyman-Saint Victor, C., et al., *Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer.* Nature, 2015. **520**(7547): p. 373-7.
20. Hoff, S., et al., *Immunomodulation by regorafenib alone and in combination with anti PD1 antibody on murine models of colorectal cancer.* Ann Oncol, 2017. **28(suppl_5)**.
21. Wu, R.Y., et al., *Regorafenib Promotes Antitumor Immunity via Inhibiting PD-L1 and IDO1 Expression in Melanoma.* Clin Cancer Res, 2019. **25**(14): p. 4530-4541.
22. Zopf, D., et al., *Pharmacologic activity and pharmacokinetics of metabolites of regorafenib in preclinical models.* Cancer Med, 2016. **5**(11): p. 3176-3185.

23. Fukuoka, S., et al., *Regorafenib plus nivolumab in patients with advanced gastric (GC) or colorectal cancer (CRC): An open-label, dose-finding, and dose-expansion phase 1b trial (REGONIVO, EPOC1603).* J Clin Oncol, 2019. **37:15_suppl, 2522-2522**

24. Schrock, A.B., et al., *Tumor mutational burden is predictive of response to immune checkpoint inhibitors in MSI-high metastatic colorectal cancer.* Ann Oncol, 2019.

25. Lenz, H.-J., et al., *Durable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC).* Ann Oncol, 2018. **Volume 29, Issue suppl_8**.

26. Piantadosi, S., *Clinical Trials, a Methodological Perspective (section 6.4.3). Wiley.* 2006.

27. Fukuoka, S., et al., *Regorafenib plus nivolumab in patients with advanced gastric (GC) or colorectal cancer (CRC): An open-label, dose-finding, and dose-expansion phase 1b trial (REGONIVO, EPOC1603).* Journal of Clinical Oncology, 2019. **37**(15_suppl): p. 2522-2522.

28. Oken, M.M., et al., *Toxicity and response criteria of the Eastern Cooperative Oncology Group.* Am J Clin Oncol, 1982. **5**(6): p. 649-55.

29. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.

30. Hodi, F.S., et al., *Evaluation of Immune-Related Response Criteria and RECIST v1.1 in Patients With Advanced Melanoma Treated With Pembrolizumab.* Journal of Clinical Oncology, 2016.

31. Dolgin, M., et al., *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels.* 9 edn (Boston, Little, Brown and Company). 1994.

19.0 APPENDIX A: ECOG PERFORMANCE STATUS

ECOG Performance Scale[28]	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

20.0 APPENDIX B: CONTRACEPTION GUIDELINES

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

- Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.); **OR**
- Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening; **OR**

  Has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

1. Practice abstinence[†] from heterosexual activity; **OR**
2. Use (or have their partner use) acceptable contraception during heterosexual activity.

<u>Single method (one of the following is acceptable)</u>:

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

<u>Combination method (requires use of two of the following):</u>

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
  - hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

21.0 APPENDIX C: RECIST V 1.1 RESPONSE CRITERIA

Based on Eisenhauer et al., 2009.[29]

- **Measurable disease**

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

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

- **Malignant lymph nodes**

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

- **Non-measurable disease**

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

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

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

- **Target lesions**

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

- **Non-target lesions**

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

Methods for Evaluation of Measurable Disease

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

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

- **Clinical lesions**

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

- **Chest x-ray**

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

- **Conventional CT and MRI**

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

  Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- **PET-CT**

  At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

- **Ultrasound**

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

- **Endoscopy, Laparoscopy**

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

- **Tumor markers**

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J ClinOncol 17, 3461-3467, 1999; J ClinOncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

- **Cytology, Histology**

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

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

- **FDG-PET**

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  - FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as

	reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

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

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

Duration of Response

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

22.0 APPENDIX D: IMMUNE RELATED RESPONSE CRITERIA

Immune related RECIST (irRECIST) is an adaptation of RECIST 1.1 to account for the unique tumor response characteristics to treatment with new immunotherapeutic agents, including ipilimumab and nivolumab. RECIST 1.1 was developed based on treatment with cytotoxic agents. Immunotherapeutic drugs, such as ipilimumab and nivolumab, may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as clinical responses after initial increases in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may not provide an accurate assessment of response to immunotherapeutic agents such as pembrolizumab[30], and will therefore be used with the adaptations referred to as irRECIST.

Antitumor response based on total measurable tumor burden

For the irRECIST, only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (up to 5 new lesions per organ; 10 visceral lesions) are added together to provide the total tumor burden: Tumor Burden = SPD index lesions + SPD new, measurable lesions.

Table 22-1: Comparison WHO and irRECIST criteria

	WHO	irRECIST
New, measurable lesions	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

Time-point response assessment using irRECIST

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening). The irRECIST were derived from WHO criteria and, therefore, the thresholds of response remain the same. However, the irRECIST response categories have been modified from those of WHO criteria as detailed in Table 22-1.

Overall response using the irRECIST

The sum of the products of diameters at tumor assessment using the immune-related response criteria (irRECIST) for progressive disease incorporates the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using irRECIST criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

Definition of Index Lesions Response Using irRECIST

irComplete Response (irCR):	Complete disappearance of all index lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
irPartial Response (irPR):	Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all index and all new measurable lesions (i.e. Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by ≥25% when compared to SPD at nadir
irStable Disease (irSD):	Does not meet criteria for irCR or irPR, in the absence of progressive disease.
irProgressive Disease (irPD)	At least 25% increase Percentage Change in Tumor Burden (i.e., taking sum of the products of all index lesions and any new lesions) when compared to SPD at nadir

Definition of Non-Index Lesions Response Using irRECIST

irComplete Response (irCR):	Complete disappearance of all non-index lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria
irPartial Response (irPR) or irStable Disease (irSD):	Non-index lesion(s) are not considered in the definition of PR, these terms do not apply
irProgressive Disease (irPD)	Increases in number or size of non-index lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the index lesions increases by the required amount)

Impact of New Lesions on irRECIST

New lesions in and by themselves do not qualify as progressive disease. However their contribution to total tumor burden is included in the SPD which in turn feeds into the irRECIST criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

Definition of Overall Response Using irRECIST

Overall response using irRECIST will be based on these criteria (Table 22-2):

irComplete Response (irCR):	Complete disappearance of all tumor lesions (index and non-index together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response
irPartial Response (irPR):	The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).
irStable Disease (irSD):	irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease
irProgressive Disease (irPD)	It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease: • At least 25% increase in the sum of the products of all index lesions over nadir SPD calculated for the index lesions. • At least a 25% increase in the sum of the products of all index lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the index lesion.

Table 22-2. Derivation of irRECIST overall responses

Measurable response	Nonmeasurable response		Overall response
Index and new, measurable lesions (tumor burden),*%	Non-index lesions	New, nonmeasurable lesions	Using irRECIST
↓100	Absent	Absent	irCR†
↓100	Stable	Any	irPR†
↓100	Unequivocal progression	Any	irPR†
↓≥50	Absent/Stable	Any	irPR†
↓≥50	Unequivocal progression	Any	irPR†
↓<50 to <25↑	Absent/Stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irSD
≥25	Any	Any	irPD†

*Decreases assessed relative to baseline (scan prior to start of any protocol therapy), including measurable lesions only

†Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

Immune-Related Best Overall Response Using irRECIST (irBOR)

irBOR is the best confirmed irRECIST overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

23.0 APPENDIX E-1: REGORAFENIBPATIENT DRUG DIARY INSTRUCTIONS

Subject ID#:	Patient Initials (F, M, L):
Institution:	Cycle #:_____ Cycle start date:_____
☐ Safety ☐ Expansion cohort	

Remember to bring this diary, all tablet bottles, and any unused tablets to each clinic visit.
Call your study doctor or nurse <u>immediately</u> if you are having any new or worsening side effects.

Study drug Instructions – When and How:

- Take regorafenib **once a day**with a full glass of water for 21 consecutive days, with the last 7 days off.
- Swallow tablets whole; do not chew them or crush them
- Do not skip any doses

What if I miss a scheduled dose?

- If **less than 6 hours** have passed from the scheduled time, then **take the missed dose** as soon as you remember.
- If **more than 6 hours** have passed from the scheduled time, then **skip the missed dose**. Wait for your next scheduled dose. Do not take extra medicine to make up the missed dose

What if I vomit a dose?

- If you vomit your tablets, write this down in your patient diary.
- Wait until the next scheduled dose; do not take extra medicine to make up the vomited dose.

Additional Instructions:

- **Write down your side effects in this diary**.
- Your dose may be adjusted based on your side effects
- Keep your study drug in the original container until you take it.
- Do NOT throw away empty study drug bottles or unused tablets.
- Bring this diary, all study drug bottles, and any unused tablets to each clinic visit.

Study Contact Information		
<u>Study Doctor</u> **Phone:** **Name:**	**<u>Study Nurse</u>** **Phone:** **Name:**	**<u>Backup Study Nurse</u>** **Phone:** **Name:**

APPENDIX E-2: REGORAFENIB PATIENT DRUG DIARY

Subject ID#:	Patient Initials (F, M, L):
Institution:	Cycle #:_____ Cycle start date:_____
☐ Safety ☐ Expansion cohort	

Call your study doctor or nurse <u>immediately</u> if you are having any new or worsening side effects. *Your study doctor or nurse will tell you what to do.*

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week 1

				# of tablets to take once daily:	
Cycle Day	**Week Day**	**Date**	**Time**	**# of tablets taken** *(Write down below)*	**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
1			___:___AM		
			___:___PM		
2			___:___AM		
			___:___PM		
3			___:___AM		
			___:___PM		
4			___:___AM		
			___:___PM		
5			___:___AM		
			___:___PM		
6			___:___AM		
			___:___PM		
7			___:___AM		
			___:___PM		

Participant/ Caregiver Signature*(please sign when submitting your diary)*	**Date:**
_____	____/_____/_____

Subject ID#:	Patient Initials (F, M, L):
Institution:	Cycle #:_____ Cycle start date:_____
☐ Safety ☐ Expansion cohort	

Call your study doctor or nurse <u>immediately</u> if you are having any new or worsening side effects. *Your study doctor or nurse will tell you what to do.*

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week 2

				# of tablets to take once daily:	
Cycle Day	**Week Day**	**Date**	**Time**	**# of tablets taken** *(Write down below)*	**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
8			___:___AM		
			___:___PM		
9			___:___AM		
			___:___PM		
10			___:___AM		
			___:___PM		
11			___:___AM		
			___:___PM		
12			___:___AM		
			___:___PM		
13			___:___AM		
			___:___PM		
14			___:___AM		
			___:___PM		

Participant/ Caregiver Signature*(please sign when submitting your diary)*	**Date:**
_____	____/_____/____

Subject ID#:	Patient Initials (F, M, L):
Institution:	Cycle #:_____ Cycle start date:_____
☐ Safety ☐ Expansion cohort	

Call your study doctor or nurse <u>immediately</u> if you are having any new or worsening side effects. *Your study doctor or nurse will tell you what to do.*

Write your side effects in this diary. Your dose may be adjusted based on your side effects.

Week 3

				# of tablets to take once daily:	
Cycle Day	**Week Day**	**Date**	**Time**	**# of tablets taken** *(Write down below)*	**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
15			___:___AM		
			___:___PM		
16			___:___AM		
			___:___PM		
17			___:___AM		
			___:___PM		
18			___:___AM		
			___:___PM		
19			___:___AM		
			___:___PM		
20			___:___AM		
			___:___PM		
21			___:___AM		
			___:___PM		

Participant/ Caregiver Signature*(please sign when submitting your diary)*	**Date:**
_____	____/_____/____

Study Team ONLY: # of Study Drug Bottles Returned: _____ # of tablets returned: _____

Compare with drug diary entries made by participant/guardian. If there is a discrepancy (in the # of bottles or the # of* tablets *returned, please reconcile (initials & date):_____

24.0 APPENDIX F: CYP3A4 INHIBITORS AND INDUCERS

- **CYP3A4 inducers and inhibitors**

Table 10–6 presents an overview of CYP3A4 inducers and **strong** CYP3A4 inhibitors. CYP3A4 inducers and **strong** CYP3A4 inhibitors are NOT allowed due to drug-drug- interaction with regorafenib.

Table 10–6: An overview of CYP3A4 inducers and strong CYP3A4 inhibitors

STRONGCYP3A4Inhibitors	CYP3A4Inducers
Boceprevir	Avasimibe
Clarithromycin	Bosentan
Cobicistat, only available in the combination with elvitegravir, emtricitabine, tenofovir or disoproxil fumarate	Carbamazepine
Conivaptan	Efavirenz
Delavirdine	Enzalutamide
Idelalisib	Etravirine
Indinavir	Fosphenytoin
Itraconazole	Hypericumperforatum (St John's Wort)
Ketoconazole	Lersivirine
Lopinavir	Lumacaftor
Mibefradil	Methylphenobarbital
Miconazole	Mitotane
Nefazodone	Modafinil
Nelfinavir	Nafcillin
Posaconazole	Phenobarbital
Ritonavir	Phenytoin
Saquinavir	Primidone
Telaprevir	Rifabutin
Telithromycin	Rifampicin
Tipranavir	Rifamycin
Troleandomycin	Semagacestat
Voriconazole	Thioridazine

A STRONG inhibitor is **NOT allowed during this clinical trial**. CYP3A4 inducers are **NOT allowed during this clinical trial**.

25.0 APPENDIX G: NEW YORK HEART ASSOCIATION CLASSIFICATION OF HEART FAILURE

Modified from Dolgin et al., 1994 [31]

NYHA Classification of Heart Failure	
Class 1	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
Class 2	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
Class 3	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
Class 4	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

26.0 APPENDIX H: MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

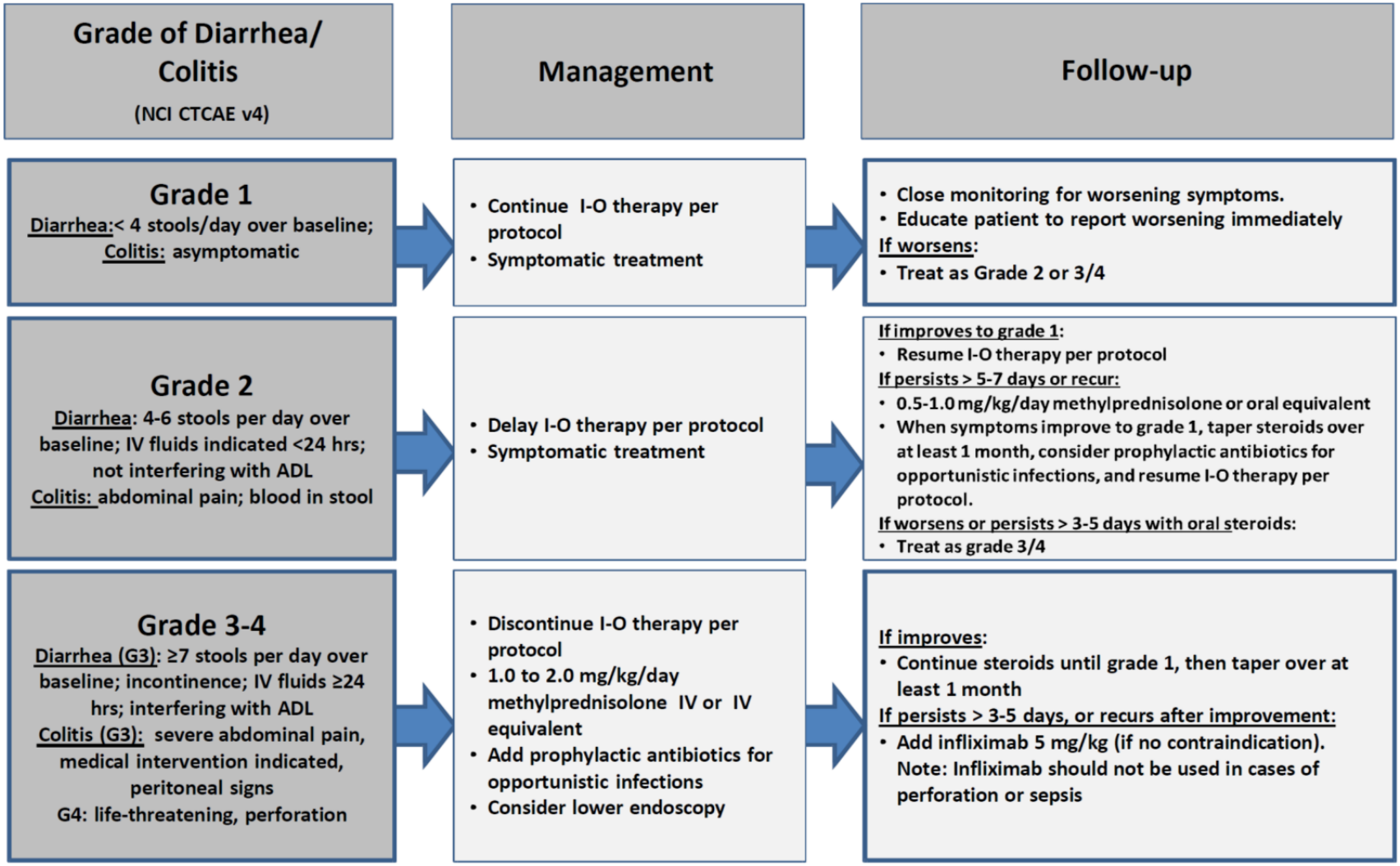
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

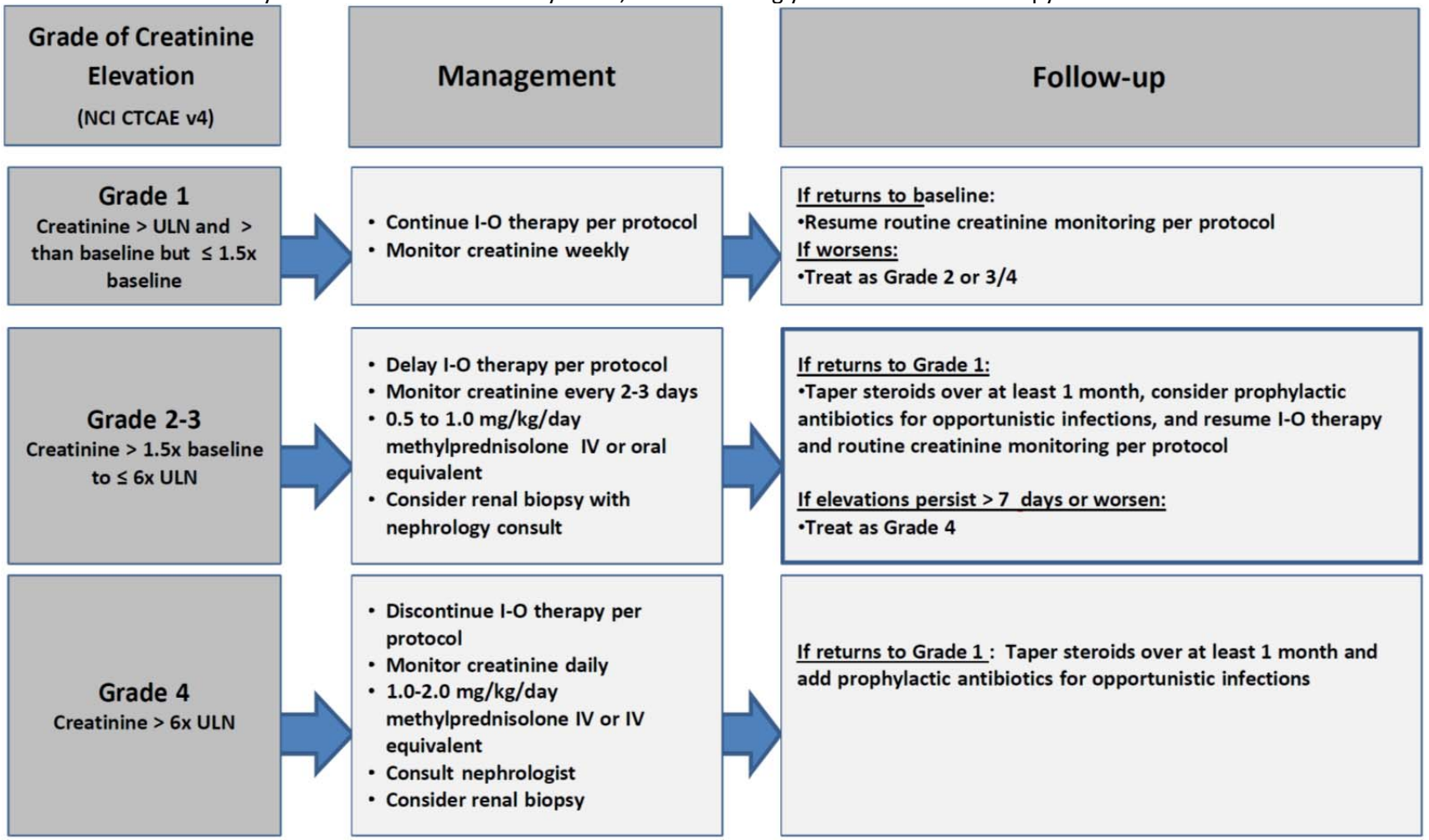
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

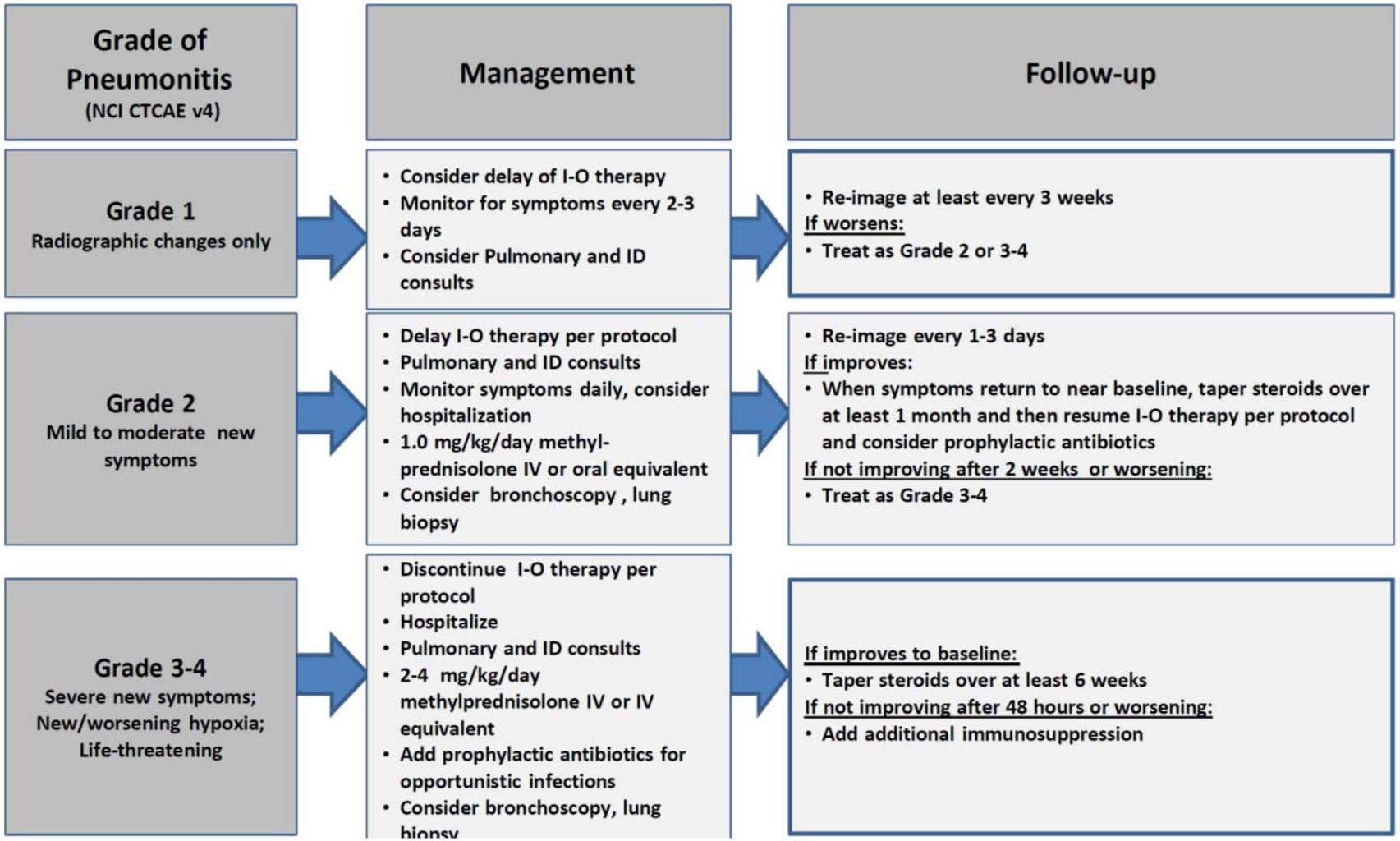
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

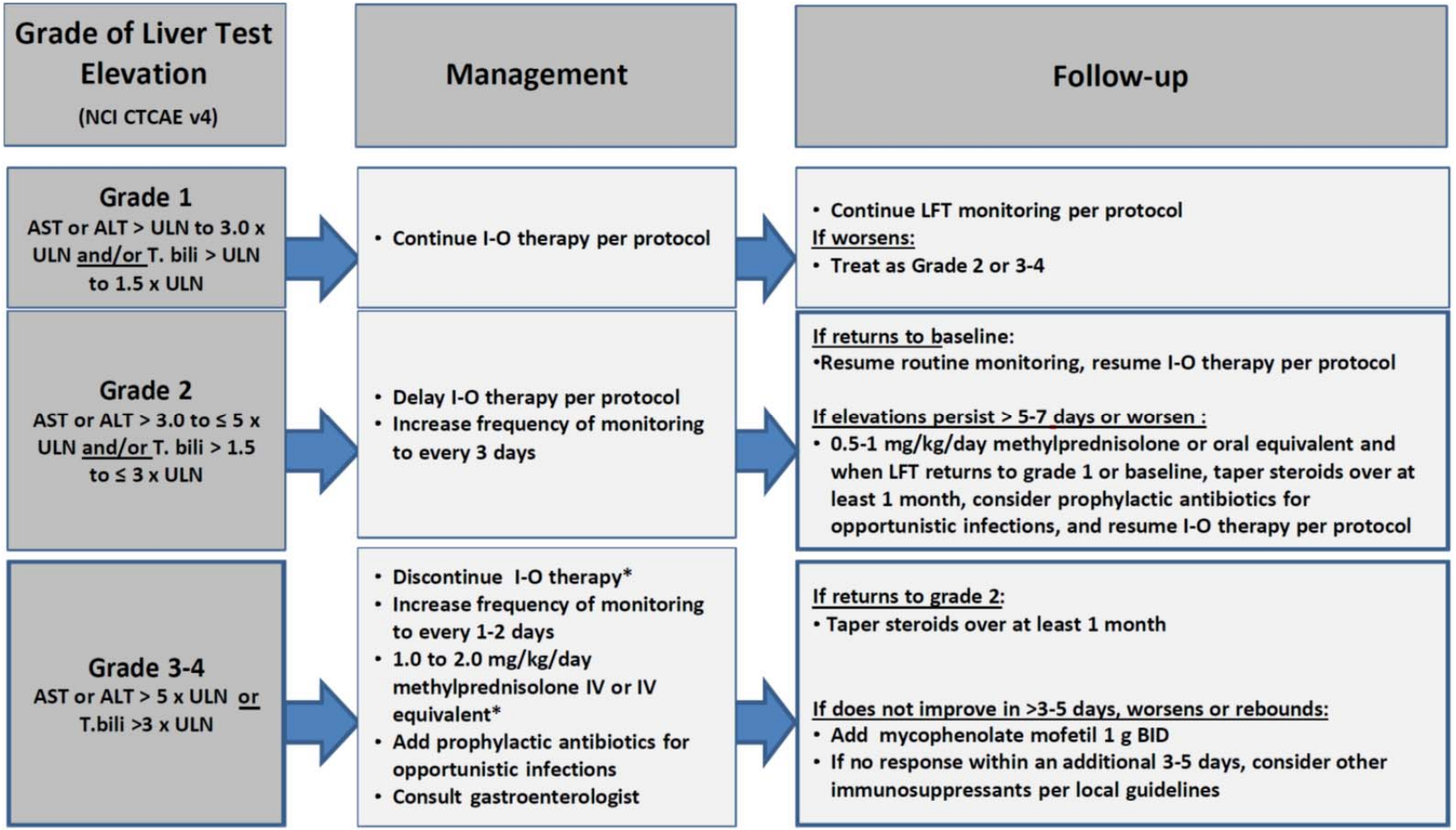
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.

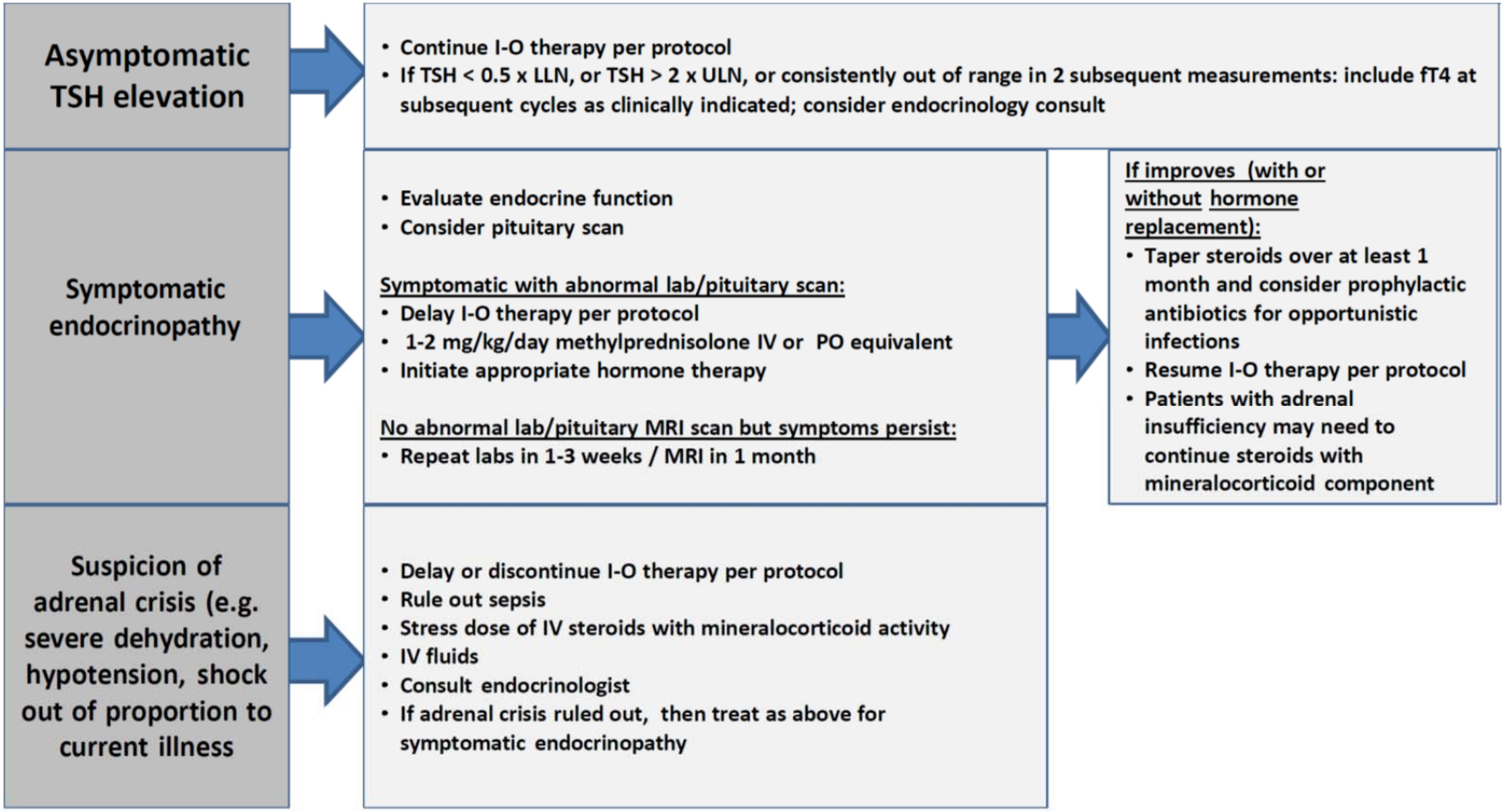


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Adverse Event Management Algorithm

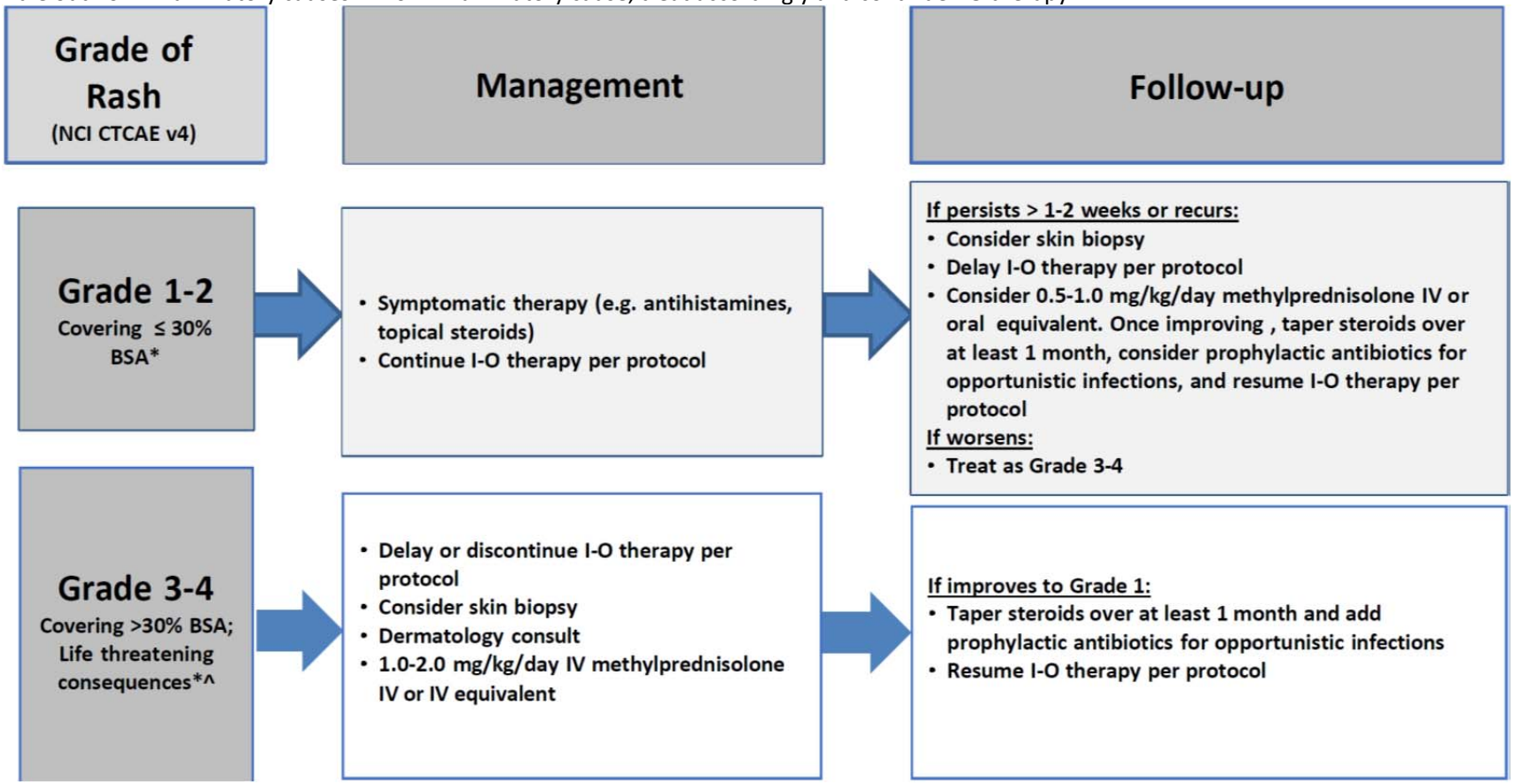
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

Skin Adverse Event Management Algorithm

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



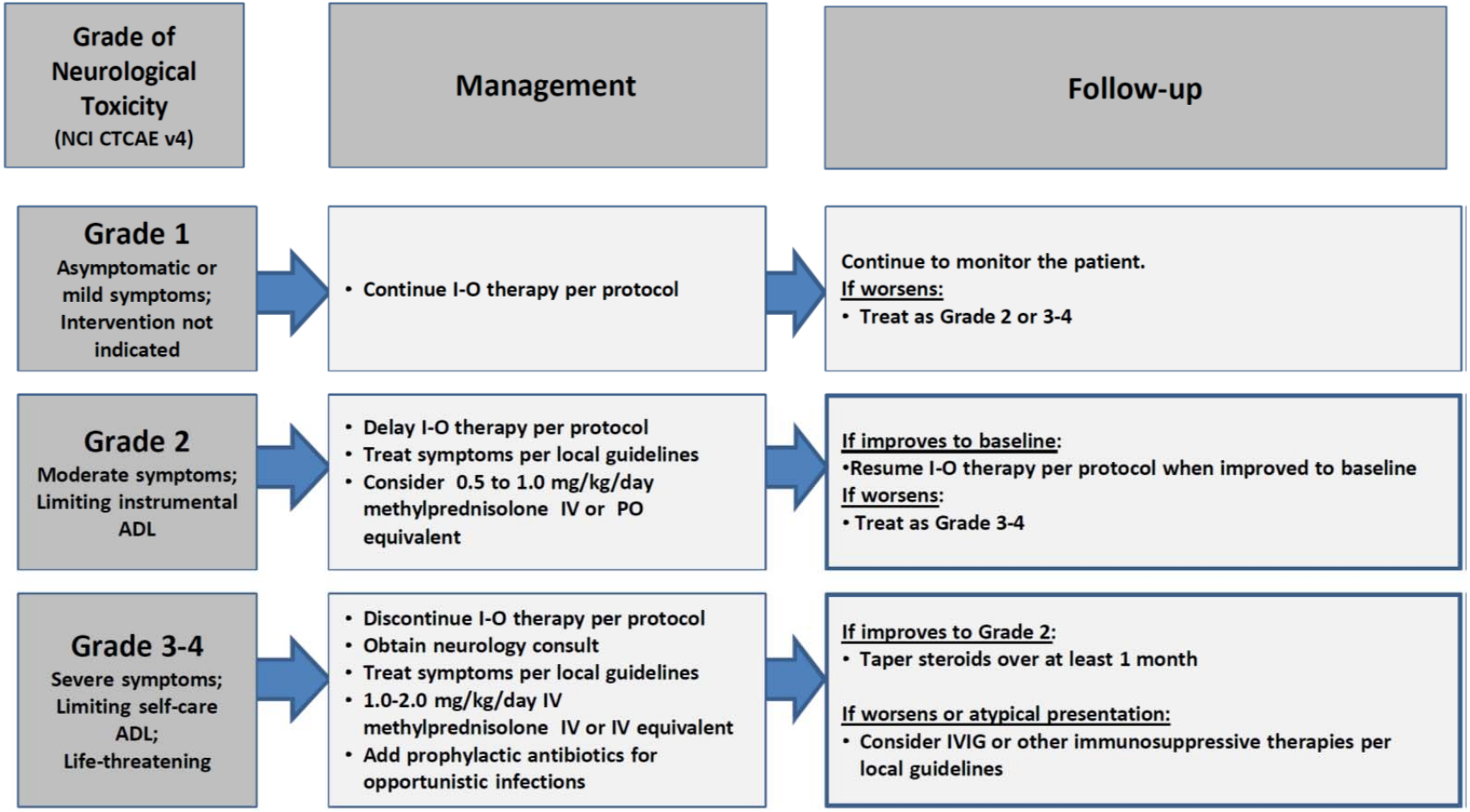
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

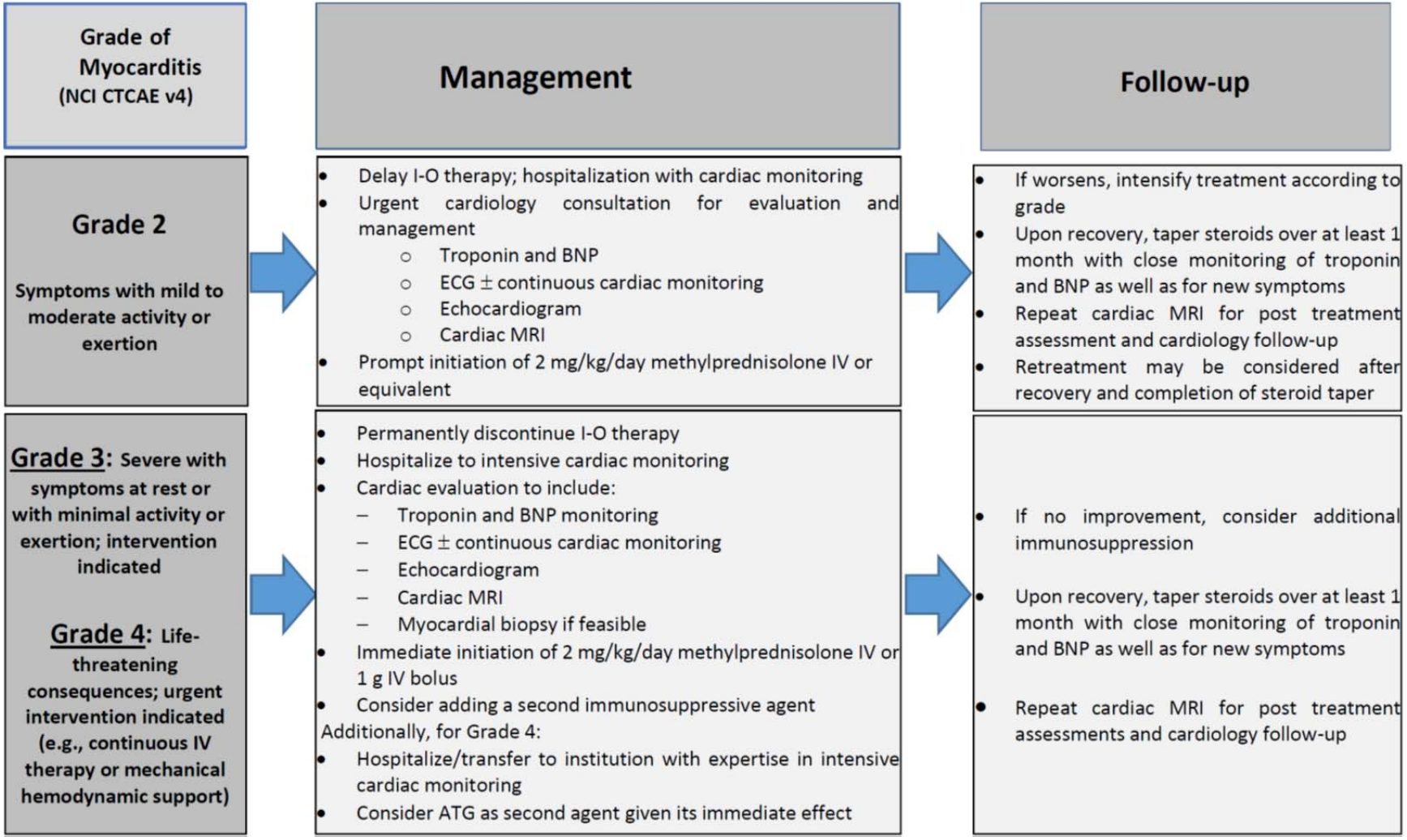
Neurological Adverse Event Management Algorithm

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

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression. ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging