

Academic and Community Cancer Research United (ACCRU)

Study Title: ACCRU-GI-1920 A phase II study of Neoadjuvant Regorafenib Plus Durvalumab (MEDI4736) in Patients with High-risk Hepatocellular Carcinoma

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A phase II study of Neoadjuvant Regorafenib Plus Durvalumab (MEDI4736) in Patients with High-risk Hepatocellular Carcinoma

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√ Study contributor(s) not responsible for patient care.

Drug Availability

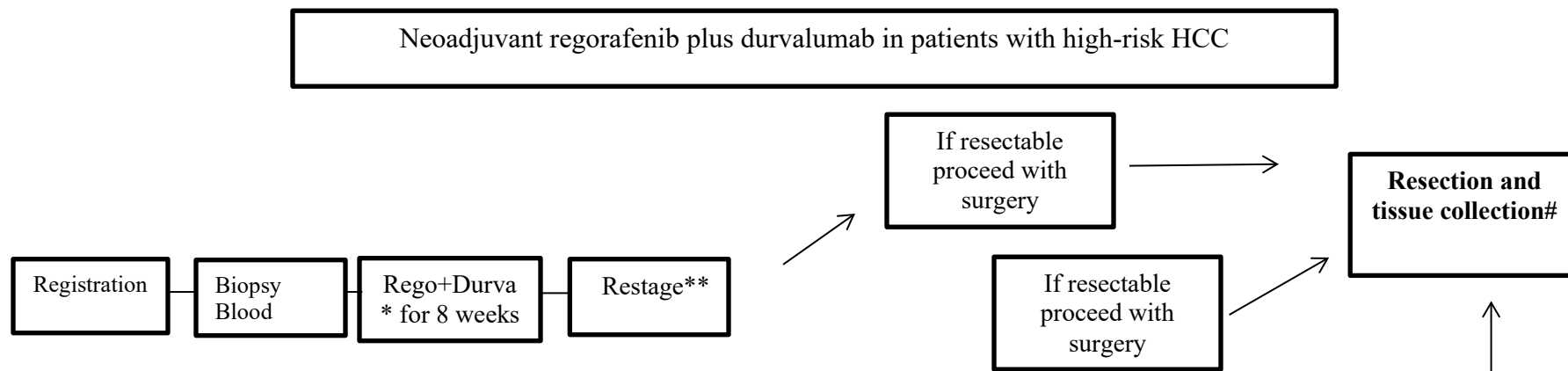
Commercial Agents: Regorafenib

Investigational Agents: Durvalumab (IND Exempt)

Research Coordinating Center
Academic and Community Cancer Research United

<u>Document History</u>	<u>(Effective Date)</u>
Initial Version	7/15/2021
Preactivation Amendment 1	4/7/2022
Amendment 2	M/XX/YEAR

Schema



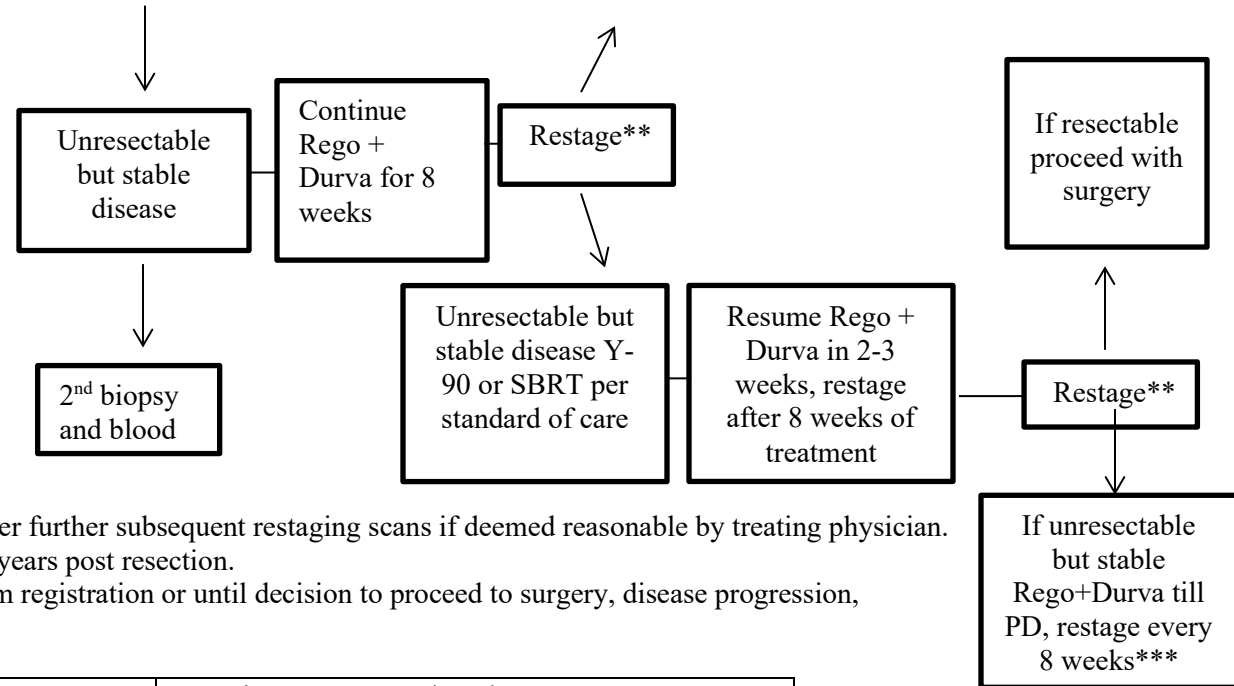
Treatment cycle equals 28 days
 *Regorafenib 80 mg po daily, 3 weeks on, 1 week off with
 Durvalumab 1500 mg IV every 4 weeks

**If progression of disease is detected with any restaging scan, the patient will come off protocol treatment. Survival follow-up will be performed every 90 days until 5 years after registration.

*** Patients could proceed to surgery after further subsequent restaging scans if deemed reasonable by treating physician.

Clinical follow-up every 90 days for 2 years post resection.

Treatment for a maximum of 2 years from registration or until decision to proceed to surgery, disease progression, excessive toxicity, or patient withdrawal.



Generic name: Regorafenib	Generic name: Durvalumab
Brand name(s): Stivarga	Brand name(s): Imfinzi
Availability: Supplied by McKesson	Availability: Supplied by McKesson

1.0 Background

1.1 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the second leading cause of cancer related mortality in the world [1]. HCC is the fastest increasing cause of cancer-related mortality in the US and 5 year survival is less than 12% [2]. About 40% of patients with HCC can be candidates for curative treatments (ablation, surgical resection, liver transplantation) [3] but most present at advanced stage. Current FDA-approved systemic treatment options in advanced HCC include sorafenib, lenvatinib, atezolizumab/bevacizumab in the first line setting, regorafenib, cabozantinib, nivolumab, pembrolizumab, ramucirumab, nivolumab/ipilimumab in the second line setting, with modest overall survival benefit in both settings. [4-10] Regorafenib improved overall survival compared placebo in patients with advanced HCC who progressed on sorafenib. [5] ORR and disease control rate was 11% and 65%, respectively by RECIST 1.1. Single agent immunotherapy and tyrosine kinase inhibitors (TKI) have an established role in advanced HCC treatment. Given emerging data for synergistic effects of immunotherapy and regorafenib combination, this approach could have a potential role in down staging and neoadjuvant setting in HCC management.

1.2 Anti-angiogenesis and immunotherapy:

Angiogenesis is crucial for cancer growth and metastasis and is predominantly regulated by vascular endothelial growth factor A (VEGF-A) and its receptors (VEGFR-1, VEGFR-2 and VEGFR-3). [11] VEGF is overexpressed in majority of non-hematological malignancies and VEGFR-2 is the primary receptor that mediates the effects of VEGF. [12] HCC is a highly vascular tumor, and blood vessels in liver tumor are associated with abnormal blood flow and excessive leaking, which in turn causes hypoxic tumor microenvironment. [13] VEGF is responsible for dysfunction of the blood vessels in the tumor and consequently hypoxic tumor tissue, which is associated with further growth of HCC, more angiogenesis, and resistance to systemic therapies. [14] Elevated VEGF level in HCC tumor tissue and circulation is associated with more aggressive disease and poorer outcomes. [13] Targeting VEGF pathway is an established treatment modality in HCC. VEGF blocks T-cell infiltration to tumor and has systemic effects on immune system by inducing proliferation of T regulatory cells (T-regs) and myeloid derived suppressor cells (MDSCs), suppressing dendritic cell maturation and inhibition of development of hematopoietic progenitor cells to T cells. [12, 15-17] Antiangiogenic agents can enhance the efficacy of immunotherapies by stimulating the immune response. [15, 17] Additionally anti-angiogenesis can improve tumor microenvironment perfusion and oxygenation by reducing the pressure on blood vessels in the tumor. [18] Synergistic effects of anti-angiogenesis therapy and anti-PD-1 therapy was reported in preclinical studies and clinical studies as well. [19, 20] VEGFR-2 blockage has been shown to improve T-cell exhaustion and tumor T-cell infiltration. Preclinical data supports combination of antiangiogenic agents and immunotherapy as shown in several different tumor types. [19] The encouraging data from preclinical studies translated into multiple currently ongoing clinical trials with antiangiogenic agent and immunotherapy combinations. [12] Atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) was recently shown to improve survival compared to sorafenib in advanced HCC in the first line setting and is an approved treatment option in advanced HCC.[9]

1.3 Tumor-associated macrophages (TAM), immunotherapy and regorafenib in HCC:

TAM have immunosuppressive and tumor promoting features therefore significant implications in carcinogenesis and progression of metastatic disease. [21] TAM and other myeloid cells contributes to immunosuppressive tumor microenvironment, which creates significant challenges for efficacy of immunotherapy with anti- PD-1 antibody. [21] TAM secretes proangiogenic growth factors and immunosuppressive cytokines. [22] TAM can have either proinflammatory (M1) or anti-inflammatory phenotype (M2). Anti-inflammatory TAM M2 phenotype has immunosuppressive features and is associated with more aggressive tumors, increased angiogenesis, invasion, metastasis and negative prognosis. [23-25] TAM with immunosuppressive features promote tumor growth and suppress immune effector cells. The immunosuppressive feature of anti-inflammatory phenotype of TAM (M2) depends of growth factors such as colony stimulating factor-1 (CSF1) also known as macrophage colony-stimulating factor (MCSF) in the tumor microenvironment (TME). CSF1 is activated by CSF-1 receptor (CSF-1R) and has crucial role in macrophage differentiation and survival. [26] CSF-1R is expressed on myeloid derived suppressor cells (MDSCs), neutrophils and dendritic cells in TME. CSF1-R mediated signals predominantly controls tumor promoting features of TAM therefore, targeting tumor promoting CSF-1R is a viable anti-tumor strategy. CSF-1R blockage has been shown to decrease immunosuppressive TAM M2 in clinical trials. [27]

- 1.4 CSF-1R expression is a poor prognostic factor for HCC and anti-CSF-1R therapy increases CD8+ T-cell infiltration in preclinical HCC models.

High CSF-1R expression in the peritumoral tissue in resected HCC is associated with early recurrence, more intrahepatic metastasis and poor survival. [28] Increased CSF-1R expression is correlated with aggressive tumors and poorer prognosis in several solid tumors. [25] In preclinical study with Hepa 1-6 tumor bearing C57BL/6 and HepG2 and HCCLM3 tumor bearing BALB/c mice models, CSF-1R blockage by oral PLX3397, highly specific tyrosine kinase inhibitor of CSF-1R, was shown to induce phenotypic change to TAM M2 from TAM M1 phenotype and subsequently delayed tumor growth and prolonged survival compared to vehicle-treated mice group. [29] It increased CD8+ T-cell infiltration and decreased CD4+ T-cell infiltration in tumors. Myeloid derived suppressors cells were decreased and the proportion of antigen presenting macrophages were increased. In essence CSF-1R inhibition ameliorated the antitumor immunity in the TME. **Regorafenib inhibits CSF1R, was shown to reduce tumor associated macrophages (TAMs) in preclinical models and a recent clinical trial with treatment resistant gastric and colorectal cancer.** [30, 31] Regorafenib, an oral multikinase inhibitor, targets vascular endothelial growth factor receptors (VEGFR) 1-3, angiopoietin-1 receptor (TIE2), c-KIT, RET, platelet-derived growth factor receptors (PDGFR) alpha and beta, fibroblast growth factor receptors (FGFR) 1 and 2, BRAF. [32, 33] **Therefore it is involved in tumor angiogenesis, metastasis, oncogenesis, tumor immunity and immunomodulation.** In light of proven efficacy of regorafenib in advanced HCC as a single agent, multikinase activity targeting several pathways in HCC and recently proven immunomodulatory properties indicative of synergistic effect combination of regorafenib and anti-PD-1 antibody is a rational approach in HCC in neoadjuvant setting.

- 1.5 Evolving neoadjuvant approach to HCC:

Resectability in HCC depends on tumor size, number of lesions, vascular invasion, absence of distant metastatic disease as well as underlying liver function and performance

status. [34, 35] Surgical guidelines recommend resection for early stage HCC defined as a single tumor <2 cm or 1-3 tumors <3 cm. [34] However, practice patterns vary significantly, and surgical resection is offered in 'borderline high-risk' cases outside the strict criteria defined by guidelines.[36, 37] Although there is no consensus on a universally accepted resectability criteria, there is published literature and agreement that patients with **large tumors (solitary tumor > 5 cm without vascular invasion), multifocal disease (T2 or T3) and vascular invasion (T2) have a high risk of recurrence post resection.** [34, 38] Therefore, these patients are many times treated with pre-operative therapy in the form of catheter directed therapy (TACE, DEB-TACE or Y90) for downstaging prior to resection. [39, 40] **With the improvement of systemic therapies, our objective is to evaluate the role of active regimens such as regorafenib and durvalumab in these high-risk borderline resectable patients with HCC in order to introduce potentially a more effective approach for downstaging as well as systemic control of disease which catheter directed therapies cannot provide.** Inhibition of VEGF and PD-1 signaling achieved 61% ORR in a phase Ib study with reasonable safety profile in advanced HCC. [41] Updated analysis of the same combination in 68 patients reported 32% ORR. [42] More recently atezolizumab and bevacizumab combination was shown to have superior ORR (27% vs 12%), OS and PFS compared to sorafenib in first line treatment of advanced HCC indicating the importance of anti-VEGF and PD-1 combination in HCC management. [9] In resectable HCC nivolumab versus nivolumab plus ipilimumab was reported to be safe and was not associated with delayed surgery. [43] A phase Ib study of first line pembrolizumab and regorafenib in 31 patients with HCC (BCLC B or BCLC C) revealed 26% ORR. [44] No new safety signals were encountered and an expansion cohort with regorafenib 80 mg/day and pembrolizumab 200 mg every 3 weeks is ongoing in advanced HCC. Furthermore in 2020 Gastrointestinal Cancers Symposium a phase Ib study of lenvatinib and nivolumab in 30 patients with BCLC-B and C HCC revealed 76.7% ORR was reported. [45] No new safety signals were encountered. Durvalumab, an anti-PD-L1 antibody, as a single agent revealed a 10.3% ORR (CR+PR) and a 33.3% disease control rate (CR+PR+SD) in a phase I study of 40 patients with advanced HCC. [46]

We propose a neoadjuvant study with regorafenib and durvalumab in patients with high risk HCC.

1.6 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors[47] PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The PD-1 receptor (CD279) is expressed on the surface of activated T cells.[48] It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273).[49] The PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by B-cells, dendritic cells, and macrophages. [50]Importantly, PD-L1 is commonly over-expressed on tumor cells or on non-transformed cells in the tumor microenvironment.[51] PD-L1 expressed on the tumor

cells binds to PD-1 receptors on the activated T-cells leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1-mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients [52] [49, 53-56]; with responses that tend to be more pronounced in patients with tumors that express PD-L1.[57-59] In addition, high mutational burden (e.g., in bladder carcinoma [60] may contribute to the responses seen with immune therapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells.[61] Blockade of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti-CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data have now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies, whilst nivolumab and pembrolizumab, two anti-PD-1 agents, and atezolizumab, an anti-PD-L1, agent have been granted approvals by agencies such as the US FDA and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and urothelial carcinoma. In addition, there are data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

1.7 Durvalumab background/non-clinical and clinical experience

The non-clinical and clinical experience is fully described in the most current version of the durvalumab Investigator's Brochure.

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1

kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.)). The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN- γ . [62] *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism. [62] Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date durvalumab has been given to more than 8000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section **Error! Reference source not found.**. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.8 Durvalumab monotherapy dose rationale

A durvalumab dose of 20 mg/kg Q4W is supported by in-vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥ 3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥ 3 mg/kg Q2W is approximately 17 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (For further information on immunogenicity, please see the current IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W). [63] Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by AUC_{ss} (4 weeks). Median C_{max,ss} is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median C_{trough,ss} is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients;

(b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab Investigator's Brochure for a complete summary of clinical information including safety, efficacy and pharmacokinetics at the 20mg/kg Q4W regimen.

1.9a Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data from a Phase I study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others [64] [65] [66] [67], Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies.[68] In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters. [67]

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

1.9b Overall risks

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism, and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune mediated effects can occur in nearly any organ system, and are most commonly seen as gastrointestinal AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

1. 9c Durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, thyroiditis, pemphigoid, myasthenia gravis, immune thrombocytopenia, other rare or less frequent inflammatory events including neurotoxicity's, infusion-related reactions, hypersensitivity reactions, and infections/serious infections.

In monotherapy clinical studies AEs (all grades) reported very commonly ($\geq 15\%$ of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9.4% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6.5 % of patients experienced an SAE that was considered to be related to durvalumab by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated (Appendix I)

For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB.

1.9d Regorafenib

The non-clinical and clinical experience is fully described in the most current version of the regorafenib Investigator's Brochure.

Regorafenib is an oral multikinase inhibitor which targets VEGFR 1-3, CSF-1R, angiopoietin-1 receptor (TIE2), c-KIT, RET, platelet-derived growth factor receptors (PDGFR) alpha and beta, fibroblast growth factor receptors (FGFR) 1 and 2, BRAF.[32] [33]. Therefore, it is involved in tumor angiogenesis, metastasis, oncogenesis, tumor immunity and immunomodulation in HCC. Regorafenib is approved for advanced HCC in the second line setting. [5] In BALB/C orthotopic HCC mouse model low dose regorafenib and anti-PD-1 antibody combination increased intratumoral CD8⁺ T cells and TAM-1 via CSF-1R inhibition.[69] A phase Ib study of first line pembrolizumab and regorafenib in 31 patients with HCC (BCLC B or BCLC C) revealed 26% ORR.[44] No new safety signals were encountered and an expansion cohort with regorafenib 80 mg/day and pembrolizumab 200 mg every 3 weeks is ongoing in advanced HCC. In a phase Ib study with regorafenib and nivolumab in patients with advanced gastric and

colorectal cancer, three dose limiting toxicity were observed with regorafenib 160 mg daily, and during dose expansion part regorafenib was reduced to 80 mg from 120 mg daily 3 weeks on 1 week off due to frequent maculopapular rash, and 80 mg daily dose combined with nivolumab had manageable safety profile and encouraging anti-tumor activity.[70] In summary regorafenib 80 mg daily 3 weeks on/1 week off dosage emerged as the optimal dose in combination with anti-PD-1 antibody therapy in preclinical and clinical studies

1.9e Treatment

Thirty patients with solitary tumor > 5 cm without vascular invasion/T2/T3 and N0M0 HCC with no prior systemic treatment will be started on **regorafenib 80 mg po daily (3 weeks on 1 week off) and durvalumab 1500 mg IV every 4 weeks combination. Restaging scans will be performed at 8 weeks.** Patients who are deemed to be surgical candidate will undergo surgical resection after at least 4 weeks from the last dose of systemic treatment. Patients who are deemed not surgically resectable will proceed with regorafenib and durvalumab combination and be restaged in 8 weeks. If resectable, patient will proceed with surgery; if patient remains unresectable but shows no progression of disease, proceed with standard of care Y-90 or Stereotactic radiation therapy (SBRT) as per institutional standards. After standard of care Y-90 or SBRT, wait at least 2-3 weeks and for recovery of any potential adverse events to resolve to Grade 2 or lower before restating systemic therapy then continue regorafenib and durvalumab for another 8 weeks and restaged, if not able to receive Y-90 or SBRT despite initial consideration can resume systemic therapy and restage 8 weeks after resuming systemic therapy. If the patient is deemed resectable, patient will proceed with surgery, otherwise patient will continue regorafenib and durvalumab until progression with restaging every 8 weeks.

1.9f Correlative Research

Correlative assays will include immune profiling of TILS and circulating lymphocytes, plasma cytokine levels. These will be performed at baseline, weeks 4, 8, and week 16, and in surgical specimens in patients undergoing resection, and at progression.

2.0 Goals

2.1 Primary

2.11 To assess the overall response rate (ORR) at 16 weeks post registration

2.2 Secondary

2.21 To assess the rate of patients who undergo surgery during the course of the study

2.22 To assess the safety and tolerability of the combination therapy of regorafenib plus durvalumab

2.23 To assess the effect of combination therapy on overall survival

- 2.24 To assess the effect of combination therapy on progression-free survival (PFS) in patients that do not undergo resection
- 2.25 To assess the effect of combination therapy on recurrent-free survival (RFS) in patients that have resection
- 2.26 To assess the rate of pathologic complete response
- 2.3 Correlative Research
 - 2.31 Analyze the effect of regorafenib and durvalumab on immune biomarkers in the tumor microenvironment and systemic circulation

3.0 Patient Eligibility

NOTE: Waivers to eligibility criteria are not allowed per ACCRU policy

- 3.1 Registration – Inclusion Criteria
 - 3.11 Age $\geq$ 18 years at time of registration
 - 3.12 Body Weight > 30kg
 - 3.13 Patients must have Hepatocellular carcinoma (HCC) diagnosis confirmed by histology/cytology or clinically by American Association for Study of liver Diseases (AASLD) criteria in cirrhotic patients
 - 3.14 Measurable disease as defined in Section 11.0
 - 3.15 ECOG Performance Status (PS) of 0 or 1. (Form is available on the ACCRU web site)
 - 3.16 Child Pugh class A (See Appendix IV for more details)
 - 3.17 The following laboratory values obtained $\leq$ 28 days prior to registration

NOTE: If your site laboratory reports use different units of measurements than what is required by the protocol eligibility requirements, please use the “Lab Test Unit Conversion Worksheet” available on the ACCRU website under “General Forms”

- Total bilirubin $\leq$ 1.5 x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) $\leq$ 5 x ULN
- Aspartate transaminase (AST) $\leq$ 5 x ULN
- PT and INR and aPTT $\leq$ 1.5 x ULN -OR-
if patient is receiving anticoagulant therapy, either INR or aPTT is within target range of therapy
- Creatinine $\leq$ 1.5x ULN -OR-
creatinine clearance $\geq$ 60 mL/min/1.73 m² for patients with creatinine

levels > 1.5 x ULN. Creatinine clearance should be calculated per institutional standard

- Urinary protein is ≤ 1+ on dipstick or routine urinalysis -OR- 24-hour urine demonstrating < 1 gram of protein.
- Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9/\text{Liter}$,
- Hemoglobin ≥ 9 grams/deciliter,
- Platelets $\geq 75 \times 10^9/\text{Liter}$.

3.18 Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

3.19a Life expectancy of ≥ 12 weeks

3.19b Negative pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only.

NOTE: If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.19c Provide informed written consent ≤ 28 days prior to registration.

3.19d Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

*Note: During the **Active Monitoring** Phase of a study (i.e., active treatment and clinical follow-up), participants must be willing to return to the consenting institution for follow-up.*

3.19e Willing to provide mandatory tissue specimens and blood specimens for correlative research purposes (see Sections 6.0, 14.0 and 17.0).

3.19f Clinical staging T1b/T2 or T3, T4 per hepatocellular cancer TNM staging AJCC UICC 8th edition (See Appendix V for more details) with one of the following:

- Solitary tumor > 5 cm without vascular invasion and N0M0
- T2: Solitary tumor > 2 cm with vascular invasion, or multiple tumors, none > 5 cm and N0M0
- T3: Multiple tumors, at least one of which is > 5 cm and N0M0
- T4: Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

3.19g Able to swallow oral medication.

3.2 Registration – Exclusion Criteria

3.21 Prior therapy with anti-PD-1, PD L-1 antibody including durvalumab, regorafenib, or other approved systemic therapies for HCC.

3.22 Mixed histology HCC or fibrolamellar HCC

- 3.23 History of upper gastrointestinal bleed ≤ 6 months from registration
- 3.24 Liver directed therapy ≤ 28 days prior to registration. Prior liver directed therapy > 28 days prior to registration is allowed
- 3.25 Evidence of extrahepatic metastatic disease
- 3.26 Suitable for liver transplant
- 3.27 Participation in another clinical study where the patient has received any dose of an investigational product ≤ 90 days prior to registration.
- 3.28 Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study
- 3.29a Any unresolved toxicity NCI CTCAE Grade ≥ 2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
 - Patients with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
 - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.
- 3.29b Any concurrent chemotherapy, investigational product (IP), biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
- 3.29c Major surgical procedure (as defined by the Investigator) ≤ 28 days prior to registration.
- 3.29d History of allogenic organ transplantation.
- 3.29e Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
 - Patients with vitiligo or alopecia
 - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
 - Any chronic skin condition that does not require systemic therapy
 - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
 - Patients with celiac disease controlled by diet alone

- 3.29f Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
- 3.29g History of another primary malignancy except for
- Malignancy treated with curative intent and with no known active disease ≥ 3 years before registration and of low potential risk for recurrence
 - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
 - Adequately treated carcinoma in situ without evidence of disease
- 3.29h History of leptomeningeal carcinomatosis
- 3.29i Single 12 Lead ECG which QTcF > 470 ms.
NOTE: In case of clinically significant ECG abnormalities, including a QTcF value > 470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (within 30 minutes) to confirm the finding.
- 3.29j Immunocompromised and HIV positive and currently receiving antiretroviral therapy.
- 3.29k Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), or **hepatitis B** (positive HBV surface antigen (HBsAg) result). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Participants with active HCV infection (as characterized by the presence of detectable HCV ribonucleic acid [RNA] or anti-HCV antibody [anti-HCV]) must be managed per local institutional practice for the study and for 6 months after the last dose of study treatment.
- 3.29l Current or prior use of immunosuppressive medication ≤ 14 days prior to registration. The following are exceptions to this criterion:
- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
 - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
 - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)
- 3.29m Receipt of live attenuated vaccine ≤ 30 days prior to registration. Note: Patients, if enrolled, should not receive live vaccine whilst receiving Investigational Products (IP) and up to 30 days after the last dose of durvalumab and regorafenib.

- 3.29n Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of protocol treatment.
- 3.29o Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
- 3.29p Prior randomization or treatment in a previous durvalumab clinical study regardless of treatment arm assignment

4.0 Test Schedule

While patients are receiving treatment (up to 24 cycles) and in clinical follow-up, please use the following table:

[illegible]

	Screening	Active Monitoring Phase												
Test and procedures	≤ 28 days prior to registration	Cycle 1 Day 1 (± 3 days)	Cycle 2 Day 1 (± 3 days)	Cycle 3 Day 1 (± 3 days)	Cycle 4 Day 1 (± 3 days)	Y-90 or SBRT	Cycle 5 Day 1 (± 3 days)	Cycle 6 Day 1 (± 3 days)	Cycle 7 Day 1 (± 3 days)	Cycle 8 Day 1 (± 3 days)	Odd Cycles 9-23 Day 1 (± 3 days)	Even Cycles 10-24 Day 1 (± 3 days)	30 day follow up after last dose (± 3 days)	Clinical follow up ¹⁹ (± 7 days)
Tumor marker – AFP	X	X ¹	X	X	X		X	X	X	X	X	X		
Liver directed therapy ¹⁴						X								
TSH (reflex free T3 and free T4) ¹⁵	X			X				X			X ¹⁵	X ¹⁵		
Coagulation panel: PT and INR and aPTT	X													
Mandatory tissue sample (see section 17.0) ^{17, R}		X		X										
Mandatory blood sample (see section 14.1) ^{18, R}		X	X ¹⁸	X ¹⁸			X ¹⁸						X ¹⁸	
Patient medication diary (App. II)		X	X	X	X		X	X	X	X	X	X		

¹ For the C1D1 tests, results from the screening tests may be used if completed within 7 days of Cycle 1 Day 1.

² Any clinically significant abnormalities detected require triplicate ECG results obtained over a brief period (within 30 minutes) to confirm the finding. A single ECG will be obtained on which QTcF must be <470 ms. In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (within 30 minutes) to confirm the finding.

³ Hepatitis B surface antigen, Hepatitis C antibodies, HIV antibodies

⁴ Height only at screening. Vitals to include temperature, HR, BP and RR.

⁵ For women of childbearing potential only. Urine pregnancy test with positive verified via blood serum pregnancy test. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

- ⁶ Imaging will be evaluated for radiographic response using RECIST 1.1 on images from CT or MRI, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands) and pelvis. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Imaging will be performed at 8 weeks (± 7 days) after initiation of neoadjuvant treatment. Same imaging modality utilized in screening should be performed in subsequent scans unless deemed not suitable or safe by the treating investigator.
- ⁷ Tumor measurements should be done at Day 28 of the specified cycle (± 7 days)
- ⁸ Patients are eligible to proceed to surgery after cycles 2, 4, 6, or further subsequent restaging scans if deemed reasonable by treating physician. Surgery will take place at least 28 days after the last dose of systemic therapy. Recurrence will be assessed every 90 days (± 7 days) for up to 2 years after surgery
- ⁹ For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed
- ¹⁰ It is recommended that patients are contacted 2 weeks after receiving the first 3 cycles of durvalumab + regorafenib (Cycle 1, 2, and 3 Day 14) of study drug(s) to ensure early identification and management of toxicities.
- ¹¹ Hematology: CBC with differential.
- ¹² Chemistry: Aspartate transaminase, alkaline phosphatase, alanine transaminase, total bilirubin, creatinine, calcium, phosphorous, glucose, sodium, and potassium.
- ¹³ Urinalysis: Urine creatinine (creatinine clearance), urine protein.
- ¹⁴ If patient remains unresectable but shows no progression of disease in the scans, proceed with standard of care Y-90 or SBRT as per institutional standards. After standard of care Y-90 or SBRT, wait at least 2-3 weeks and for recovery of any potential adverse events to resolve to Grade 2 or lower before restating systemic therapy then continue regorafenib and durvalumab for another 8 weeks and restage if not able to receive Y-90 or SBRT despite initial consideration can resume systemic therapy and restage 8 weeks after resuming systemic therapy.
- ¹⁵ If TSH is measured ≤ 14 days prior to Cycle 1 Day 1, it does not need to be repeated at day 1. TSH will be measured every 3 cycles. Free T3 and free T4 will only be measured if TSH is abnormal.
- ¹⁶ Refer to Appendix I Toxicity Management Guidelines for further instruction on increased liver biochemistry and evaluation of Hy's Law.
- ¹⁷ As part of the trial all participants will undergo paired image-guided biopsy after registration, but prior to initiation of systemic therapy and prior to Cycle 3 Day 1 (if they have unresectable, but stable disease) and patients who undergo resection will have surgical tumor samples collected at the time of surgery. Tumor samples will be collected fresh at the time of liver biopsy and at the time of liver resection. All tumor samples will be paraffin embedded and frozen at all participating sites except for Emory which can be fresh samples sent directly to [REDACTED] lab (see Section 17.0 for more details). If available, archival tissue obtained within the previous 3 months is acceptable instead of pre-treatment biopsy.
- ¹⁸ Blood for correlative studies will be collected after registration, but prior to initiation of systemic therapy, prior to treatment on Cycle 2 day 1, Cycle 3 Day 1, Cycle 5 Day 1, and at off protocol treatment.
- ¹⁹ Clinical Follow Up is for patients that had surgical resection of tumor, until recurrence, withdrawal, or removal
- ²⁰ Patients who have undergone surgical resection do not need RECIST v1.1 measurement in clinical follow-up. However, these patients should be reevaluated for recurrence of HCC via CT or MRI each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands) and pelvis every 90 days ± 7 days for up to 2 years after surgery. Refer to Table 4.1 for more details.
- ^R Research funded (see Section 19.0)

4.1 Surgery Table

Patients are eligible to proceed to surgery *after* cycles 2, 4, 6, or further subsequent restaging scans if deemed reasonable by treating physician. Surgery will take place at least 28 days after the last dose of systemic therapy. Disease recurrence after surgery will be assessed every 90 days ($\pm$ 7 days) by CT or MRI for up to 2 years after surgery

Test and procedure	Surgery ($\geq$ 28 days after last dose of therapy)	Every 90 days post-surgery ($\pm$ 7 days)
Recurrence Assessment (CT or MRI)		X
Surgical tissue sample (see section 17.0)	X	

4.2 Survival Follow-Up

	Survival Follow-up Phase ^{1, 2}				
	Every 3 months until subsequent treatment or PD (+/- 14 days)	At subsequent treatment or PD (+/- 14 days)	After subsequent treatment or PD Every 6 months (+/- 14 days)	Death	New Primary
Survival Follow Up	X	X	X	X	At each occurrence

¹ If a patient is still alive 5 years after registration and they have completed protocol therapy, no further follow-up is required.

² Patients in survival follow-up who decline to return to the site for evaluations should be contacted by telephone.

5.0 Grouping Factors:

None

6.0 Registration Procedures

6.1 Site Procedures

- 6.11 Study staff will need to complete the required training prior to gaining access to the registration application. This is located on the ACCRU web page at [REDACTED]. Refer to Study Resources → Applications. Near the bottom of the page there will be a link to the “Research Registration Application Training.” After training is complete, study staff must complete the “Attestation of Training” and send to the ACCRU Registration Office at [REDACTED].
- 6.12 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using the online Florence system.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with ACCRU. Approvals should be uploaded using the online Florence system. If the necessary documentation is not submitted in advance of attempting patient registration, the randomization will not be accepted, and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals is required until the study has been closed through your IRB.

6.2 Registration Procedures

- 6.21 To register a patient, access the ACCRU web page at [REDACTED], go to the Study Resources → Application section and click on “Registration” and enter the registration application. The registration application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, email the Academic and Community Cancer Research United (ACCRU) Registration Office at [REDACTED].

Instructions for the registration application are available on the above web page under the Study Resources → Application section. Please refer to the “Research Registration Application Training” or Quick Reference Guide for instructions.

Prior to initiation of protocol treatment, this process must be completed in its entirety and a ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office at [REDACTED]. If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to the Research Registration Application training on the ACCRU website under Study Resources → Applications.

- 6.22 Prior to accepting the registration, the registration application will verify the following:
- IRB approval at the registering institution
 - Patient eligibility
 - Existence of a signed consent form
 - Existence of a signed authorization for use and disclosure of protected health information

6.23 Correlative Research

6.231 Mandatory

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (See Section 3.0, 14.0, and 17.0).

- 6.24 At the time of registration, the following will be recorded:
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn about, prevent, or treat cancer.
 - Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
 - Patient has/has not given permission for ACCRU to give his/her sample(s) to outside researchers.
- 6.25 Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.
- 6.26 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.
- 6.27 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.
- 6.28 All required baseline symptoms (see Section 10.62) must be documented and graded.
- 6.29a Study drug is available on site.
- 6.29b Blood draw kit is available on site.

7.0 Protocol Treatment

- 7.1 Treatment Schedule - Use actual weight or estimated dry weight if fluid retention

7.11 Treatment medication table

Agent	Dose	Route	Day
Regorafenib	80 mg	Oral	1-21 daily (3 weeks on, 1 week off)
Durvalumab*	1500 mg	IV	Day 1 of each cycle

* If weight falls to ≤ 30 kg weight-based dosing at 20 mg/kg will be administered using an IV bag size selected such that the final concentration is within 1 to 15 mg/mL.
Cycle length = 28 days

This is a single-arm Phase II study which is designed to assess initial evidence of the efficacy of regorafenib plus durvalumab in patients with high-risk resectable hepatocellular carcinoma (HCC) who have received no prior systemic treatment. Patients meeting the eligibility criteria will be started on **regorafenib 80 mg po daily (3 weeks on 1 week off) and durvalumab 1500 mg IV every 4 weeks combination. Restaging scans will be performed at 8 weeks.** Patients who are deemed to be surgical candidate by the treating surgeon will undergo surgical resection after at least 4 weeks from the last dose of systemic treatment. Patients whose tumor(s) are deemed not surgically resectable will have a research biopsy and will proceed with regorafenib and durvalumab combination for cycles 3-4 and be restaged in 8 weeks. If resectable, patient will proceed with surgery; if patient remains unresectable but shows no progression of disease, proceed with standard of care Y-90 or SBRT as per institutional standards. After standard of care Y-90 or SBRT, wait at least 2-3 weeks and for recovery of any potential adverse events to resolve to Grade 2 or lower before restating systemic therapy at cycle 5. The patient will continue regorafenib and durvalumab for another 8 weeks and restage. If patient is not able to receive Y-90 or SBRT despite initial consideration, the patient can resume systemic therapy and restage 8 weeks after resuming systemic therapy. If the patient is deemed resectable, patient will proceed with surgery, otherwise patient will continue regorafenib and durvalumab until progression with restaging every 8 weeks. Patients could proceed to surgery after further subsequent restaging scans if deemed reasonable by treating physician. **Each cycle is 28 days.** The trial test schedule in 4.0 summarizes the trial procedures to be performed at each visit.

Screening: ≤ 28 days Prior to Registration

- Informed Consent
- Review of study eligibility criteria
- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam
- ECOG performance status
- 12 Lead ECG- a single ECG will be obtained on which QTcF must be <470 ms. In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (within 30 minutes) to confirm the finding.
- Laboratory Assessments
 - Hematology laboratory tests
 - Clinical chemistry tests
 - Tumor marker AFP
 - TSH
 - Urinalysis

- Pregnancy test (if applicable)
- Hepatitis B surface antigen, Hepatitis C antibodies, HIV antibodies
- Baseline tumor measurement (CT or MRI) per RECIST 1.1

Cycle 1:

- Baseline research biopsy of the tumor (after registration, prior to treatment)
- Correlative peripheral blood sample to be collected at baseline (after registration, prior to treatment)
- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam
- ECOG performance status
- Patient medication diary
- Adverse event assessment
- Laboratory Assessments (For cycle 1 day 1, results from the screening tests may be used if completed within 7 days of day 1)
 - Hematology laboratory tests
 - Clinical chemistry tests
 - Pregnancy test (if applicable)
 - Tumor marker – AFP
 - Urinalysis
- Regorafenib
- Durvalumab

Cycle 2:

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam
- ECOG performance status
- Patient medication diary
- Adverse event assessment
- Laboratory Assessments
 - Hematology laboratory tests
 - Clinical chemistry tests
 - Pregnancy test (if applicable)
 - Tumor marker – AFP
 - Urinalysis
- Regorafenib
- Durvalumab
- Correlative peripheral blood sample to be collected prior to treatment on C2D1.
- Cross sectional imaging (CT or MRI) for restaging at the end of cycle 2
- Surgery if deemed resectable by treating surgeon, proceed with surgery at least 4 weeks after the last dose of systemic therapy, collect surgical tissue sample for correlative research
OR
- If unresectable but stable disease, collect second biopsy and continue with cycle 3 if no progression of disease is encountered.

Cycle 3:

- Record concomitant medications

- Vitals (temperature, HR, BP and RR)
- History and physical exam
- ECOG performance status
- Patient medication diary
- Adverse event assessment
- Laboratory Assessments
 - Hematology laboratory tests
 - Clinical chemistry tests
 - Pregnancy test (if applicable)
 - Tumor marker – AFP
 - Urinalysis
 - TSH
- Correlative peripheral blood sample to be collected prior to treatment on C3D1
- Regorafenib
- Durvalumab

Cycle 4:

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam
- ECOG performance status
- Patient medication diary
- Adverse event assessment
- Laboratory Assessments
 - Hematology laboratory tests
 - Clinical chemistry tests
 - Pregnancy test (if applicable)
 - Tumor marker – AFP
 - Urinalysis
- Regorafenib
- Durvalumab
- Cross sectional imaging (CT or MRI) for restaging at the end of cycle 4
- Surgery if deemed resectable by treating surgeon, proceed with surgery at least 4 weeks after the last dose of systemic therapy, collect surgical tissue sample for correlative research
- OR**
- If unresectable but stable disease proceed with Y-90 or stereotactic radiation therapy (SBRT) as per institutional standards, at 2-3 weeks and recovery of any potential adverse events to resolve to Grade 2 or lower before restating systemic therapy and proceed with cycle 5. If not able to receive Y-90 or SBRT despite initial consideration can resume systemic therapy and restaged 8 weeks after resuming systemic therapy.

Cycle 5:

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam
- ECOG performance status
- Patient medication diary
- Adverse event assessment
- Laboratory Assessments

- Hematology laboratory tests
- Clinical chemistry tests
- Pregnancy test (if applicable)
- Tumor marker – AFP
- Urinalysis
- Correlative peripheral blood sample to be collected prior to treatment on C5D1
- Regorafenib
- Durvalumab

Cycle 6:

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam
- ECOG performance status
- Patient medication diary
- Adverse event assessment
- Laboratory Assessments
 - Hematology laboratory tests
 - Clinical chemistry tests
 - Pregnancy test (if applicable)
 - Tumor marker – AFP
 - Urinalysis
 - TSH
- Regorafenib
- Durvalumab
- Cross sectional imaging (CT or MRI) for restaging at the end of cycle 6
- Surgery if deemed resectable by treating surgeon, proceed with surgery at least 4 weeks after the last dose of systemic therapy, collect surgical tissue sample for correlative research
- OR**
- If unresectable but stable disease, proceed with cycle 7

Cycle 7:

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam
- ECOG performance status
- Patient medication diary
- Adverse event assessment
- Laboratory Assessments
 - Hematology laboratory tests
 - Clinical chemistry tests
 - Pregnancy test (if applicable)
 - Tumor marker – AFP
 - Urinalysis
- Regorafenib
- Durvalumab

Cycle 8 and beyond:

- Record concomitant medications

- Vitals (temperature, HR, BP and RR)
 - History and physical exam
 - ECOG performance status
 - Patient medication diary
 - Adverse event assessment
 - Laboratory Assessments
 - Hematology laboratory tests
 - Clinical chemistry tests
 - Pregnancy test (if applicable)
 - Tumor marker – AFP
 - Urinalysis
 - TSH (C9D1-C24D1) - to be completed every 3 cycles
 - Regorafenib
 - Durvalumab
 - Cross sectional imaging (CT or MRI) for restaging at the end of cycle 8 and subsequent even cycles (10, 12, 14, etc.)
 - Patient will continue regorafenib and durvalumab until progression with restaging every 8 weeks
- 7.2 Patients can be instructed in administration techniques for Regorafenib and granted treatment independence with nursing staff approval.
- 7.3 For this protocol, the patient must return to the consenting ACCRU institution for evaluation at least every 28 days during treatment and every 90 ($\pm$ 7 days) days during clinical follow-up (Active Monitoring Phase).
- 7.4 Study treatment with durvalumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.
- Note: Any administered treatment outside of this window will require deviation reporting in the EDC.
- 7.5 Treatment by a local medical doctor (LMD) is not allowed.
- 7.6 Patients in the durvalumab and regorafenib treatment group will receive 1500 mg durvalumab via IV infusion Q4W (every 4 weeks) until surgery or up to 2 years post registration unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.
- 7.7 Permanent discontinuation of Regorafenib plus Durvalumab
- 7.71 Discontinuation of study treatment, for any reason, does not impact the patient's participation in the study. A patient who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AE. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits during survival follow-up, a modified survival follow-up must be arranged to ensure the collection of endpoints and safety information. This survival follow-up could be a telephone contact with the patient, a contact with a relative or treating physician, or information from

medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified survival follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

- 7.72 Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up (see Section 13.0).
- 7.73 All patients will be followed for survival until 5 years after registration. Patients who decline to return to the site for evaluations during survival follow up should be contacted by telephone as indicated in the test schedule as an alternative.

8.0 Dosage Modification Based on Adverse Events

Durvalumab and regorafenib have class-specific safety profiles based on their mechanism of action but may also cause AEs that overlap. For management of AEs which can be clearly attributed to durvalumab or regorafenib, independent dose modification or discontinuation for either agent is allowed. For AEs without clear attribution to either study treatment, management of toxicity should include dose modifications of both agents. Dosing modification and toxicity management for regorafenib is outlined in section 8.0. Patients requiring a delay of > 4 weeks of regorafenib should go off regorafenib treatment but can continue single agent durvalumab. Patients with dose reductions below 40 mg of Regorafenib should go off treatment with Regorafenib but can continue single agent durvalumab. **Refer to Appendix I for dosing modification and toxicity management guidelines for durvalumab.** Patients requiring a delay $\geq$ 6 weeks of durvalumab should go off the durvalumab but can continue single agent regorafenib at the study dose if deemed clinically beneficial per the investigator.

ALERT: ADR reporting may be required for some adverse events (See Section 10)

8.1 Regorafenib Dose Escalation/Reduction (Based on Adverse Events in Tables 8.21-8.25)

Dose Level	Regorafenib
0*	80 mg
-1	40 mg
-2	Discontinue Regorafenib

*Dose level 0 refers to the starting dose.

- 8.11 Patients with dose reductions below 40 mg should go off treatment with Regorafenib but can continue single agent Durvalumab.
- 8.12 Any patients with toxicities requiring > 4-week delay should go off Regorafenib treatment but can continue single agent Durvalumab,
- 8.13 Regorafenib may be dose reduced per the table(s) in Section 8.2 in case of intolerable toxicity such as weight loss, fatigue, rash or anorexia.

8.2 Regorafenib Dose Modifications

If greater than 1 dose level reduction is required, regorafenib will be discontinued and the rest of the study follow up may be continued. Patients with dose reductions below 40 mg should go off treatment with Regorafenib can continue single agent Durvalumab.

The table below outlines dose adjustments for hematologic and non-hematologic toxicities related to regorafenib except for palmar-plantar erythrodysesthesia syndrome, hypertension, and liver function test abnormalities. In addition to these recommended dose modifications, subjects who develop diarrhea, mucositis, anorexia or other events predisposing to fluid loss or inadequate fluid intake should be carefully monitored and rehydrated as clinically necessary. This is in order to minimize the risk of postural hypotension and renal failure. If multiple adverse events are seen, administer dose based on greatest reduction required for a single adverse event observed.

Table 8.21 Recommended regorafenib dose modification for hematologic and non-hematologic toxicities except palmar-plantar erythrodysesthesia syndrome, hypertension and ALT/AST/bilirubin			
NCI-CTCAE v5.0^a	Dose Interruption	Dose Modification ^b	Dose for Subsequent Cycles
Grade 0-2	Treat on time	No change	
Grade 3	Delay until $\leq$ Grade 2 ^c	Reduce by 1 dose level	If toxicity remains < Grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity ($\geq$ Grade 3) recurs, institute permanent dose reduction.
Grade 4	Delay until $\leq$ Grade 2 ^c	Reduce by 1 dose level. Permanent discontinuation can be considered at treating investigator's discretion.	
a. NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, version 5.0 b. Excludes alopecia, non-refractory nausea/vomiting, lymphocyte count decreased, non-refractory hypersensitivity and nonclinical and asymptomatic laboratory abnormalities. c. If no recovery after a 4 week delay*, treatment with regorafenib should be permanently discontinued unless subject is deriving clinical benefit, but can continue single agent Durvalumab			

Table 8.22: Grading for Palmar-plantar erythrodysesthesia syndrome			
	Grade 1	Grade 2	Grade 3
NCI-CTCAE v5.0 Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain
Further description / examples of skin changes	Numbness, dysesthesia / paresthesia tingling, painless swelling, or erythema of the hands and/or feet	Painful erythema and swelling of the hands and/or feet	Moist desquamation, ulceration, blistering, or severe pain of the hands and/or feet
Effect on activities	Does not disrupt normal activities	Limiting instrumental activities of daily life (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money)	Limiting self-care activities of daily life (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications) and not bedridden
a. Palmer-planter erythrodysesthesia syndrome is a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of hands or the soles of the feet.			

Table 8.23 Recommended regorafenib dose modification for Palmar-plantar erythrodysesthesia syndrome reaction^a		
Grade of event (NCI-CTCAE v5.0)	Occurrence	Suggested Dose Modification
Grade 1 Palmar-plantar erythrodysesthesia syndrome reaction	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief
Grade 2 Palmar-plantar erythrodysesthesia syndrome reaction	1 st occurrence	Consider decreasing dose by one dose level and immediately institute supportive measures. If no improvement, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1 ^{b,d}
	No improvement within 7 days or 2 nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resuming treatment, treat at reduced dose level ^b
	3 rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one dose level. ^{b,d}
	4 th occurrence	Discontinue therapy
Grade 3 Palmar-plantar erythrodysesthesia syndrome reaction	1 st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. ^c When resuming treatment, decrease dose by one dose level. ^{b,d}
	2 nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. ^c When resuming treatment, decrease dose by one additional dose level ^{b,d}

Table 8.23 Recommended regorafenib dose modification for Palmar-plantar erythrodysesthesia syndrome reaction^a		
Grade of event (NCI-CTCAE v5.0)	Occurrence	Suggested Dose Modification
	3 rd occurrence	Discontinue treatment permanently.
a. More conservative management is allowed if judged medically appropriate by the investigator. b. If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is not permitted. c. If there is no recovery after a 4-week delay, treatment with regorafenib will be discontinued permanently. d. Patients with dose reductions below 40 mg should go off treatment with Regorafenib but can continue single agent Durvalumab e. The maximum daily dose is 80 mg.		

8.24 Hypertension

Hypertension is a known AE associated with regorafenib treatment. Subject will have their blood pressure measured at every clinic visit. The management of hypertension, including the choice of antihypertensive medication, will be performed according to local standards and to the usual practice of the investigator. Every effort should be made to control blood pressure by medical means other than study drug dose modification. If necessary, Table 8.24 outline suggested dose reductions.

Table 8.24: Management of Treatment-Emergent Hypertension		
Grade (CTCAE v5.0)	Antihypertensive Therapy	Regorafenib Dosing
1 Prehypertension (systolic BP120 - 139 mmHg or diastolic BP 80 - 89 mmHg)	None	Continue regorafenib Consider increasing blood pressure (BP) monitoring
2 (Systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg) OR (Symptomatic increase by >20 mmHg (diastolic) if previously within normal limits)	Treat with the aim to achieve diastolic BP $\leq$ 90 mm Hg: If BP previously within normal limits, start anti-hypertensive monotherapy If patient already on anti-hypertensive medication, titrate up the dose.	Continue regorafenib If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP $\leq$ 90 mm Hg ^a . When regorafenib is restarted, continue at the same dose level.
3 (Systolic BP $\geq$ 160 mmHg or diastolic BP $\geq$ 100 mmHg) OR More than one drug or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP $\leq$ 90 mm Hg: Start anti-hypertensive medication AND/OR Increase current anti-hypertensive medication AND/OR	Hold regorafenib until diastolic BP $\leq$ 90 mm Hg, and if symptomatic, until symptoms resolve ^a When regorafenib is restarted, continue at the same dose level. If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level.

Table 8.24: Management of Treatment-Emergent Hypertension		
Grade (CTCAE v5.0)	Antihypertensive Therapy	Regorafenib Dosing
	Add additional anti-hypertensive medications.	If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level.
4 Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Per institutional guidelines	Discontinue therapy
a. Patients requiring a delay of >4 weeks should go off Regorafenib treatment but can continue single agent Durvalumab b. If BP remains controlled for at least one cycle, dose re-escalation permitted per investigator's discretion. c. Patients with dose reductions below 40 mg should go off treatment with Regorafenib but can continue single agent Durvalumab		

8.25 Liver Function Abnormalities

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

Regorafenib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome.

Table 8.25: Dose modifications/interruption for AST and/or AST and/or bilirubin increases related to study drug regorafenib			
Increases in ASL/ALT (per NCI-CTCAE v 5.0)	1st Occurrence	Restart	Re-occurrence
AST and/or ALT >3.0-5.0 x ULN if baseline was normal; >3-5 X baseline if baseline was abnormal (< Grade 3)	Continue dosing, with weekly monitoring of liver function until transaminases return to <3 X ULN (≤ Grade 1) or baseline.		
ALT and/or AST >5.0 x ULN if baseline was normal; >5.0 x baseline if baseline was abnormal (≥ Grade 3)	Interrupt dosing, with weekly monitoring until transaminases return to <3 X ULN or baseline.	If the potential benefit for reinitiating regorafenib is considered to outweigh the risk of hepatotoxicity: Reduce one dose level and measure serum liver tests weekly for at least 4 weeks.	Discontinue
ALT and/or AST >20.0 x ULN if baseline was	Discontinue		

Table 8.25: Dose modifications/interruption for AST and/or AST and/or bilirubin increases related to study drug regorafenib			
Increases in ASL/ALT (per NCI-CTCAE v 5.0)	1st Occurrence	Restart	Re-occurrence
normal; >20.0 x baseline if baseline was abnormal ($\geq$ Grade 4)			
ALT and/or AST >3.0 x ULN ($\geq$ Grade 2) with concurrent bilirubin >2.0 x ULN if baseline was normal; > 3.0 x baseline with concurrent bilirubin >2.0 baseline if baseline was abnormal	Discontinue treatment and measure serum liver tests weekly until resolution. Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the recommendations outlined above for ALT/AST elevations.		

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is completed with no further adverse events >Grade 2, then the dose may be increased, at the investigator's discretion, one level at a time, in the following cycles.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics

Antiemetic's may be used at the discretion of the attending physician.

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Volume 33, No 28 (October 1), 2015: pp. 3199-3212 (WBC growth factors) AND Journal of Clinical Oncology, Volume 28, No 33 (November 20), 2010: pp. 4955-5010 (darbepoetin/epoetin).

9.3 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Prohibited medications

The following medications are prohibited while on durvalumab therapy:

- Any investigational anticancer therapy other than those under investigation in this study
- Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding <<10 mg/day>> of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor- α blockers
- Live attenuated vaccines
- Herbal and natural remedies which may have immune-modulating effects

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all adverse events to the sponsor as described within the protocol. Refer to the adverse event and serious adverse event sections of the protocol for detailed information.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting

Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting

Events reported to sponsor via case report forms

Events of Interest

Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:

- a. Adverse event monitoring and reporting is a routine part of every clinical trial.
 - b. Identify the grade and severity of the event using the CTCAE version 5.0.
 - c. Determine whether the event is expected or unexpected (see Section 10.2).
 - d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
 - e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
 - f. Determine if other reporting is required (see Section 10.5).
- Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

- Definite - The adverse event *is clearly related* to the agent(s).
- Probable - The adverse event *is likely related* to the agent(s).
- Possible - The adverse event *may be related* to the agent(s).
- Unlikely - The adverse event *is doubtfully related* to the agent(s).
- Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably, or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship

between the drug/device and the adverse event.

10.4 Protocol Exceptions to Expedited Reporting

10.41 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6). *

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported.
General disorders and administrations site conditions	Fatigue	< Grade 3
	Malaise	< Grade 3
Gastrointestinal disorders	Diarrhea	< Grade 3
	Colitis	< Grade 3
	Small Intestinal perforation	< Grade 3
	Pancreatitis	< Grade 3
Investigations	Serum amylase increased	< Grade 3
	Lipase increased	< Grade 3
	Creatinine increased	< Grade 3
	Alkaline phosphatase increased	< Grade 3
	Aspartate aminotransferase increased	< Grade 3
	Blood bilirubin increased	< Grade 3
	Neutrophil count decreased	< Grade 3
	Lymphocyte count decreased	< Grade 3
	Platelet count decreased	< Grade 3
Respiratory, thoracic and mediastinal disorders	Pneumonitis	< Grade 3
	Pulmonary fibrosis	< Grade 3
Infection and infestations	Hepatitis viral	< Grade 3
	Papulopustular rash	< Grade 3
	Rash pustular	< Grade 3
Endocrine disorders	Hypophysitis	< Grade 3
	Hypopituitarism	< Grade 3
	Adrenal insufficiency	< Grade 3
	Hyperthyroidism	< Grade 3
	Hypothyroidism	< Grade 3
Renal and urinary disorders	Acute kidney injury	< Grade 3
Metabolism and nutrition disorders	Hyperglycemia	< Grade 3
Cardiac Disorders	Myocarditis	< Grade 3
Nervous system disorders	Peripheral motor neuropathy	< Grade 3
	Peripheral sensory neuropathy	< Grade 3
	Guillain-Barré syndrome	< Grade 3
	Myasthenia gravis	< Grade 3

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported.
Musculoskeletal and connective tissue disorders	Myositis	< Grade 3
Skin and Subcutaneous tissue disorders	Bullous Dermatitis	< Grade 3

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to:

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported.
Cardiac Disorders	Pericarditis	< Grade 3
Eye disorders	Uveitis	< Grade 3
Eye disorders	Other events involving the eye and skin	< Grade 3
Blood and lymphatic system disorders	Anemia	< Grade 3
	Neutrophil count decreased	< Grade 3
	Lymphocyte count decreased	< Grade 3
	Platelet count decreased	< Grade 3
Musculoskeletal and connective tissue disorders	Myositis	< Grade 3
	Arthritis	< Grade 3
Vascular disorders	Vasculitis	< Grade 3
Infections and infestations	Meningitis	< Grade 3

- It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.
- Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (Appendix 1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol or to administer protocol directed treatment (i.e. 131I therapy)
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)

- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study registration

A list of known/expected AEs is reported in the investigator brochure, package insert or the literature, including AEs resulting from a drug overdose.

- *Report any clinically important increase in the **rate** of a serious suspected adverse reaction (at your study) site over that which is listed in the protocol or investigator brochure as an expedited event.
- *Report an expected event that is greater in severity or specificity than expected as an expedited event
- *An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

10.42 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease that cannot be attributed to a CTCAE term associated with Grade 5 should be reported as **Grade 5 “Disease progression”** under the system organ class (SOC) of General Disorders and Administration Site Conditions. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.43 Secondary Malignancy

- A **secondary malignancy** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:
 - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
 - Myelodysplastic syndrome (MDS)
 - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.44 Pregnancy

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting [ACCRU Adverse Event Report reports for “Pregnancy”, “Pregnancy loss”, or “Neonatal loss”](#), the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the “Description of Event” section. Include any available medical documentation.

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

Female patient of child-bearing potential

- Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Section 10.441) from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Non-sterilized male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential

- Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must

use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). However, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Section 10.441).
- N.B Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.
- Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
 - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
 - Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.
- Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Section 10.441. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

10.441 Highly effective methods of Contraception List (<1% Failure Rate):

Hormonal Methods:

- Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant®
- Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing®
- Injection: Medroxyprogesterone injection: e.g. Depo-Provera®
- Combined Pill: Normal and low dose combined oral contraceptive pill

- Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra®
- Minipill: Progesterone based oral contraceptive pill using desogestrel:
- Cerazette® is currently the only highly effective progesterone-based

Basic/Intrauterine Methods:

- Copper T intrauterine device
- Levonorgestrel-releasing intrauterine system (e.g., Mirena®)

10.5 Expedited Reporting Requirements for Studies that are IND Exempt

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent^{1, 2}

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)				
NOTE: Investigators MUST immediately report to the sponsor ANY Serious Adverse Events, whether they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)				
An adverse event is considered serious if it results in ANY of the following outcomes:				
1) Death 2) A life-threatening adverse event 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5) A congenital anomaly/birth defect. 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). 7) Adverse Events (AEs) for malignant tumors reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a Non-Serious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfil the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy. 8) The above instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is <i>not</i> the tumor for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.				
ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.				
Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days			24-Hour; 3 Calendar Days

Not resulting in Hospitalization ≥ 24 hrs	Not required	7 Calendar Days	
<u>Expedited AE reporting timelines are defined as:</u> ○ “24-Hour; 3 Calendar Days” - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report. ○ “7 Calendar Days” - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.			
¹ Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: Expedited 24-hour notification followed by complete report within 3 calendar days for: • All Grade 4, and Grade 5 AEs Expedited 7 calendar day reports for: • Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization • Grade 3 adverse events			
² For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period. Effective Date: May 5, 2011			

Additional Instructions:

1. An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AE's are reported in the package insert or the literature, including AE's resulting from a drug overdose.
2. Follow site-specific reporting guidelines.
3. Submit MedWatch form 3500A

_____ found on the ACCRU web site) along with the MedWatch Fax Cover Sheet (found on the ACCRU web site) to the ACCRU SAE Coordinator via email _____. The ACCRU SAE Coordinator will forward the report to _____ via email to Astra Zeneca and to _____ via email or Fax: _____ to Bayer.

4. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

Adverse Event	Form(s) Needed	Site timeline to report to ACCRU	ACCRU timeline to report to sponsor
Non-Serious Adverse Event (Section 10.6)	Adverse Events form (see CRF packet)	At each evaluation	Quarterly
Adverse Events of Special Interest (Section 10.51 special instructions)	Adverse Events of Special Interest Form**	At each occurrence	Within 1 business day of receipt
	Adverse Events form (if criteria in 10.5 is met)		Quarterly

Adverse Event	Form(s) Needed	Site timeline to report to ACCRU	ACCRU timeline to report to sponsor
Pregnancy (Section 10.44)	ACCRU Adverse Event Expedited Report Form**	At each occurrence	Within 1 business day of receipt
	Adverse Events form (if criteria in 10.5 is met)		Quarterly
Serious Adverse Events (Section 10.5) *	ACCRU Adverse Event Expedited Report Form**	At each occurrence	Within 1 business day of receipt
	Adverse Events form (see CRF packet)		Quarterly

*If an adverse event meets the criteria for both an AE of Special Interest and a Serious Adverse Event, please report only as a Serious Adverse Event.

** The Adverse Events of Special Interest Form and ACCRU Adverse Event Expedited Report Form are available on the ACCRU web site

10.51 Adverse Event of Special Interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious.

If the Investigator has any questions in regard to an event being an AESI, the Investigator should promptly contact the Study Physician.

AESIs (CTCAE Grade ≥ 3) observed with durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- Hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, thyroiditis, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Intestinal Perforations

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to:

- Pericarditis

- Neuromuscular toxicities (such as Guillain-Barre syndrome and myasthenia gravis)
- Sarcoidosis
- Uveitis
- Other events involving the eye and skin
- Hematological events
- Rheumatological events
- Vasculitis
- Non-infectious meningitis
- Non-infectious encephalitis

It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor. The Sponsor must report these events to AstraZeneca Patient Safety using the designated Safety e-mailbox within 7 calendar days or sooner when required, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

10.6 Other Required Reporting

- 10.61 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:
1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
 2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
 3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.62 Baseline and Adverse Events Evaluations

The following pre-treatment symptoms/conditions are to be graded at baseline and adverse events are to be graded at each evaluation using CTCAE v5.0 grading.

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Infections and infestations	Lung infection	X	X
Gastrointestinal disorders	# of stools per day	X	
	Diarrhea		X
Investigations	Alanine aminotransferase increased	X	X
	Aspartate aminotransferase increased	X	X
Skin and subcutaneous tissue disorders:	Palmar-plantar erythrodysesthesia syndrome (Hand-foot syndrome)	X	X
Nervous system disorders	Encephalopathy	X	X
Vascular disorders	Hypertension	X	X

10.63 Case Report Forms - Academic and Community Cancer Research United (ACCRU). Submit the following AEs not specified in Section 10.5:

10.631 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.632 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.633 Grade 5 AEs (Deaths)

10.6331 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6332 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least

possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.64 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.65 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to Appendix I, Toxicity Management Guidelines, for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

10.7 Reporting of serious adverse events to AstraZeneca

If the study is being conducted in multiple countries or multiple sites, Investigators or other site personnel inform Sponsor representatives of the SAE. The coordinating centre/Sponsor is responsible for informing Company of the SAE. All SAEs have to be reported to Company, whether or not considered causally related to the investigational product.

SAEs related to the Investigational Product (IP) must be provided to Company in an ongoing basis as individual case reports.

SAEs unrelated to the IP must be provided to the Company as individual case reports as a quarterly line listing.

At the end of the Study a final unblinded summary line listing of all SAEs notified to the regulatory authority and/or Company during the Study, must be provided to the Company to enable reconciliation of safety information held by Company for its product(s).

Send SAE reports (individual case reports and line listings) and accompanying cover page to Company (TCS) via Email: [REDACTED]

SAEs that do not require expedited reporting to the Regulatory Authority/IRB/IEC still need to be reported to Company provided as a quarterly listing.

Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported to company at the same time these events are notified to the Regulatory Authority.

Reporting of deaths to AstraZeneca

All deaths must be recorded and reported as outlined in Section 10.42. In addition, all SAEs resulting in death or death of unknown cause must be reported to AstraZeneca via [REDACTED] within 7 calendar days of awareness or sooner when required (See Section 10.5).

11.0 Treatment Evaluation

NOTE: This study uses protocol RECIST v1.1 for evaluations prior to resection. See the footnote for the table regarding measurable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression prior to resection will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1)⁵⁰. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

Following surgical resection, recurrence of HCC after resection will be evaluated via CT or MRI each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands) and pelvis.

11.1 Schedule of Evaluations

Prior to resection: For the purposes of this study, patients should be reevaluated via RECIST v1.1 every 56 days +/- 7 days while on active treatment.

After surgical resection: patients should be reevaluated every 90 days +/- 7 days for up to 2 years after surgery to monitor disease recurrence. RECIST 1.1 is not required for recurrence evaluation.

11.2 Definitions of Measurable and Non-Measurable Disease for RECIST v1.1

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥ 2.0 cm with chest x-ray, or as ≥ 1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥ 1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to < 1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: '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. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease for RECIST v1.1

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- 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.
- 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. The lesions should be measured on the same pulse sequence. 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: 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.

11.33 Measurement at Follow-up Evaluation:

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

11.4 Measurement of Effect for RECIST v1.1

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions representative of all involved organs, should be identified as “Target Lesions” and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non-target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

- 11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may

need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:
 - a. Disappearance of all non-target lesions.
 - b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).
- Progression (PD): At least one of the following must be true:
 - a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
 - b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
 - c. See Section 11.32 for details in regard to the requirements for PD via FDG-PET imaging.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:
 - a. Disappearance of all non-target lesions.

- b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.
- Progression (PD): At least one of the following must be true:
 - a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to $\geq$ 1.0 cm short axis during follow-up.
 - b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
 - c. See Section 11.32 for details in regard to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR*
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

- 11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to “symptomatic deterioration” if any of the following occur that are not either related to study treatment or other medical conditions:
- Weight loss >10% of body weight.
 - Worsening of tumor-related symptoms.
 - Decline in performance status of >1 level on ECOG scale.

11.5 Recurrence Assessment (following surgical resection)

Presence of recurrent HCC will be documented based on review via CT or MRI each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands) and pelvis.

12.0 Descriptive Factors

- Child-Pugh Score: A5 vs. A6
- Barcelona Clinic Liver Cancer Stage (BCLC): A vs. B vs. C
- Cause of HCC: HBV vs. HCV vs. Non-viral (NASH/NAFLD, Alcohol, Other, Unknown)
- Vascular Invasion: Yes vs. No vs. Unknown
- Prior Local Treatment for HCC: Liver Directed Therapy vs. TACE vs. Y-90, Bland-Embolization vs. Other

13.0 Treatment/Follow-up Decision at Evaluation of Patient

13.1 Continuation of treatment

Patients who are CR, PR, or SD will continue treatment per protocol until decision to proceed surgery, disease progression, excessive toxicity, or patient withdrawal. The maximum of 24 cycles of treatment is allowed per protocol. Subsequent treatment beyond 24 cycles is at the discretion of their attending physician.

13.2 Progressive disease (PD)

Patients who develop PD while receiving therapy will go to the survival follow-up phase.

13.3 Surgery

Patients who are deemed to be surgical candidates by the treating surgeon will undergo surgical resection. Surgery and last dose of systemic treatment should be at least 4 weeks apart. If a patient is scheduled for surgery but does not undergo the planned surgery due to reasons other than disease progression the patient can resume systemic therapy and be restaged after 8 weeks of systemic therapy and reassessed for surgery or Y-90 or SBRT (if not already administered in the study).

13.4 Radiation

After the second restaging scan, if a patient remains unresectable but shows no progression of disease (per RECIST 1.1), proceed with standard of care Y-90 or SBRT as per institutional standards. Systemic therapy can be restarted after at least 2-3 weeks since last fraction of radiation and after any potential adverse events have resolved to be Grade 2 or lower. If not able to receive Y-90 or SBRT despite initial consideration can resume systemic therapy and restage 8 weeks after resuming systemic therapy. Systemic therapy can be restarted even if the radiation therapy was interrupted or not completed after at least 2-3 weeks since last fraction of radiation and after any potential adverse events have resolved to be Grade 2 or lower.

13.5 Off protocol treatment

Follow the table below for patient follow-up after patient goes off protocol treatment.

CFU=Clinical Follow-Up

SFU=Survival Follow-Up

Reason Off Treatment (from the Off-Treatment Form)	Does patient intend to go to surgery once they are off protocol treatment?	Go to CFU, SFU, or end follow-up
Patient Withdrawal/Refusal After Beginning Protocol Therapy (Intervention)	Yes	CFU
Patient Withdrawal/Refusal After Beginning Protocol Therapy (Intervention)	No	SFU
Adverse Events/Side Effects/Complications	Yes	CFU
Adverse Events/Side Effects/Complications	No	SFU
Disease Progression, Relapse During Active Treatment (Intervention)	N/A	SFU
Alternative Therapy	Yes	CFU
Alternative Therapy	No	SFU
Patient Off-Treatment (Intervention) For Other Complicating Disease	Yes	CFU
Patient Off-Treatment (Intervention) For Other Complicating Disease	No	SFU
Death On Study	N/A	No follow-up
Other	Yes	CFU
Other	No	SFU
Disease Progression Before Active Treatment (Intervention)	N/A	No follow-up

Reason Off Treatment (from the Off-Treatment Form)	Does patient intend to go to surgery once they are off protocol treatment?	Go to CFU, SFU, or end follow-up
Patient Withdrawal/Refusal Prior To Beginning Protocol Therapy (Intervention)	N/A	No follow-up

13.6 For patients who have surgical resection within 4 months of last dose of protocol treatment, clinical follow-up occurs every 90 days ($\pm$ 7 days) for a maximum of 2 years after registration

13.7 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for registration.

- If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

13.8 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are no safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol, and all data submission should continue per protocol. If the patient does not continue with treatment, the patient will go off treatment and be followed in Clinical Follow-up.

13.9 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the Off-Treatment form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Research	Specimen Purpose	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline (after registration, but prior to initiation of systemic therapy)	Prior to treatment on Cycle 2 day 1, Cycle 3 day 1 & Cycle 5 day 1	At off Protocol Treatment	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Immune sample profiling (Section 14.2)	Correlative	Mandatory	Whole Blood	EDTA (Purple)	10 mL (3)	X	X	X	No	Ambient Cold Pack ³

1. After all samples have been collected and processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.25 for detailed shipping instructions.)
2. Blood draws should not be collected and submitted until after the patient is registered onto the study
3. **Samples collected at Emory can be sent to [REDACTED] lab fresh**

14.2 Blood/Blood Products Handling

14.21 **Kits are required for this study. (For Emory ONLY: tubes can be obtained on site at Emory or a kit request can be submitted if preferred)**

14.211 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.212 Participating institutions may obtain kits from the BAP Lab via the Mayo Clinic Research Client Request Portal (MCRCRP). Detailed instructions for using MCRCRP are available on the ACCRU website located under the study specific 'Manuals and Forms'. Because we are charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Unused/expired kits should be disposed per institution policy. Do not send unused kits back to BAP. Kit requests must be filled in completely and accurately for quick processing. For questions regarding your kit order contact 

14.213 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.** Kits will arrive inside the shipping boxes.

14.214 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. **ACCRU will not cover the cost for rush delivery of kits.**

14.22 All samples must be collected **Monday-Friday ONLY.**

14.23 Label specimen tube(s) with protocol number, ACCRU patient ID number, and time and date blood are drawn.

14.24 Collect and process all blood/blood products according to specific kit instructions.

14.25 Shipping

14.251 Verify ALL sections of the Blood Specimen Submission Form (see Forms Packet), BAP Requisition Form (provided in kit) and specimen collection labels are completed and filled in correctly.

14.252 Specimens must be shipped the same day they are drawn.

14.253 Ship all whole blood EDTA tubes via Priority Overnight service with a properly prepared cold pack. See kit instructions for specific details for ambient cold pack preparation (i.e. frozen or refrigerated) with proper packing of blood and cold pack to avoid freezing of the specimens.

- 14.254 Ship specimens via Priority Overnight service, **Monday – Friday ONLY**, to BAP Receiving according to kit instructions. **Do not send samples on weekends or just prior to federal holidays.**

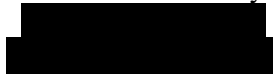
The BAP kits will include a smart shipper label (3x5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an airbill. Shipping costs will be covered by ACCRU if the shipping box provided with the BAP kit is used for shipping specimens to BAP Receiving. Ship refrigerated samples to:

BAP FREEZER

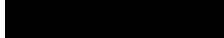


- 14.255 BAP Freezer will receive the samples and forward them to accessioning and processing. BAP will process one of the whole blood EDTA tubes for PPP and the other two tubes for PBMC's and store. Samples will be batch shipped upon request for immune profiling analysis to:

Lesinski Laboratory



Winship Cancer Institute of Emory University



14.3 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

IND exempt

15.1 Durvalumab (MEDI4736, IMFINZI™):

- 15.11 **Background:** Durvalumab is a human immunoglobulin (Ig) G1 kappa (IgG1κ) monoclonal antibody (mAb) that blocks the interaction of programmed cell death ligand 1 (PD-L1) (but not programmed cell death ligand-2) with programmed cell death 1 (PD-1) on T-lymphocyte (T-cells) and cluster of differentiation

(CD)80 (B7.1) on immune cells (IC) and is engineered to reduce antibody-dependent cell-mediated cytotoxicity (ADCC).

15.12 **Formulation:**

- **Liquid product for IV administration:** Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; pH of 6.0. Each vial contains either 500 mg (nominal, 10 mL fill) or 120 mg (nominal, 2.4 mL fill) of active investigational product at a concentration of 50 mg/mL.

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Investigational product should be kept in original packaging until use to prevent prolonged light exposure.

15.13 **Preparation and storage:**

IV formulation: Withdraw desired volume from vial and dilute in either 0.9% sodium chloride or 5% Dextrose in Water to a final concentration of 1 to 20 mg/mL. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed 24 hours at 2°C to 8°C (36°F to 46°F) or 4 hours at room temperature. Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Please refer to local prescribing information for in-use storage conditions and times.

A dose of 1500 mg (for patients >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30 mL (i.e. 1500 mg) of durvalumab to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time is one hour, however if there are interruptions, the total allowed time must not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

15.14 **Administration:**

IV administration: Durvalumab is delivered through an IV administration set

with a 0.2 or 0.22 micron filter. The standard infusion time is 1 hour. Do not co-administer other drugs through the same infusion line. Flush the IV line with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered.

Monitoring of IV dose administration: Patients will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment. Patients are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped). In the event of a $\leq$ Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a $\leq$ Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g. diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature (otherwise requires new infusion preparation). Do not co-administer other drugs through the same infusion line. For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines.

15.15 **Pharmacokinetic information:**

Volume of Distribution: The mean volume of distribution at steady state was 5.6 liters

Half-life elimination: The mean terminal half-life at steady state was approximately 18 days.

Excretion: Mean steady state clearance was 8.2 mL/hr

15.16 **Potential Drug Interactions:** Durvalumab is an immunoglobulin; therefore, no formal pharmacokinetic drug-drug interaction studies have been conducted.

15.17 **Known potential adverse events:**

Very common known potential adverse events, > 10%:

Cough/productive cough, diarrhea, abdominal pain, hypothyroidism, rash, pruritus, pyrexia, upper respiratory tract infections, fatigue, decreased appetite, nausea, dyspnea, constipation, anemia, vomiting, asthenia, back pain, arthralgia

Common known potential adverse events, 1% - 10%:

Pneumonitis, dysphonia, ALT/AST increased, hyperthyroidism, blood creatinine increased, dysuria, night sweats, pneumonia, oral candidiasis, dental and oral soft tissue infections, influenza, myalgia, infusion related reaction, headache, peripheral edema, insomnia, weight decreased, musculoskeletal pain, dizziness, urinary tract infection, myalgia, upper respiratory tract infection, hypernatremia, pain in extremity

Rare known potential adverse events, <1% (Limited to important or life-threatening):

Interstitial lung disease, hepatitis, colitis, thyroiditis, adrenal insufficiency, Type I diabetes mellitus (which may present as diabetic ketoacidosis),

hypophysitis/hypopituitarism, diabetes insipidus, nephritis, dermatitis, pemphigoid, myocarditis, polymyositis, myasthenia gravis, immune thrombocytopenia, pancreatitis, encephalitis, uveitis

Overall, the presence of durvalumab anti-drug antibodies did not have an influence on durvalumab exposure metric, and there was no apparent effect on the safety of durvalumab. These results support a low immunogenicity risk of durvalumab.

- 15.18 **Drug procurement:** AstraZeneca will supply Durvalumab to McKesson. Each participating ACCRU treating location will order the drug from McKesson. Fax or email the Drug Order Request Form (found on the ACCRU web site) to:

McKesson

Fax: [REDACTED]

Email: [REDACTED]

Each participating ACCRU treating location will be responsible for monitoring the supply of Durvalumab and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.19 **Nursing Guidelines:**

- 15.191 Anti PD-L1 side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids
- 15.192 Diarrhea can be common and can be very severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.
- 15.193 Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Treat per section 8.0 and monitor for effectiveness.
- 15.194 Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.
- 15.195 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

- 15.196 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are a concern given the mechanism of action of this agent. Patients may present only with the vague sense of fatigue and “not feeling well”. Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.
- 15.197 Pancreatitis is possible with anti PD-L1 therapy based on mechanism of action. Instruct patients to report abdominal pain, nausea and vomiting to the study team.
- 15.198 Patients who are started on steroid therapy for any side effects of anti PD-L1 toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

15.2 Regorafenib (BAY 73-4506, Stivarga®)

- 15.21 **Background:** Regorafenib is a novel oral multi-kinase inhibitor that targets tumor cells and the tumor microenvironment. It inhibits tumor growth, progression and metastasis by inhibiting the proliferation of tumor cells, the formation of new tumor vasculature and stromal signaling in the microenvironment of the tumor.
- 15.22 **Formulation:** Regorafenib Tablets 40 mg are IR dosage forms with rapid dissolution under in vitro test conditions. The tablet formulations contain the active substance regorafenib, povidone, croscarmellose sodium, microcrystalline cellulose, colloidal anhydrous silica, and magnesium stearate and are film coated with a coating composed of partially hydrolyzed polyvinyl alcohol, talc, macrogol, soya lecithin, ferric oxide red, ferric oxide yellow, and titanium dioxide.
- Regorafenib tablets 40 mg are light pink in color and are oval-shaped (modified oblong) with a length of 16 mm and a width of 7 mm.
 - Regorafenib tablets 40 mg are available both as uncoded tablets and as coded tablets, which are debossed with “40” on one side of the tablet and “BAYER” on the other side.
- 15.23 **Preparation and storage:** The tablets are stored in high-density polyethylene (HDPE) bottles with a desiccant cartridge inside. The tablets have to be stored in the original bottle, in a secure, dry location at a temperature not above 25°C.

The tablets have to be stored in the original pack provided in order to protect from moisture and swallowed immediately after they have been taken out of the packaging. The bottle has to be kept tightly closed after first opening, and the desiccant has to remain in the bottle.

Once the bottle is opened the tablets have to be discarded after 7 weeks.

- 15.24 **Administration:** Regorafenib tablets should be taken in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (<30% fat) breakfast. Regorafenib should not be taken with grapefruit juice.
- 15.25 **Pharmacokinetic information:**
- a) Absorption – A high-fat meal increased the mean AUC of the parent drug by 48% compared to the fasted state and decreased the mean AUC of the M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl) active metabolites by 20% and 51%, respectively. A low-fat meal increased the mean AUC of regorafenib, M-2 and M-5 by 36%, 40% and 23%, respectively (as compared to the fasted state).
 - b) Distribution – Regorafenib undergoes enterohepatic circulation with multiple plasma concentration peaks observed across the 24-hour dosing interval. Regorafenib is highly bound (99.5%) to human plasma proteins. The apparent volume of distribution after oral administration is 88L.
 - c) Metabolism – Regorafenib is metabolized by CYP3A4 and UGT1A9. The main circulating metabolites measured at steady state are M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), both of them having similar *in vitro* pharmacological activity and steady-state concentrations as regorafenib. M-2 and M-5 are highly protein bound (99.8% and 99.95%, respectively).
 - d) Excretion – 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 (range) elimination half-life of 51 hours (32 to 70 hours). Feces (71%; 47% as parent compound; 24% as parent compound; 24% as metabolites); Urine (19%).
- 15.26 **Potential Drug Interactions:** Avoid concomitant use of strong CYP3A4 inducers (i.e. rifampin, phenytoin, carbamazepine, phenobarbital and St. John's Wort) and strong CYP3A4 inhibitors (i.e. clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin and voriconazole).
- 15.27 **Known potential toxicities:**
- Serious Adverse Effects:**
- Hepatotoxicity: [U.S. Boxed Warning]: Severe liver toxicity and hepatic failure (sometimes resulting in death) have been observed in clinical trials; hepatocyte necrosis with lymphocyte infiltration has been demonstrated with liver biopsy. Monitor hepatic function at baseline and during treatment. Interrupt therapy for hepatotoxicity; dose reductions or discontinuation are necessary depending on the severity and persistence.
- Most Common Adverse Events, >10%**
- Cardiovascular: Hypertension
 - Central nervous system: Fatigue, dysphonia, pain, fever, headache.
 - Dermatologic: Palmar-plantar erythrodysesthesia, rash, alopecia
 - Endocrine & metabolic: Hypocalcemia, hypophosphatemia, hyponatremia, hypokalemia, hypothyroidism
 - Gastrointestinal: Appetite decreased, lipase increased, diarrhea, mucositis, weight loss, amylase increased, nausea, vomiting, stomatitis
 - Hematologic: Anemia, lymphopenia, thrombocytopenia, INR increased, hemorrhage, neutropenia
 - Hepatic: AST increased, ALT increased, hyperbilirubinemia
 - Neuromuscular & skeletal: Asthenia, muscle spasm

Renal: Proteinuria
Miscellaneous: Infection

Less Common Adverse Events, 1% - 10%

Cardiovascular: Myocardial ischemia and infarction
Dermatologic: Exfoliative dermatitis
Gastrointestinal: Mucocutaneous candidiasis, pancreatitis
Genitourinary: Urinary tract infection
Infections: Fungal infection
Neuromuscular & skeletal: Tremor
Respiratory: Nasopharyngitis, pneumonia

Rare Adverse Events (Important or life-threatening), <1%

Erythema multiforme, gastrointestinal fistula, gastrointestinal perforation, hypertensive crisis, liver injury (severe), liver failure, reversible posterior encephalopathy syndrome (RPLS), Stevens-Johnson syndrome, toxic epidermal necrolysis, acute myocardial infarction, ischemic heart disease, arterial aneurysm, aortic aneurysm, aortic dissection, cardiac failure, coronary artery dissection, myocardial rupture, nephrotic syndrome, hypersensitivity reaction

- 15.28 **Study agent procurement:** Bayer HealthCare Pharmaceuticals will supply regorafenib tablets to McKesson. Each participating ACCRU treating location will order the drug from McKesson. Fax or email the Drug Order Request Form (found on the ACCRU web site) to:

McKesson

Fax: [REDACTED]

Email: [REDACTED]

Each participating ACCRU treating location will be responsible for monitoring the supply of regorafenib and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution and use. Please use the Unused Drug Disposition Form in Appendix VI and mail form to:

BAYER HealthCare Pharmaceuticals Inc.,
[REDACTED]

15.29 Nursing Guidelines

- 15.291 Liver toxicity and liver failure have resulted from this agent. Monitor LFT's closely and instruct patients to report any abdominal pain, jaundice or significant fatigue to the study team. Dose reduce or interrupt treatment as per protocol.
- 15.292 Hypertension has been seen. Monitor blood pressure as outlined in protocol.

- 15.293 Instruct patient to report and rash, or signs symptoms of palmar-plantar erythrodysesthesia to study team. Rarely SJS and TENS have been seen with this agent. Instruct patients to seek immediate medical attention if they experience rash with fever, blisters, sloughing of tissue (especially in the mouth and vaginal, anal regions). Treat symptomatically and monitor for effectiveness.
- 15.294 Warn patients of possibility of alopecia.
- 15.295 Gastrointestinal side effects can include, diarrhea, nausea, vomiting, decreased appetite, weight loss, mucositis and less commonly taste changes, dry mouth, and reflux. Treat symptomatically and monitor for effectiveness.
- 15.296 Cytopenias are seen with agent. Monitor CBC w/diff and instruct patient to report signs, symptoms of infection or any unusual bruising or bleeding to the study team.
- 15.297 Secondary skin cancers have been reported. Instruct patients to report new or changing lesions to study team.
- 15.298 Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a rare (<1%) but serious condition. Presenting symptoms may include changes in mental status, visual disturbance, seizure, or other CNS changes. Patients with this syndrome generally had HTN as well, therefore BP monitoring is important. Instruct patient to report any mental status changes, visual changes, seizures, or other CNS changes to the MD immediately. These may be a sign of RPLS or more serious condition, such as hemorrhagic event in the CNS.
- 15.999 Patients may experience secondary skin cancers including keratoacanthomas, and cSCC. Instruct patient to report new skin growths to the study team.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a single-arm Phase II study which is designed to assess initial evidence of the efficacy of regorafenib plus durvalumab in patients with high-risk resectable hepatocellular carcinoma (HCC) who have received no prior systemic treatment. Single agent anti-PD-1 antibody revealed 15% objective response rate (ORR) in advanced HCC, but ORR is not known in the neoadjuvant setting. Regorafenib improved overall survival compared placebo in patients with advanced HCC who progressed on sorafenib. Objective response (unconfirmed) will be used as the primary endpoint. Based on historical data and clinical experience, an ORR of 10% or less would not be of interest (null hypothesis) as single agent durvalumab achieves 10.6% ORR in advanced HCC in second line setting[70], and an ORR of 28% or more would be considered of interest for this study. To assess this endpoint, a Simon two-stage minimax design will be used. In addition to ORR, progression-free survival, overall survival, adverse event rate, and surgery rates will be of specific interest.

The primary evaluable population for this trial will consist of patients who are eligible, consented, and received any protocol treatment.

The resectable evaluable population will consist of patients who are eligible, consented, received any protocol treatment, and are deemed eligible by their treating surgeon as a candidate for surgery and had at least a partial resection within 3 months of the last treatment dose.

16.2 Statistical Design

A Simon two-stage minmax design will be used. The largest success proportion where the proposed treatment regimen would be considered ineffective is 10%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 28%. The following two-stage design uses 16 or 27 evaluable patients to test the null hypothesis that the true success proportion in this given patient population is at most 10%.

16.21 Primary Endpoint

The primary endpoint in this trial is objective response (unconfirmed) within 16 weeks post-registration. An objective response is defined as a complete response (CR) or partial response (PR). Disease status will be assessed using RECIST v.1.1 criteria. Objective response rate (ORR) is defined as the proportion of evaluable patient who experience a CR or PR. The primary evaluable population will be used for the analysis of this endpoint. To clarify, patients who undergo surgery after at least 8 weeks of systemic therapy will be treated as evaluable for the primary endpoint (i.e. the objective response will be used for endpoint evaluation). In addition, only scans prior to surgery will be evaluable for the assessment of objective response. The final ORR point estimate and corresponding 95% confidence interval will be reported.

16.211 STAGE 1:

Enter 16 evaluable patients into the study. If 1 or fewer patients experience objective response within the predefined time period, we will consider this treatment ineffective in this patient population and terminate the study. Otherwise, if 2 or more patients experience objective response, we will proceed to Stage 2.

16.212 STAGE 2:

Enter an additional 11 patients into the study. If 5 or fewer patients among the 27 total evaluable patients accrued experience objective response within the predefined time period, we will consider this treatment ineffective in this patient population. If 6 or more patients out of the 27 total evaluable patients accrued experience objective response, we may recommend further testing of this regimen in subsequent studies.

16.213 NOTE:

Accrual will not be suspended between stages to allow the first 16 patients to become evaluable, unless undue toxicity is observed.

16.22 Power and Sample Size

This two-stage study design outlined in 16.21 assumes the number of successes is binomially distributed, the null success proportion is 0.1, and the alternative success proportion is 0.28. Given these, the exact type 1 error rate (α) is 0.0461, and the exact power is 80.36% when the true response rate is 28%.

A minimum of 16 and maximum of 27 evaluable patients are required under the stated assumptions, unless undue toxicity is observed. We anticipate accruing an additional 3 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Maximum projected accrual is therefore 30 patients. All sample size calculations were computed using PASS 2020 software.

16.23 Operating Characteristics

The probability of declaring that this regimen warrants further studies (i.e. statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is:	0.1	0.15	0.19	0.23	0.28
then the probability of stopping early is:	0.512	0.283	0.160	0.089	0.038
and the probability of declaring that the regimen warrants further studies is:	0.046	0.212	0.405	0.602	0.804

16.24 Accrual Time and Study Duration

The anticipated accrual rate is 2 patients per month. Therefore, the accrual period for the first stage of this study is expected to be approximately 8 months. If patients are accrued to the second stage, the total accrual period is expected to be approximately 15 months. Should the study continue to full accrual, the primary analysis can begin approximately 19 months after the trial begins; as soon as the last patient has either experienced objective response or been observed for 16 weeks.

16.25 Over Accrual

If more than the target number of patients is accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision-making process. However, they will be included in final point estimates and confidence intervals as though they were accrued in the final stage.

16.3 Secondary Endpoints

16.31 Rate of Surgery during the course of the study

The primary evaluable population will be used for the analysis of this endpoint. The proportion of patients who underwent surgery within 4 months of the last treatment dose during the course of the study will be reported. The 95%

confidence interval calculated by Clopper and Pearson will be reported.

16.32 Adverse Event Rates

The primary evaluable population will be used for the analysis of this endpoint. The rate of patients experiencing a grade 3+ adverse event will be reported. Further analyses of adverse event rates will be considered exploratory.

16.33 Progression-Free Survival

Progression-free survival (PFS) is defined as the time from registration to the first of either disease progression or death from any cause, where disease progression is determined based on RECIST 1.1 criteria. Patients who do not experience disease progression or death while on protocol will be censored at the last disease assessment date. PFS will be estimated using the Kaplan-Meier method. Patients in the primary evaluable population who are not in the resectable evaluable population will be eligible for the analysis of this endpoint. The median PFS and corresponding 95% confidence interval (by Brookmeyer and Crowley) will be reported.

16.34 Overall Survival

Overall survival (OS) is defined as the time from registration to death from any cause. Patients who are alive will be censored at the last follow-up date. OS will be estimated using the Kaplan-Meier method. Patients in the primary evaluable population will be eligible for the analysis of this endpoint. The median OS and corresponding 95% confidence interval (by Brookmeyer and Crowley) will be reported.

16.35 Recurrence-Free Survival

Recurrence-free survival (RFS) is defined as the time from surgical resection to first of either disease recurrence or death from any cause. Patients who do not experience disease recurrence or death while on protocol will be censored at the last disease assessment date. RFS will be estimated using the Kaplan-Meier method. The resectable evaluable population will be used for the analysis of this endpoint. The median RFS and corresponding 95% confidence interval (by Brookmeyer and Crowley) will be reported.

16.36 Pathologic Complete Response

The resectable evaluable population will be used for the analysis of this endpoint. A pathologic complete response must satisfy all of the following:

- No metastatic disease (i.e. pM0 or pMx, pNo or pNx)
- Zero percent residual tumor cells in the specimen including the presumed prior tumor bed and elsewhere
- Negative resection margin on all margin examined

The proportion of patients experiencing pathologic complete response and corresponding 95% confidence interval will be reported.

16.4 Correlative Research

Correlative peripheral blood samples (at baseline, week 8, 12, 20, and at off protocol treatment) baseline research biopsy and post treatment biopsies at 8th week (surgical sample if patient undergoes surgery, research biopsy if no surgery planned after 8 weeks of systemic therapy) will be collected from all patients. Immune profiling of circulating lymphocytes in peripheral blood and tumor infiltrating lymphocytes (TILs) **in pre and post treatment tissue samples will be performed.** This approach provides a unique opportunity to explore mechanistic effects of the combination in the TME by utilizing paired tissue samples. It will further our knowledge of changes in the TME induced by the combination treatment, help understand synergy and mechanisms of resistance and define the next steps in improving the current regimen.

16.5 Safety Monitoring

16.51 Adverse Event Stopping Rule(s)

The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time, we observe events considered to be at least possibly related to study treatment (i.e., an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy the following:

If at any time, 4 of the initial 10 treated patients or 40% or more of all patients (i.e., when accrual is greater than 10 patients) have experienced a Grade 4+ adverse event at least possibly related to study treatment per NCI Common Terminology Criteria for Adverse Events v.5.0, excluding the following:

- Grade 4 anemia lasting ≤ 3 days
- Grade 4 white blood cell decreased lasting ≤ 3 days
- Grade 4 platelet count decreased lasting ≤ 3 days
- Grade 4 electrolyte alteration* lasting ≤ 3 days

*Electrolyte alterations include the following events in SOC “Metabolism and nutrition disorders”

- Hypercalcemia or Hypocalcemia
- Hyperglycemia or Hypoglycemia
- Hyperkalemia or Hypokalemia
- Hypermagnesemia or Hypomagnesemia
- Hyponatremia or Hyponatremia
- Hyperphosphatemia or Hypophosphatemia

We note that we will review Grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.6 Data Monitoring and Reporting

16.61 DSMB Reporting

The study chair(s) and the study statistician will review the study at least twice per year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice per year, based on reports provided by the MCCC Statistical Office.

16.62 CT.gov Reporting

Expected durations and timelines for certain events (e.g. accrual) and endpoints for CT.gov reporting purposes can be found in sections 16.21 and 16.3 respectively.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Research Tissue Biospecimens to be collected for this Protocol

Research Study	Specimen Purpose	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	Baseline (after registration, but prior to initiation of systemic therapy)	Prior to treatment on Cycle 3 Day 1 if no surgery	At Surgery	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Immuno-histochemistry	Correlative	Mandatory	Formalin Fixed Paraffin Embedded (FFPE) ²	1 FFPE tissue block (preferred) (blocks created for research only)	X ¹	X	X	Yes	Ambient ²
FROZEN Tumor Tissue	Correlative	Mandatory	Tumor Biopsy Core	1	X ¹	X	X	Yes	Frozen ²
FRESH Tumor Tissue (Emory only)	Correlative	Mandatory (Emory only)	Tumor Biopsy Core	1-2	X	X	X	Yes	n/a (Emory only)

1. Baseline tissue specimens must be shipped ≤ 14 days after registration

2. Biopsy/tumor samples collected at Emory can be sent to [REDACTED] lab fresh. Fresh tumor tissue will only be collected at Emory.

17.2 Correlative Tissue Collection

17.21 Tissue kits will not be provided for this protocol

17.211 Tumor Tissue Collection Plan

a) Research tumor core specimens

- Research tumor specimens will be obtained by mandatory core needle biopsy (18 gauge or larger).
- The research tumor specimens will be assigned for the following use:
 - 1 core will be processed into FFPE and 1*H&E slide is to be made from one of the cores
 - 1 core will be frozen and stored at -70°C until shipment.
 - 1-2 cores will be placed fresh on wet ice. **(Emory only)**

All sites (except Emory): A total of 2 cores will be obtained from subjects enrolled.

Emory only: A total of 3-4 cores will be obtained from subjects enrolled.

17.212 Biopsy/tumor samples collected at **Emory only** can be sent to [REDACTED] lab fresh

17.22 The FFPE tissue block is preferred; FFPE blocks will be created from research use tissue samples only. Paraffin embedded samples accepted if FFPE blocks unavailable

17.23 Submit one formalin fixed paraffin embedded (FFPE) tumor tissue block with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection). **A corresponding H&E slide for each submitted block must be provided.**

17.24 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

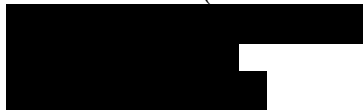
- FFPE tissue blocks with corresponding H&E slide (preferred) OR 10 unstained slides with corresponding H&E(s).
- Specimen Submission: Tissue (Baseline) (if applicable)
- Specimen Submission: Tissue form (if applicable)
- Surgical Pathology Report
- Operative Report (*optional*)
- **Note: Please include the ACCRU patient ID number on all materials listed above.**

17.25 The tissue must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Frozen tissue will need to be shipped on dry ice. Fresh tissue (Emory only)

should be placed on wet ice. Label the bag with the protocol number, ACCRU patient ID number, and patient initials. During warm weather months, paraffin blocks should be shipped using a refrigerant pack to avoid heat that may melt paraffin and damage blocks.

- 17.26 Baseline tissue specimens should be collected and shipped ≤ 14 days after registration and prior to initiation of systemic therapy.
- 17.27 Tissue specimens must be shipped within **24 hours, priority overnight** after collection.
- 17.28 Verify that the appropriate sections of the Specimen Submission: Tissue form are completed and filled in correctly. Enter information from the Specimen Submission: Tissue form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).
- 17.29a Ship all **ambient tissue blocks** and accompanying materials to the ACCRU Research Base: **Do NOT ship body fluid samples or frozen tissue to this address.**

ACCRU Operations Office
Attn: PC Office (ACCRU-GI-1920)



- 17.29b Ship all **frozen tissue specimens** and accompanying materials to the Mayo Clinic BAP Freezer:

Biorepository at Mayo Clinic BAP Freezer



17.3 Study Methodology and Storage Information

- 17.31 Submitted tissue samples will be analyzed as follows: Upon request the ACCRU Research Base Pathology Research Core will batch ship blocks for immunohistochemistry at:

Lesinski Laboratory



Winship Cancer Institute of Emory University



- 17.32 At the completion of the study, any unused/remaining material will be stored in Lesinski Laboratory Winship Cancer Institute of Emory University, Atlanta, GA for future research according to the patient consent permission (see Section 6.5). Potential future research may include immunohistochemistry (IHC) analyses to analyze predictive biomarkers, changes in expression pattern with therapy, and

correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval.

- 17.33 Blocks requested to accommodate individual patient management will be returned promptly upon request.

- 17.34 Return of Genetic Testing Research Results:
Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

18.0 Records and Data Collection Procedures

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Patient data protection.

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Survival Follow-up

See [Section 4](#).

18.3 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on the organization roster at the enrolling site.

18.4 Site responsibilities

Each site will be responsible for ensuring that all materials contain the patient's initials, ACCRU registration number, and ACCRU protocol number. All PHI must be redacted from any documentation.

18.5 Supporting documentation

Upload a copy of documentation of response or progression in RAVE on the Supporting Documentation Form.

Baseline: The following documents are required for diagnosis and eligibility verification: imaging report and lab report. Pathology report if available. Operative report and clinic notes are optional. These documents should be submitted within 14 days of registration.

Treatment: The following documents are required: imaging report, lab report, and pathology report (if available).

At patient progression or restaging for evidence of response: imaging report

18.6 Labeling of materials

Each site will be responsible for ensuring that all materials contain the patient's initials, ACCRU registration number, and ACCRU protocol number. Patient's name must be removed.

18.7 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition to this, the Overdue Materials report is available on the ACCRU website. Only site staff rostered with the Rave CRA role will have access to these reports.

All data must be entered by Remote Data Entry (RDE) and completed by qualified and authorized personnel. Access the RAVE RDE system through the iMedidata portal at [REDACTED]. All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions [REDACTED].

19.0 Budget

- 19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

20.0 References

1. Ferlay, J., et al., *Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012*. Int J Cancer, 2015. **136**(5): p. E359-86.
2. Mittal, S. and H.B. El-Serag, *Epidemiology of hepatocellular carcinoma: consider the population*. J Clin Gastroenterol, 2013. **47 Suppl**: p. S2-6.
3. Llovet, J.M. and J. Bruix, *Molecular targeted therapies in hepatocellular carcinoma*. Hepatology, 2008. **48**(4): p. 1312-27.
4. Llovet, J.M., et al., *Sorafenib in advanced hepatocellular carcinoma*. N Engl J Med, 2008. **359**(4): p. 378-90.
5. Bruix, J., et al., *Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial*. Lancet, 2017. **389**(10064): p. 56-66.
6. El-Khoueiry, A.B., et al., *Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial*. Lancet, 2017. **389**(10088): p. 2492-2502.
7. Kudo, M., et al., *Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial*. Lancet, 2018. **391**(10126): p. 1163-1173.
8. Zhu, A.X., et al., *Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial*. Lancet Oncol, 2019. **20**(2): p. 282-296.
9. Finn, R.S., et al., *Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma*. New England Journal of Medicine, 2020. **382**(20): p. 1894-1905.
10. Yau, T., et al., *Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Results from CheckMate 040*. Journal of Clinical Oncology, 2019. **37**(15_suppl): p. 4012-4012.
11. Ferrara, N., H.P. Gerber, and J. LeCouter, *The biology of VEGF and its receptors*. Nat Med, 2003. **9**(6): p. 669-76.
12. Zirlik, K. and J. Duyster, *Anti-Angiogenics: Current Situation and Future Perspectives*. Oncol Res Treat, 2018. **41**(4): p. 166-171.
13. Zhu, A.X., et al., *HCC and angiogenesis: possible targets and future directions*. Nat Rev Clin Oncol, 2011. **8**(5): p. 292-301.
14. Wu, X.Z., G.R. Xie, and D. Chen, *Hypoxia and hepatocellular carcinoma: The therapeutic target for hepatocellular carcinoma*. J Gastroenterol Hepatol, 2007. **22**(8): p. 1178-82.
15. Manegold, C., et al., *The Potential of Combined Immunotherapy and Antiangiogenesis for the Synergistic Treatment of Advanced NSCLC*. J Thorac Oncol, 2017. **12**(2): p. 194-207.
16. Osada, T., et al., *The effect of anti-VEGF therapy on immature myeloid cell and dendritic cells in cancer patients*. Cancer Immunol Immunother, 2008. **57**(8): p. 1115-24.
17. Gabrilovich, D., et al., *Vascular endothelial growth factor inhibits the development of dendritic cells and dramatically affects the differentiation of multiple hematopoietic lineages in vivo*. Blood, 1998. **92**(11): p. 4150-66.
18. Farsaci, B., et al., *Immune consequences of decreasing tumor vasculature with antiangiogenic tyrosine kinase inhibitors in combination with therapeutic vaccines*. Cancer Immunol Res, 2014. **2**(11): p. 1090-102.
19. Allen, E., et al., *Combined antiangiogenic and anti-PD-L1 therapy stimulates tumor immunity through HEV formation*. Sci Transl Med, 2017. **9**(385).
20. Tian, L., et al., *Mutual regulation of tumour vessel normalization and immunostimulatory reprogramming*. Nature, 2017. **544**(7649): p. 250-254.

21. Cannarile, M.A., et al., *Colony-stimulating factor 1 receptor (CSF1R) inhibitors in cancer therapy*. J Immunother Cancer, 2017. **5**(1): p. 53.
22. Ries, C.H., et al., *Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy*. Cancer Cell, 2014. **25**(6): p. 846-59.
23. Noy, R. and J.W. Pollard, *Tumor-associated macrophages: from mechanisms to therapy*. Immunity, 2014. **41**(1): p. 49-61.
24. Ostuni, R., et al., *Macrophages and cancer: from mechanisms to therapeutic implications*. Trends Immunol, 2015. **36**(4): p. 229-39.
25. Zhang, Q.W., et al., *Prognostic significance of tumor-associated macrophages in solid tumor: a meta-analysis of the literature*. PLoS One, 2012. **7**(12): p. e50946.
26. Stanley, E.R. and V. Chitu, *CSF-1 receptor signaling in myeloid cells*. Cold Spring Harb Perspect Biol, 2014. **6**(6).
27. Gomez-Roca, C.A., et al., *Phase I study of RG7155, a novel anti-CSF1R antibody, in patients with advanced/metastatic solid tumors*. Journal of Clinical Oncology, 2015. **33**(15_suppl): p. 3005-3005.
28. Jia, J.B., et al., *High expression of macrophage colony-stimulating factor-1 receptor in peritumoral liver tissue is associated with poor outcome in hepatocellular carcinoma after curative resection*. Oncologist, 2010. **15**(7): p. 732-43.
29. Ao, J.Y., et al., *Colony-Stimulating Factor 1 Receptor Blockade Inhibits Tumor Growth by Altering the Polarization of Tumor-Associated Macrophages in Hepatocellular Carcinoma*. Mol Cancer Ther, 2017. **16**(8): p. 1544-1554.
30. 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.
31. Abou-Elkacem, L., et al., *Regorafenib inhibits growth, angiogenesis, and metastasis in a highly aggressive, orthotopic colon cancer model*. Mol Cancer Ther, 2013. **12**(7): p. 1322-31.
32. Bruix, J., et al., *Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, phase II safety study*. Eur J Cancer, 2013. **49**(16): p. 3412-9.
33. Wilhelm, S.M., et al., *Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity*. Int J Cancer, 2011. **129**(1): p. 245-55.
34. Marrero, J.A., et al., *Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases*. Hepatology, 2018. **68**(2): p. 723-750.
35. Forner, A., M. Reig, and J. Bruix, *Hepatocellular carcinoma*. Lancet, 2018. **391**(10127): p. 1301-1314.
36. Giovanardi, F., et al., *Resection for hepatocellular cancer: overpassing old barriers*. Transl Gastroenterol Hepatol, 2018. **3**: p. 64.
37. Wei, X., et al., *Neoadjuvant Three-Dimensional Conformal Radiotherapy for Resectable Hepatocellular Carcinoma With Portal Vein Tumor Thrombus: A Randomized, Open-Label, Multicenter Controlled Study*. Journal of Clinical Oncology, 2019. **37**(24): p. 2141-2151.
38. Tabrizian, P., et al., *Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis*. Ann Surg, 2015. **261**(5): p. 947-55.
39. Akateh, C., et al., *Neoadjuvant and adjuvant treatment strategies for hepatocellular carcinoma*. World J Gastroenterol, 2019. **25**(28): p. 3704-3721.
40. Zhang, Y., et al., *Is Salvage Liver Resection Necessary for Initially Unresectable Hepatocellular Carcinoma Patients Downstaged by Transarterial Chemoembolization? Ten Years of Experience*. Oncologist, 2016. **21**(12): p. 1442-1449.
41. Stein, S., et al., *Safety and clinical activity of IL atezolizumab + bevacizumab in a phase Ib study in hepatocellular carcinoma (HCC)*. Journal of Clinical Oncology, 2018. **36**(15_suppl): p. 4074-4074.

42. Pishvaian, M.J., et al., *LBA26Updated safety and clinical activity results from a phase Ib study of atezolizumab + bevacizumab in hepatocellular carcinoma (HCC)*. Annals of Oncology, 2018. **29**(suppl_8).
43. Kaseb, A.O., et al., *Randomized, open-label, perioperative phase II study evaluating nivolumab alone versus nivolumab plus ipilimumab in patients with resectable HCC*. Journal of Clinical Oncology, 2019. **37**(4_suppl): p. 185-185.
44. El-Khoueiry, A.B., et al., *Phase Ib study of regorafenib (REG) plus pembrolizumab (PEMBRO) for first-line treatment of advanced hepatocellular carcinoma (HCC)*. Journal of Clinical Oncology, 2020. **38**(4_suppl): p. 564-564.
45. Ikeda, M., et al., *A phase Ib trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients (pts) with unresectable hepatocellular carcinoma (uHCC)*. Journal of Clinical Oncology, 2018. **36**(15_suppl): p. 4076-4076.
46. Wainberg, Z.A., et al., *Safety and clinical activity of durvalumab monotherapy in patients with hepatocellular carcinoma (HCC)*. Journal of Clinical Oncology, 2017. **35**(15_suppl): p. 4071-4071.
47. Dunn, G.P., L.J. Old, and R.D. Schreiber, *The three Es of cancer immunoediting*. Annu. Rev. Immunol., 2004. **22**: p. 329-360.
48. Keir, M.E., et al., *PD-1 and its ligands in tolerance and immunity*. Annu. Rev. Immunol., 2008. **26**: p. 677-704.
49. Iwai, Y., et al., *Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade*. Proceedings of the National Academy of Sciences, 2002. **99**(19): p. 12293-12297.
50. Qin, A., et al., *Mechanisms of immune evasion and current status of checkpoint inhibitors in non-small cell lung cancer*. Cancer medicine, 2016. **5**(9): p. 2567-2578.
51. Pardoll, D.M., *The blockade of immune checkpoints in cancer immunotherapy*. Nature Reviews Cancer, 2012. **12**(4): p. 252-264.
52. Brahmer, J.R., et al., *Safety and activity of anti-PD-L1 antibody in patients with advanced cancer*. New England Journal of Medicine, 2012. **366**(26): p. 2455-2465.
53. Hirano, F., et al., *Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity*. Cancer research, 2005. **65**(3): p. 1089-1096.
54. Okudaira, K., et al., *Blockade of B7-H1 or B7-DC induces an anti-tumor effect in a mouse pancreatic cancer model*. International journal of oncology, 2009. **35**(4): p. 741-749.
55. Topalian, S.L., et al., *Safety, activity, and immune correlates of anti-PD-1 antibody in cancer*. New England Journal of Medicine, 2012. **366**(26): p. 2443-2454.
56. Zhang, C., et al., *Anti-tumor immunotherapy by blockade of the PD-1/PD-L1 pathway with recombinant human PD-1-IgV*. Cytotherapy, 2008. **10**(7): p. 711-719.
57. Powles, T., et al., *MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer*. Nature, 2014. **515**(7528): p. 558-562.
58. Rizvi, N.A., et al., *Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in patients with non-small cell lung cancer (NSCLC)*. 2015, American Society of Clinical Oncology.
59. Segal, N.H., et al., *Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort*. 2015, American Society of Clinical Oncology.
60. Alexandrov, L.B., et al., *Erratum: Signatures of mutational processes in human cancer (Nature (2013) 500 (415-421)*. Nature, 2013. **502**(7470): p. 258.
61. Fife, B.T. and J.A. Bluestone, *Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways*. Immunological reviews, 2008. **224**(1): p. 166-182.
62. Stewart, R., et al., *Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody*. Cancer immunology research, 2015. **3**(9): p. 1052-1062.

63. Fairman, D., et al., *Pharmacokinetics of MEDI4736, a fully human anti-PDL1 monoclonal antibody, in patients with advanced solid tumors*. 2014, American Society of Clinical Oncology.
64. Narwal, R., L.K. Roskos, and G.J. Robbie, *Population pharmacokinetics of sifalimumab, an investigational anti-interferon- α monoclonal antibody, in systemic lupus erythematosus*. Clinical pharmacokinetics, 2013. **52**(11): p. 1017-1027.
65. Ng, C.M., et al., *Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis*. Pharmaceutical research, 2006. **23**(6): p. 1275-1284.
66. Wang, E., et al., *Population pharmacokinetic and pharmacodynamic analysis of tremelimumab in patients with metastatic melanoma*. The Journal of Clinical Pharmacology, 2014. **54**(10): p. 1108-1116.
67. Zhang, S., et al., *Fixed Dosing Versus Body Size—Based Dosing of Therapeutic Peptides and Proteins in Adults*. The Journal of Clinical Pharmacology, 2012. **52**(1): p. 18-28.
68. Wang, D.D., et al., *Fixed dosing versus body size—based dosing of monoclonal antibodies in adult clinical trials*. The Journal of Clinical Pharmacology, 2009. **49**(9): p. 1012-1024.
69. Chen, C.-W., et al., *Regorafenib may enhance efficacy of anti-program cell death-1 (PD-1) therapy in hepatocellular carcinoma (HCC) through modulation of macrophage polarization*. International Liver Congress. J Hepatol, 2019. **70**(suppl): p. e605-e606.
70. Kelley, R., et al., *O-6 The novel regimen of tremelimumab in combination with durvalumab provides a favorable safety profile and clinical activity for patients with advanced hepatocellular carcinoma*. Annals of Oncology, 2020. **31**: p. 233-234.

Appendix I: Toxicity Management Guidelines

The Toxicity Management Guidelines (TMGs) have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitors durvalumab [MEDI4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these two compounds, these TMGs are applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either drug is used alone or both drugs are used in combination and, also, other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) are administered concurrently or sequentially as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with monotherapy or combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

Dosing modification and toxicity management for immune-mediated, infusion-related, and non-immune-mediated reactions associated with the use of a checkpoint inhibitor or checkpoint inhibitors in this protocol – whether that is durvalumab alone, tremelimumab alone, or durvalumab + tremelimumab in combination, or durvalumab +/- tremelimumab in combination with other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) administered concurrently or sequentially – should therefore be performed in accordance with this Annex to Protocol, which for the purposes of submission and approval of substantial updates is maintained as a standalone document. TMG updates are iterated by date, and should be used in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version specified in the clinical study protocol.

Although the TMG versioning is independent of the protocol, the TMG Annex to Protocol should be read in conjunction with the Clinical Study Protocol, where if applicable additional references for the management of toxicities observed with other anti-cancer treatment are included in the specific section of the Clinical Study Protocol.

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy – 28 October 2021

General Considerations Regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated adverse events (imAEs).

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO)) in the management of these events. Refer to the section of the table titled “Other -Immune-Mediated Reactions” for general guidance on imAEs not noted in the “Specific Immune-Mediated Reactions” section.

Early identification and management of imAEs is essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying imAEs. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Based on the severity of the imAE, durvalumab and/or tremelimumab should be withheld and corticosteroids administered. Upon improvement to Grade $\leq$ 1, corticosteroid should be tapered over $\geq$ 28 days. More potent immunosuppressive agents should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis, gastrointestinal protection, and glucose monitoring. Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.

Relevant Society Guidelines for Management of imAEs

These society guidelines are provided as references to serve in support of best clinical practice and the TMGs. Please note, these were the current versions of these guidelines at the time of updating TMGs. Please refer to the most up to date version of these guidelines.

1. Brahmer JR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *J Immunother Cancer* 2021;9:e002435
2. Brahmer JR, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2018;36(17):1714-1768.
3. Haanen JBAG, et al. Management of toxicities for immunotherapy: European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up. *Annals Oncol* 2017;28(Suppl4):i119-i1142.
4. Sangro B, et al. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. *J Hepatol* 2020;72(2):320-341.
5. Thompson JA, et al. National Comprehensive Cancer Network Guidelines: Management of immunotherapy-related toxicities version 3.2021. Published May 14, 2021.

Pediatric Considerations Regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTCAE grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid $\leq$ a dose equivalent to that required for corticosteroid replacement therapy within 12 weeks of initiating corticosteroids.	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for steroid dosing (i.e., mg/kg/day) provided for adult patients should also be used for pediatric patients. – The recommendations for intravenous immunoglobulin (IVIG) and plasmapheresis use provided for adult patients may be considered for pediatric patients. – The infliximab 5 mg/kg IV one time dose recommended for adults is the same as recommended for pediatric patients $\geq$ 6 years old. For subsequent dosing and dosing in children $<$ 6 years old, consult a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult a pediatric specialist. – With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

^aASCO Educational Book 2015 “Managing Immune Checkpoint Blocking Antibody Side Effects” by [REDACTED] MD.

^bFDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

^cNCCN Clinical Practice Guidelines in Oncology “Management of Immunotherapy-Related Toxicities” Version 1.2020 – December 2019

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	Any Grade (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	For Any Grade – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. infection, progressive disease) – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution computed tomography (CT) scan. – Consider Pulmonary and Infectious Diseases consults.
	Grade 1	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	For Grade 1 – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up, and then as clinically indicated.
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤ 1 . • If toxicity improves to Grade ≤ 1, then the decision to reinstitute study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper (≤ 10 mg prednisone or equivalent).	For Grade 2 – Monitor symptoms daily and consider hospitalization. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed.

		– Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider chest CT with contrast and repeat in 3-4 weeks. – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy, such as tumor necrosis factor (TNF) inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Consider, as necessary, discussing with Clinical Study Lead.
Grade 3 or 4	Permanently discontinue study drug/study regimen.	For Grade 3 or 4 – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 2 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution:

		rule out sepsis and refer to infliximab label for general guidance before using infliximab.	
Diarrhea/Colitis	Any Grade (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	For Any Grade
			– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for <i>Clostridium difficile</i> toxin, etc. – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY. – PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade events, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1	No dose modifications.	For Grade 1
			– Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2

		below. If negative and no infection, continue Grade 1 management.
Grade 2	Hold study drug/study regimen until resolution to Grade ≤ 1 If toxicity improves to Grade ≤ 1, then study drug/study regimen can be resumed after completion of steroid taper (<10 mg prednisone, or equivalent).	For Grade 2 - Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. - Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. - If event is not responsive within 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consult a gastrointestinal (GI) specialist for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation. - If still no improvement within 2 to 3 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start additional immunosuppressant agent such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines. Caution: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. - Consider, as necessary, discussing with Clinical Study Lead if no resolution to Grade ≤ 1 in 3 to 4 days.
Grade 3 or 4	Grade 3 For patients treated with durvalumab monotherapy, hold study drug/study regimen until resolution to Grade ≤ 1; study drug/study regimen can be resumed	For Grade 3 or 4 - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. - Monitor stool frequency and volume and maintain hydration.

		after completion of steroid taper (≤ 10 mg prednisone per day, or equivalent). - For patients treated with durvalumab in combination with other products (not tremelimumab), decision to be made at the discretion of the study investigator, in discussion with AstraZeneca Clinical Study Lead. <u>For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy, Permanently</u> discontinue study drug for 1) Grade 3 diarrhea colitis or 2) Any grade of intestinal perforation in any patient treated with immune checkpoint inhibitor (ICI). Grade 4 Permanently discontinue study drug/study regimen.	- Urgent GI consult and imaging and/or colonoscopy as appropriate. - If still no improvement within 2 days, continue steroids and promptly add further immunosuppressants. (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.
Hepatitis (elevated liver function tests (LFTs))	Any Grade (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	For Any Grade
			- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications). - Monitor and evaluate LFTs: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin (T. bili.).
	Grade 1	- No dose modifications. - If it worsens, then consider holding therapy.	For Grade 1
	Grade 2	- Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤ 1. - If toxicity improves to Grade ≤ 1 or baseline and there were no elevations in bilirubin, resume study drug/study	For Grade 2
			Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until LFT elevations improve or resolve.

Infliximab should not be used for management of immune-related hepatitis.	- regimen after completion of steroid taper (<10 mg prednisone or equivalent). • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT $\geq 3 \times$ ULN + bilirubin $\geq 2 \times$ ULN without initial findings of cholestasis (i.e., elevatedALP) and in the absence of any alternative cause.	– If no resolution to Grade ≤ 1 in 1 to 2 days, consider discussing with Clinical Study Lead, as needed. – If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.		
PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma (HCC) patients	Grade 3 or 4	For Grade 3	For Grade 3 or 4	
	• Hold study drug/study regimen For elevations in transaminases $\leq 8 \times$ ULN (and no elevations in bilirubin), or elevations in bilirubin $\leq 5 \times$ ULN until resolution to Grade ≤ 1 <u>or baseline</u>Resume study drug/study regimen if elevations downgrade to Grade ≤ 1 or baseline after completion of steroid taper (<10 mg prednisone, or equivalent). • If in combination with tremelimumab, do not restart tremelimumab. Permanently discontinue study drug/study regimen for elevations in transaminases $>8 \times$ ULN or any elevations in bilirubin $>5 \times$ ULN		– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. Infliximab should NOT be used.	
	For Grade 4			– Perform Hepatology Consult, abdominal workup, and imaging as appropriate.
	Permanently discontinue study drug/study regimen.			

Hepatitis (elevated LFTs) Infliximab should not be used for management of	Any Elevations of AST, ALT, or T. Bili as Described Below	General Guidance	For Any Elevations Described
THIS shaded area is guidance <i>only</i> for management of “Hepatitis (elevated LFTs)” in HCC patients immune-related hepatitis. See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of			– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – Monitor and evaluate liver function test: AST, ALT, ALP, and T. Bili. – For hepatitis B (HBV) + patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBeAg). – For hepatitis C (HCV) + patients: evaluate quantitative HCV viral load. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥ 2-fold. – For HCV+ with Hepatitis B core antibody (HBcAb) +; Evaluate for both HBV and HCV as above.
DILI/liver decompensation	Isolated AST or ALT >ULN and $\leq 5.0 \times \text{ULN}$, whether normal or elevated at baseline	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. • For all transaminase elevations, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of DILI/liver decompensation	

Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN . • If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤5.0×ULN , resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.^b	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Clinical Study Lead. – If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. If still no improvement within 2 to 3 days despite 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting additional immunosuppressants. (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss Clinical Study Lead if mycophenolate mofetil is not available. Infliximab should NOT be used.
Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline		
Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN and after completion of steroid taper (<10 mg prednisone, or equivalent). • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider discussing with Clinical Study Lead, as needed. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric
Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if		

	elevated >ULN at baseline		IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an additional immunosuppressant. (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist or relevant practice guidelines). Discuss with Study Clinical Lead if mycophenolate is not available. Infliximab should NOT be used.
	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	Same as above (except recommend obtaining liver biopsy early)
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin ($\geq 1.5 \times \text{ULN}$, if normal at baseline; or $2 \times \text{baseline}$, if $> \text{ULN}$ at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise - For example, manage dosing for second level of transaminase rise (i.e., AST or ALT $> 5.0 \times \text{ULN}$ and $\leq 8.0 \times \text{ULN}$, if normal at baseline, or AST or ALT $> 2.0 \times \text{baseline}$ and $\leq 12.5 \times \text{ULN}$, if elevated $> \text{ULN}$ at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT $> 8.0 \times \text{ULN}$ and $\leq 20.0 \times \text{ULN}$, if normal at baseline, or AST or ALT $> 12.5 \times \text{ULN}$ and $\leq 20.0 \times \text{ULN}$, if elevated $> \text{ULN}$ at baseline) - For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen			
Nephritis or renal dysfunction (elevated serum creatinine)	Any Grade (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	For Any Grade - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). - Consult a nephrologist. - Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and

		creatinine, decreased creatinine clearance, electrolyte imbalance, decreased urine output, or proteinuria).
		Consider using steroids in the absence of a clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade events.
Grade 1	No dose modifications.	For Grade 1 - Monitor serum creatinine weekly and any accompanying symptoms. - If creatinine returns to baseline, resume its regular monitoring per study protocol. - If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. - Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
Grade 2	Hold study drug/study regimen until resolution to Grade ≤ 1 or baseline. If toxicity improves to Grade ≤ 1 or baseline, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	For Grade 2 - Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. - Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. - Consult nephrologist and consider renal biopsy if clinically indicated. - If event is persistent beyond 3 to 5 days or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. - If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup. When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
Grade 3 or 4	Permanently discontinue study drug/study regimen.	For Grade 3 or 4

			- Carefully monitor serum creatinine daily. - Consult nephrologist and consider renal biopsy if clinically indicated. - Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. - If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant in consultation with a nephrologist.
Rash or Dermatitis (Including Pemphigoid)	Any Grade (Refer to NCI CTCAE applicable version in study protocol for definition of severity/grade depending on type of skin rash)	General Guidance	For Any Grade - Patients should be thoroughly evaluated to rule out any alternative etiology. - Monitor for signs and symptoms of dermatitis (rash and pruritus). HOLD STUDY DRUG IF STEVENS-JOHNSON SYNDROME (SJS), TOXIC EPIDERMAL NECROLYSIS (TEN), OR OTHER SEVERE CUTANEOUS ADVERSE REACTION (SCAR) IS SUSPECTED. PERMANENTLY DISCONTINUE STUDY DRUG IF SJS, TEN, OR SCAR IS CONFIRMED.
	Grade 1	No dose modifications.	For Grade 1 Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emollient, lotion, or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	For Grade 2 - Obtain dermatology consult. - Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy - Consider moderate-strength topical steroid.

		- If no improvement of rash/skin lesions occurs within 3 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with Clinical Study Lead, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. - Consider skin biopsy if the event persists for >1 week or recurs.	
Grade 3 or 4		For Grade 3 • Hold study drug/study regimen until resolution to Grade ≤ 1 or baseline. • If toxicity improves to Grade ≤ 1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). For Grade 4 Permanently discontinue study drug/study regimen.	For Grade 3 or 4 - Consult dermatology. - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. - Consider hospitalization. - Monitor extent of rash [Rule of Nines]. - Consider skin biopsy (preferably more than 1) as clinically feasible. Consider, as necessary, discussing with Clinical Study Lead.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	Any Grade (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	For Any Grade - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). - Consider consulting an endocrinologist for endocrine events. - Consider discussing with Clinical Study Lead, as needed. - Monitor patients for signs and symptoms of endocrinopathies. (Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits,

		polydipsia, polyuria, hypotension, and weakness.) - Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin A1c (HbA1c)). If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing. - Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
Grade 1	No dose modifications.	For Grade 1 - Monitor patient with appropriate endocrine function tests. - For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide assessment of early-morning adrenocorticotropin hormone (ACTH), cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). - If TSH < 0.5 × LLN, or TSH > 2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2, 3, or 4	For Grade 2-4 endocrinopathies <u>other than hypothyroidism and type 1 diabetes mellitus (T1DM)</u>,	For Grade 2, 3, or 4 Consult endocrinologist to guide evaluation of endocrine function and, as indicated by

		consider holding study drug/study regimen dose until acute symptoms resolve. • Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (<10 mg prednisone, or equivalent). • Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.	suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or T1DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated T1DM may be treated with appropriate diabetic therapy, and without corticosteroids. Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis. – For patients with normal endocrine workup (laboratory assessment or magnetic resonance imaging (MRI) scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/Lipase increased	Any Grade	General Guidance	
	(Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)		
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	For Grade 2, 3, or 4	
		In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, viral infection, concomitant medications, substance abuse). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – Assess for signs/symptoms of pancreatitis – Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT)

			– If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase – If evidence of pancreatitis, manage according to pancreatitis recommendations
Acute Pancreatitis	Any Grade (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	For Any Grade – Patients should be thoroughly evaluated to rule out any alternative etiology. – Consider Gastroenterology referral
	Grade 2, 3, or 4	For Grade 2 or 3 Hold study drug/study regimen dose until resolution to Grade ≤ 1 . If toxicity improves to Grade ≤ 1 or baseline, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). For Grade 4 Permanently discontinue study drug/study regimen.	For Grade 2, 3, or 4 – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration
Neurotoxicity (to include but not limited to non-infectious meningitis, non-infectious encephalitis, and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	Any Grade (Depending on the type of neurotoxicity, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	For Any Grade – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.

		– FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE.
Grade 1	No dose modifications.	For Grade 1 – See “Any Grade” recommendations above.
Grade 2	- For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤ 1. - For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤ 1. - Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤ 1 within 30 days.	For Grade 2 - Consider, as necessary, discussing with the Clinical Study Lead. - Obtain neurology consult. - Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). - Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. - If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with an additional immunosuppressant (e.g., IV IG or other immunosuppressant depending on the specific imAE).
Grade 3 or 4	For Grade 3 or 4 Permanently discontinue study drug/study regimen.	For Grade 3 or 4 - Consider, as necessary, discussing with Clinical Study Lead. - Obtain neurology consult. - Consider hospitalization. - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. - If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with an additional immunosuppressant (e.g., IV IG or other immunosuppressant depending on the specific imAE).

Peripheral neuromotor syndromes	Any Grade	General Guidance	For Any Grade
(such as Guillain-Barre and myasthenia gravis)	(Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)		– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and “repetitive stimulation” if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

Grade 1	No dose modifications.	For Grade 1 – Consider discussing with the Clinical Study Lead, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Consult a neurologist.
Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤ 1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	For Grade 2 – Consult a neurologist. – Consider discussing with the Clinical Study Lead, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). <i>MYASTHENIA GRAVIS:</i> ○ Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. ○ If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy,

Grade 3 or 4**For Grade 3 or 4**

Permanently discontinue study drug/study regimen.

if successful, can also serve to reinforce the diagnosis.

- Avoid medications that can worsen myasthenia gravis (e.g. some antibiotics, beta blockers, calcium channel blockers, muscle relaxants).

GUILLAIN-BARRE:

- It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.
- Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

For Grade 3 or 4

- Consider discussing with Clinical Study Lead, as needed.
- Recommend hospitalization.
- Monitor symptoms and consult a neurologist.

MYASTHENIA GRAVIS:

- Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist.
- Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG.
- If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.

- Avoid medications that can worsen myasthenia gravis (e.g. some antibiotics, beta blockers, calcium channel blockers, muscle relaxants).

GUILLAIN-BARRE:

- It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.
- Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

Myocarditis	Any Grade	General Guidance	For Any Grade
	(Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections) – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, B-type natriuretic peptide (BNP),

			cardiac enzymes, electrocardiogram (ECG), echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.
Grade 2, 3 or 4	• If Grade 2-4, permanently discontinue study drug/study regimen.	For Grade 2-4	– Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.
Myositis/ Polymyositis	Any Grade (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	For Any Grade – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble

swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up.

- If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation.
- Consider, as necessary, discussing with the Clinical Study Lead.
- Initial work-up should include clinical evaluation, creatine kinase, aldolase, lactate dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia.

Grade 1

- No dose modifications.

For Grade 1

- Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated.
- Consider Neurology consult.

Grade 2	• Hold study drug/study regimen dose until resolution to Grade ≤ 1. • Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency.	– Consider, as necessary, discussing with the Clinical Study Lead.
Grade 3 or 4	For Grade 3 • Hold study drug/study regimen dose until resolution to Grade ≤ 1. • Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency.	For Grade 2 – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the Clinical Study Lead. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids <u>along with receiving input</u> from Neurology consultant – If clinical course is <i>not</i> rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. For Grade 3 or 4 – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult – Consider discussing with the Clinical Study Lead, as needed.

For Grade 4

- Permanently discontinue study drug/study regimen.
- Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant.
 - If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
 - Consider whether patient may require IV IG, plasmapheresis.
-

Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – The Clinical Study Lead may be contacted for immune-mediated reactions not listed in the “specific immune-mediated reactions” section – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
Grade 2	• Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. • Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. • Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	For Grade 2, 3, or 4 Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and society guidelines. (See page 4).
Grade 3	Hold study drug/study regimen	
Grade 4	Permanently discontinue study drug/study regimen	

Note: As applicable, for early phase studies, the following sentence may be added: “Any event greater than or equal to Grade 2, please discuss with Clinical Study Lead.”

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	For Any Grade – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	For Grade 1 The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. For Grade 2 • The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. • Subsequent infusions may be given at 50% of the initial infusion rate.	For Grade 1 or 2 – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard or study protocol prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤ 2 infusion reactions.
Grade 3 or 4	For Grade 3 or 4 Permanently discontinue study drug/study regimen.	For Grade 3 or 4 – Manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines, and society guidelines.

Non-Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to $\leq$ Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to $\leq$ Grade 1 or baseline. For AEs that downgrade to $\leq$ Grade 2 within 7 days or resolve to $\leq$ Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Clinical Study Lead."

List of Abbreviations

ACH	Acetylcholinesterase	ILD	Interstitial lung disease
ACTH	Adrenocorticotrophic hormone	imAE(s)	Immune-mediated adverse event(s)
ALT	Alanine aminotransferase	INR	International normalized ratio
ASCO	American Society of Clinical Oncology	IU	International units
AST	Aspartate aminotransferase	IV	Intravenous
(T) Bili	(Total) Bilirubin	IVIG	Intravenous immunoglobulin
BNP	B-type natriuretic peptide	LDH	Lactate dehydrogenase
BUN	Blood urea nitrogen	LFTs	Liver function tests
CRP	C-reactive protein	LLN	Lower limit of normal
CT	Computed tomography	MRCP	Magnetic resonance cholangiopancreatography
CTCAE	Common Terminology Criteria for Adverse Events	MRI	Magnetic resonance imaging
CTLA-4	Cytotoxic T-lymphocyte antigen-4	NCCN	National Comprehensive Cancer Network
DILI	Drug-induced liver injury	NCI	National Cancer Institute
ECG	Electrocardiogram	PD-L1	Programmed cell death ligand-1
ECHO	Echocardiogram	PJP	Pneumocystis jirovecii pneumonia
ESMO	European Society of Medical Oncology	PO	By mouth
GI	Gastrointestinal	SCAR	Severe cutaneous adverse reaction
HBcAb	Hepatitis B core antibody	SITC	Society for Immunotherapy of Cancer
HBeAg	Hepatitis B envelope antigen	SJS	Stephen Johnson Syndrome
HBsAg	Hepatitis B surface antigen	T1DM	Type 1 diabetes mellitus
HBV	Hepatitis B virus	T3	Triiodothyronine
HCC	Hepatocellular cancer	T4	Thyroxine
HCV	Hepatitis C virus	TEN	Toxic Epidermal Necrolysis
HgA1c	Hemoglobin A1C	TMG(s)	Toxicity management guideline(s)
ICI(s)	Immune checkpoint inhibitor(s)	TSH	Thyroid stimulating hormone
		ULN	Upper limit of normal

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Appendix II: ACCRU-GI-1920 SUBJECT MEDICATION DIARY

Name:	Subject ID Number:
Cycle:	
You will take:	

ORAL MEDICATION DIARY**Subject Instructions**

- Please bring your Medication Diary and any empty or unused medication container(s) with you to every appointment
- Please use an ink pen when completing the Medication Diary as these will be retained in our research record.
- Please contact your physician and study coordinator any time you go into the hospital. Your physician can advise if you should continue or stop taking your medication.
- To correct a mistake, please make a single line through that entry and write your initials and the date next to the mistake.
- Please indicate on the calendar on the next page that you took your study medication by recording the date and dose taken on the line under the date.
- If you miss a dose, place a “0” under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- If you accidentally take more than you are instructed to, contact your doctor or the emergency room immediately.
- If you miss a dose, do not make up the dose. Wait until your next dose is due.

ACCRU-GI-1920 SUBJECT MEDICATION DIARY

Study Drug/Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date							
Time							
Regorafenib / _ mg							

Study Drug/Dose	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Date							
Time							
Regorafenib / _ mg							

Study Drug/Dose	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Date							
Time							
Regorafenib / _ mg							

Date: _____ Subject's Signature _____

Area Below Only to be Completed only by Coordinator

Week	1	2	3	4	Discrepancy (Yes or No)
Date of Pill Count					
Number of Pills Returned					
Study Coordinator Initials					

Appendix III: American Association for the Study of Liver Diseases (AASLD)
Liver Imaging Reporting and Data System (LI-RADS) 5 Criteria by MRI/CT.

American Association for the Study of Liver Diseases (AASLD)
Liver Imaging Reporting and Data System (LI-RADS) 5 Criteria by MRI/CT.

TABLE 2. LI-RADS 5 CRITERIA

Size	Criteria	Comments
≥20 mm	APHE (nonrim) AND one or more of following: • "Washout" (nonperipheral) • Enhancing "capsule" • Threshold growth	Equivalent to OPTN 5B or 5X
10-19 mm	APHE (nonrim) AND the following: • "Washout" (nonperipheral) • Enhancing "capsule" • Threshold growth	Equivalent to OPTN 5A
	APHE (nonrim) AND "Washout" (nonperipheral)	Equivalent to 2010 AASLD criteria
	APHE (nonrim) AND threshold growth	Equivalent to OPTN 5A-5G

Threshold growth = size increase of a mass by ≥ 50% in ≤ 6 months; "Washout" = washout appearance; "Capsule" = capsule appearance.

Abbreviation: APHE, arterial phase hyperenhancement.

Table Source: Hepatology, Vol. 68, No. 2, 2018 Marrero et al.

[34] Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology (Baltimore, Md) 2018;68:723-50

Appendix IV: Child Pugh Score

Child Pugh Score

Score	Points
Child-Pugh A	5-6
Child Pugh B	7-9
Child Pugh C	>9

Measure	1 point	2 points	3 points
Ascites	Absent	Slight	Moderate
Serum Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Serum bilirubin (mg/dL)	<2	2.0-3.0	>3
INR or Prothrombin time prolongation	<1.7 <4 sec	1.7-2.2 4-6 sec	>2.2 >6 sec
Encephalopathy	None	Grade I-II	Grade III-IV

Encephalopathy grade:

- Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
- Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
- Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
- Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
- Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Appendix V: American Joint Committee on Cancer (AJCC) TNM Staging for Hepatocellular Cancer (8th ed. 2017)

**American Joint Committee on Cancer (AJCC)
TNM Staging for Hepatocellular Cancer (8th ed., 2017)**

Table 1. Definitions for T, N, M

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤ 2 cm, or > 2 cm without vascular invasion
T1a	Solitary tumor ≤ 2 cm
T1b	Solitary tumor > 2 cm without vascular invasion
T2	Solitary tumor > 2 cm with vascular invasion, or multiple tumors, none > 5 cm
T3	Multiple tumors, at least one of which is > 5 cm
T4	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

**Appendix VI: Bayer Unused Drug Disposition Form
Unused Drug Disposition Form**

ACCRU

PRINCIPAL INVESTIGATOR: [REDACTED] M.D.

BAYER STUDY Number: **IIR-US-00139**

Study Title: **ACCRU-GI-1920, Neoadjuvant Regorafenib Plus Durvalumab in Patients with High-Risk Hepatocellular Carcinoma**

Unused Study Drug Disposition Form
Destruction or Return Confirmation

STUDY DRUG Provided	STUDY DRUG Unused	STUDY DRUG Destroyed	STUDY DRUG Returned

I hereby confirm that the product described above was destroyed or returned (select one) to
BAYER on (date) _____ at
(address) _____ -
_____.

Witness (Pharmacist or PI): _____
(Print Name)

Witness: _____
Signature

Telephone Number: _____

Fax Number: _____

E-Mail: _____

Please return this form to (VP of Medical Affairs named in contract) at BAYER HealthCare
Pharmaceuticals Inc., [REDACTED]