Clinical Trial Protocol:

Adjuvant durvalumab plus regorafenib in stage IV NED colorectal cancer**:**

VIVA trial

Study Title:	A randomized, phase IIb study of adjuvant durvalumab (MEDI4736) plus regorafenib vs untreated control in stage IV colorectal cancer patients with no evidence of disease (NED): VIVA trial
Study Number:	
Study Phase:	IIb
Product Name:	Durvalumab (MEDI4736) Regorafenib
EudraCT Number:	2020-001588-10
Indication:	Colorectal Cancer
Investigators:	Multicentre
Sponsor:	IRCCS Ospedale Policlinico San Martino

Study Site Contact	Fondazione GISCAD Gruppo Italiano per lo studio dei carcinomi dell'apparato digerente *Contacts with Clinical Sites, Meetings, Newsletter*
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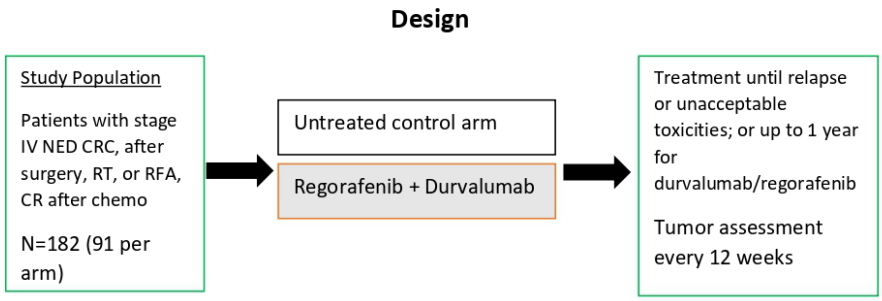
SYNOPSIS

Study title	A randomized, phase IIb study of adjuvant durvalumab plus **r**egorafenib vs untreated control in stage IV colorectal cancer patients with no evidence of disease (NED): VIVA trial
Study phase	Phase IIb
Study design	Randomized, open-label, multicenter, crossover
Sponsor details	IRCCS Ospedale Policlinico San Martino
Principal investigator(s)	Alberto Sobrero IRCCS Ospedale Policlinico San Martino Largo Rosanna Benzi 10, 16132 Genova, Italy
Countries	Italy
Centre(s)	35 (GISCAD)
Planned sample size (N)	182 patients 91 patients per arm (2 arms)
Planned study start/end dates	First Patient First Visit 2020 Q4 Last Patient Last Visit 2022 Q4 Study end date 2025 Q4
Recruitment period	24 months
Rational and Objectives	To date, the introduction of new effective drugs, improvements in surgical and locoregional techniques and supportive care have led to a median overall survival of over 30 months in patients with metastatic colon-rectal cancer (CRC). Thanks to this survival prolongation, medical oncologists and patients are more and more attracted by the possibility to reach a non-evidence of disease (NED) state not only under the classical favourable condition of a single or double liver metastases, but also under the less favourable conditions of multiple metastases even at different sites and even after 2 or 3 lines of treatment, whenever the clinical course allows. Therefore, this population of stage IV NED patients is growing. Previous studies showed that median relapse-free survival (RFS) ranges from 8 to 16-18 months in R0 patients, but up to 90% of these patients eventually relapse: hence, there is an unmet clinical need for effective systemic treatment to reduce the chances of recurrence in stage IV NED patients. After curative resection, international guidelines suggest regimens like FOLFOX, CAPOX, capecitabine or 5-FU/leucovorin alone as potential “adjuvant” therapy, but no standard treatments have been established and active surveillance with no treatment is the standard of care, especially if the patient has received prior chemotherapy as it will be the case for most of our patient population. A phase Ib trial (EPOC1603) tested safety and toxicity profile of Regorafenib combined with an immune-checkpoint inhibitor (ICI) (Nivolumab) in gastric and colorectal cancer. The rather promising results of the phase Ib study has been presented to the ASCO 2019 Annual Meeting, suggesting the activity of Regorafenib in combination with ICIs. The combination of Durvalumab and Tremelimumab showed to prolong median overall survival by 2.5 months compared with best supportive care alone in patients with advanced treatment-refractory colorectal cancer (phase II Canadian Cancer Trials Group (CCTG) CO.26 study). However,

	no data are available about the role of Durvalumab as adjuvant therapy together with a tyrosin-kinase inhibitor (TKI) like Regorafenib in CRC. Given the promising results of these drugs in the metastatic setting, the main objective of this study is to evaluate the efficacy (DFS) of Regorafenib plus Durvalumab versus untreated control in the adjuvant setting for stage IV NED CRC patients.
Design	 Control arm: no treatment. Crossover to Regorafenib + Durvalumab upon relapse Experimental arm: Regorafenib 90mg d1-21 q28 + Durvalumab 1500mg (Q4W) up to 1 year
Run-in phase	The combination of an immune-checkpoint inhibitor plus TKI anti-angiogenic agents has been extensively investigated in several trials (phase II and III) in different types of tumors, with no evidence of new safety signals. Although specific data are not available on the combination of durvalumab and regorafenib, we would not expect major toxicity issues. The run-in phase will be conducted on the first 4 patients randomized to the experimental arm using a starting dose of 60 mg/die of Regorafenib (and fixed 1500 mg of Durvalumab), to be escalated after 2 months to 90 mg/die if < 2 patients report serious adverse events (SAE). If Regorafenib 90 mg/die is well tolerated for other 2 months (< 2 patients with SAE) the run-in phase will be closed with the dose of 90 mg/die. In case of > 2 patients report SAE with 90 mg/die, additional 4 patients will be enrolled and treated with the same dose of Regorafenib (90 mg/die) and if < 2 of them report SAE the run-in will be closed at 90 mg/die. Conversely, if > 2 patients report SAE the dose of Regorafenib will be reduced again to 60 mg/die and the run-in will be closed with Regorafenib 60 mg/die. If during the first part of the run-in > 2 patients report SAE with Regorafenib 60 mg/die, additional 4 patients will be treated with Regorafenib 30 mg/die for 2 months and, in case of > 2 patients with SAE, the trial will be revised. In case of good tolerance of Regorafenib 30 mg/die (< 2 patients with SAE), additional 4 patients will be enrolled and treated with Regorafenib 60 mg/die: if > 2 patients will report SAE the run-in phase will be closed with Regorafenib 30 mg/die, instead if Regorafenib 60 mg/die will be well tolerated (< 2 SAE) this will be the final dose of the run-in phase.

Feasibility: need for crossover	Any trial randomizing active treatments vs a no –treatment-control presents feasibility problems. In this setting, where the large majority of patients will relapse within a few months, randomizing to an inactive control vs the possibility of receiving entirely innovative treatments will constitute a prohibitive feasibility obstacle. This may be overcome by offering the most innovative treatment (REGO DURVA) to patients randomized to control whenever they relapse. This will also provide an opportunity for the conduct of a "satellite" phase IIa trial among a patient population that should present very good conditions and with a not too bulky disease load. Because this crossover will not affect the primary endpoint of the study, this part of the study will be addressed and better specified only if the main protocol is approved. As to the amount of Durvalumab to be provided for this part, we may expect that 1/3 of patients will not be eligible for the cross over and we may postulate that among those starting palliative Durvalumab + Regorafenib, patients will receive a median of 4 months of therapy.
Primary Endpoint	Disease-Free Survival (DFS) will be defined by Punt, JNCI 2007 In addition to the Punt definition, the following condition will be considered DFS event: Two consecutive increases in CEA levels above upper limit level (time gap decided by the clinical investigator but no longer than 30 days).
Secondary Endpoints	• 18-months Disease-Free Survival (DFS) • Adverse events and Toxicity • Overall Survival (OS) • Compliance to the experimental treatment.
Exploratory Endpoints	• Association of translational research data (ctDNA, NGS) with the outcomes
Main Inclusion criteria	To be enrolled in this study each patient must meet all of the following criteria at the time of randomization: 1. Signed ICF, after oral as well as written information; 2. ≥ 18 years; 3. Body weight >30 kg 4. Histologically confirmed diagnosis of colorectal adenocarcinoma; 5. Patients must be in NED after completion of any treatments for stage IV CRC, including resections, RFA; RT with or without neoadjuvant/adjuvant therapies or CR after chemotherapy; 6. Patients must be randomized within 10 weeks since the achievement of the NED state. Those who have also received adjuvant therapy following the locoregional treatment are still eligible, provided they are randomized within 4 weeks since the last chemotherapy cycle; 7. NED state ascertained by means of CT scan and/or PET scan and/or MRI scan;

	8. ECOG Performance Status ≤ 1; 9. Must have a life expectancy of at least 12 weeks 10. CEA within normal limits 11. No residual toxicity from previous chemotherapy; 12. Women of childbearing potential must use safe contraception. 13. Adequate organ and marrow function as defined below: Absolute neutrophil count ≥1.5 × 10^9 /L • Platelet count ≥100 × 10^9/L • Haemoglobin ≥9.0 g/dL • Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician. • Serum Creatinine ≤ 1,5 x ULN o measured creatinine clearance (CL) >40 mL/min or Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance • AST (SGOT)/ALT (SGPT) ≤2.5 x ULN, or ≤ 5 x ULN in the presence of liver metastases
Main Exclusion criteria	A patient who meets any of the following criteria at the time of randomization will be excluded from the study: 1. Participation in another clinical study with an investigational product during the last 4 weeks 2. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study 3. Prior randomisation or treatment in a previous durvalumab clinical study regardless of treatment arm assignment. 4. Patients with microsatellite instability (MSI) or DNA Mismatch Repair Deficiency (dMMR) are not allowed. 5. Any form of systemic disease that, in the opinion of the Investigator, would make the subject unsuitable for the study (including autoimmunity) or would prevent compliance with the study protocol; 6. 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 a. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician. b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.

	7. Any concurrent chemotherapy, 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. 8. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable. 9. History of allogenic organ transplantation. 10. 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: a. Patients with vitiligo or alopecia b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement c. Any chronic skin condition that does not require systemic therapy d. Patients without active disease in the last 5 years may be included but only after consultation with the study physician e. Patients with celiac disease controlled by diet alone 11. 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. 12. History of another primary malignancy except for: f. Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence g. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease h. Adequately treated carcinoma in situ without evidence of disease 13. History of leptomeningeal carcinomatosis 14. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart) 15. History of active primary immunodeficiency 16. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C. 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. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. 17. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion: a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection) b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication) 18. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP. 19. 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 durvalumab monotherapy. 20. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients. 21. Any condition that, in the opinion of the investigator, would interfere with evaluation of the study drug or interpretation of patient safety or study results.

Investigational Treatments	Name - Dosage form - Dosage - Mode of administration - Schedule 1. Regorafenib – film-coated tablets – 90 mg – orally – once daily for the first 21 days of each 28-day cycle, up to 1 year 2. Durvalumab – solution for infusion after dilution – 1500mg – IV – infusion every four weeks up to 1 year Patients in the durvalumab+regorafenib treatment group will receive 1500 mg durvalumab via IV infusion Q4W and 90 mg Regorafenib d1-21 q28 for up to a maximum of 12 months (up to 12 doses/cycles), confirmed disease progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion. (N.B If a patient's weight falls to 30kg or below (≤30 kg), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W after consultation between Investigator and Study Physician, until the weight improves to above 30 kg (>30 kg), at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W).
Justification of Sample Size	The study is set up as an exploratory phase 2B trial with sufficient patient numbers to broadly explore the differences between the experimental arm regimen and the control group. The randomization plan is 1 to 1. Patients will be stratified by center. The main aim of this study is to estimate the effect of the experimental arm relative to control group on the endpoint of interest: disease-free survival. In view of the treatment setting, disease-free survival is considered as the most sensitive clinical endpoint. The sample size is calculated according to a median DFS estimate of 6 months in the control group and to a forecast of 2 years duration of uniform accrual and 2 years of follow-up after the end of accrual. To achieve 90% power at a 0.05 two-sided significance level to detect a 40% fall in DFS event rate (corresponding to a median increase from 6 to 10 months), 172 patients have to be accrued and followed up for at least 2 years in order to achieve the requested 164 events (recurrences or deaths). Assuming an attrition rate of approximately 5%, a total of 182 patients (91 per arm) have to be randomized.
Statistical considerations	All randomized patients will be included in the primary assessment of efficacy (the intention-to-treat population). Safety analyses will include all treated patients (randomized patients receiving at least one dose of study drug). A log-rank test, will be used to assess disease-free survival and overall survival. A Cox proportional hazards model will be used to calculate HRs and 95% CIs). Sensitivity analysis of disease-free survival will be also done with a restricted mean survival time approach that does not assume the proportional hazards model, as outlined by Anderson and colleagues. For patients in the control group after progression, a cross-over is allowed. A descriptive summary of the duration of this crossover treatment (overall and from the time of initial progression) will be done. The proportions of patients achieving an objective response or disease control will be compared with a logistic regression model adjusted for relevant covariates. Effect on survival of regorafenib plus durvalumab regimen within this

	crossover part of the study will be analyzed by means of proportional hazard time-depended analysis. Median disease-free survival will be calculated with the Kaplan-Meier method. All statistical testing is two-sided at the nominal 5% significance level, with no adjustment for multiplicity. All patients who receive at least one regorafenib plus durvalumab dose will be included in the safety analysis.
Publication plan	- Timelines 2025 Q4 - Target Journals: Lancet, Lancet Oncology, JCO.

Table 1. SCREENING PHASE

	28 to 1 day before randomization [d]	
Informed consent	X	
Inclusion / Exclusion criteria	X	
General disease medical history	X	
Prior / Concomitant medications	X	
Complete physical examination	X	
ECOG PS	X	
Weight	X	
Vital Signs[a]	X	
12-lead ECG[b]	X	
Tumor imaging[c]	X	Must be performed within 10 weeks before D1C1. Tumor imaging can be accepted even if performed before the procedures to obtain NED status.
Hematology, chemistry, coagulation and pregnancy test[d]	X	
Biomarkers[d]	X	CEA and CA 19-9 must be on normal range
Histologic Confirmation	X	Only if surgery performed to obtain NED state, resection of the metastases must be R0

Table 2. Experimental arm

	From -7 days to Day 1 Cycle 1	Day 1 Cycle 1	Day 8, 15,22 Cycle 1	Day 1 Cycle 2	Day 15 Cycle 2	Day 1 Cycle 3 and above up to 1-year (12 cycles)	QW12 from C1D1 (+/- 7 days)	End of treatment visit	Treatment discontinuation 30-days from last treatment or at initiation of other anticancer therapy (whichever occurs first)	Follow-up period [g]
Prior / Concomitant medications								X		X
Complete physical examination								X		X
Limited physical examination[a]		X	X	X	X	X				
ECOG PS		X	X	X	X	X		X		X
Weight		X		X		X				
Vital Signs[a]		X	X	X	X	X		X		X
12-lead ECG[b]								X		

Tumor imaging/ response assessments[c]							X	X		X
Hematology[d]	X		X	X	X	X		X		
Coagulation[d]	X							X		
Chemistry[d]	X		X	X	X	X		X		
Biomarkers[d]							X	X		X
Durvalumab Administration		X[e]		X[e]		X[f]				
Regorafenib Administration		X[e]		X[e]		X[f]				
AEs assessments	X		X	X	X	X		X	X	X
Survival and anti-cancer therapy									X	X

Table 3 - Control arm

	QW12 from C1D1 (+/- 7 days)	End of treatment visit	Treatment discontinuation 30-days from last treatment or at initiation of other anticancer therapy (whichever occurs first)	Follow-up period [g]
Prior / Concomitant medications	X	X		X
Complete physical examination	X	X		X
ECOG PS	X	X		X
Weight	X	X		
Vital Signs[a]	X	X		X
Tumor imaging/ response assessments[c]	X	X		X
Hematology[d]	X	X		X
Chemistry[d]	X	X		X
Biomarkers[d]	X	X		X
AEs assessments	X	X	X	X
Survival and anti-cancer therapy			X	X

Abbreviation: CBC: cell blood count; RBC: red blood cell; WBC: White blood cell; aPTT: activated partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio; AST: Aspartate aminotransferase; ALT: alanine aminotransferase; LDH: Lactate dehydrogenase; β-hCG: beta-human chorionic gonadotropin; Na: sodium; K: potassium; Cl: chloride; Mg: magnesium; Ca: calcium; P: phosphate; CEA: Carcinoembryonic antigen; Ca 19-9: Carbohydrate antigen 19-9; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ECG: electrocardiogram; AEs: adverse events

a) Vital signs and Physical examination
   Patients will have a complete physical exam to include an examination of major body systems and an assessment for emergent toxicities or changes from prior visits. Limited physical examination should be performed symptom-directed.
   Examinations will be conducted by a physician, trained physician's assistant, or nurse practitioner, as acceptable according to local regulation.
   Vital signs include: blood pressure and heart rate, body temperature, respiratory rate.
b) Electrocardiogram (ECG)
   Perform a 12-lead resting electrocardiogram (ECG) before the beginning of the treatment, at the end-of-treatment and if clinically indicated. Patients should be in a supine position for at least 10 min before recording. ECG tracings will be reviewed by a qualified physician for assessment of QT interval as well as signs of qualitative abnormalities, including evaluation of rhythm, ST segment morphology, T wave morphology, and presence/absence of U wave.
   The original ECG tracing will be maintained in the source documentation of each patient.
c) Tumor imaging/ response assessments
   Including computed tomography (CT) scan / magnetic resonance imaging (MRI) / PET scan. The same radiographic procedure should be used throughout the study for each patient.
   Tumor assessment should be performed every 12 weeks ± 1 week for the first year (relative to the date of randomization), every 16 ± 1 week in the second year and then every 24 weeks ± 1 week thereafter until RECIST 1.1-defined radiological PD or death (whichever comes first).
d) Local laboratory assessments will include the following:
   - Hematology profile (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils] and platelet count)
   - Coagulation profile (aPTT, PT, INR)
   - Chemistry profile includes Na, K, Cl, Mg, Ca, P, blood urea nitrogen, creatinine, glucose, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, LDH, amylase, lipase
   - Pregnancy test (a positive urine test will be confirmed with a serum pregnancy test) during the study (for woman of childbeating potential). If a patient becomes pregnant while in the study, the study treatment must be immediately discontinued. Pregnancy information for a female patient or for the female partner of a male patient should be reported within 24 hours from the time the Investigator first becomes aware of a pregnancy or its outcome.
   - Biomarkers: CEA, Ca19.9, backup plasma sample.

   Samples for hematology, serum chemistry, coagulation, pregnancy test and biomarkers will be analyzed at the study site's local laboratory. Investigator may have additional blood tests performed for the purpose of planning treatment administration, dose modification, or following AEs.
   Procedure does not have to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (i.e. first day of dosing)

e) The first administration of Regorafenib + Durvalumab must be done within 10 weeks from NED state. Patients who are rendered NED and have received an adjuvant program are still eligible, provided they are randomized within 1 month since the last chemotherapy cycle

f) Up to 1 year

g) During the early follow up phase (Month 13-Month 24) all patients will undergo the following visit every 4 months. During the late follow up phase (Month 25 to Month 60) all patients will undergo the following visit every 6 months.

1 INTRODUCTION

1.1 Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer and the third leading cause of cancer mortality in the United States (US) as well as in Europe[1]. CRC incidence and mortality rates vary markedly around the world. Globally, CRC is the third most commonly diagnosed cancer in males and the second in females, with 1.8 million new cases and almost 861,000 deaths in 2018 according to the World Health Organization GLOBOCAN database [2]. Liver metastases are detected in 40-50% of patients diagnosed with CRC either as synchronous or as metachronous metastases[3]. Sites of metastasis in colorectal cancer patients are most often seen in the liver and lungs. The average median survival time after diagnosis for patients with metastatic colorectal cancer in the absence of treatment is about 6 months [4].

To date, the introduction of new effective drugs, improvements in surgical and locoregional techniques and supportive care have led to a median overall survival of over 30 months in patients with metastatic disease [5]. Thanks to this survival prolongation, medical oncologists and patients are even more attracted by the possibility to reach a NED state and they increase the efforts to obtain it also in advanced stages or in further lines.

Previous studies showed that median RFS ranges from 8 to 16-18 months in R0 patients, but up to 80% of these patients would eventually relapse: hence, there is a unmet clinical need of effective systemic treatment to reduce the chances of recurrence in stage IV NED patients.

After curative resection, international guidelines suggest regimens like FOLFOX, CAPOX, capecitabine or 5-FU/leucovorin alone as potential “adjuvant” therapy, but no standard treatments have been established.

2 BACKGROUND AND RATIONALE

2.1 Pursuing the NED state in stage IV CRC

2.1.1 Liver limited disease

Liver is the most frequent metastatic site in colorectal cancer and 95% of the whole literature on loco-regional approaches to stage IV CRC regards the management of liver metastases, mainly by surgery. The surgical approach to limited liver metastases has produced a 40 and 20% OS at 5 and 10 years and a DFS of 20 and 12% at the same long terms, respectively, as stated by the international registry of patients operated for colorectal liver metastases[6]

With the advent of more active combination chemotherapy than just single agent FU, resections of unresectable liver metastases have been reported[7],[8],[9].

Since then, disease down-staging has become a relevant endpoint of “conversion therapy”.

In nonresectable metastases the Tournigand study[10] reported higher RR for FOLFOX with corresponding R0 resection rate of 22% compared to 9% with FOLFIRI. In 2 randomized phase III trial, Falcone et al.[11],[12] demonstrated an increased RR and R0 resection rate for the triplet regimen FOLFOXIRI alone or with bevacizumab compared with FOLFIRI alone. These data were not confirmed in a similar randomized study from Greece[13], but were corroborated in the most recent Olivia study where FOLFOXIRI bevacizumab was compared to FOLFOX in patients with unresectable liver metastases[14].

At least 3 studies showed consistent improvements in RR (ranging from 59% to 79%) with addition of Cetuximab to chemotherapy in K-RAS wild type tumors[15],[16],[17], and despite the New Epoc results, the contribution of this anti EGFR compound to enhancing resectability is highly valued (in combination with FOLFIRI).

The NO16966 trial, which compared XELOX/FOLFOX with or without Bevacizumab, demonstrated a non-statistically significant increase in the resection rate with the antibody (17.1% vs 12.6% for patient with liver metastases only)[18]. Higher credit to bevacizumab in this setting is provided by the Olivia study mentioned above.

On a separate track, the old-fashioned loco-regional treatment via HAI combined with systemic doublets has recently been reported extremely efficacious from a conversion viewpoint[19], although the limitation of this approach continues to be the lack of widespread experience that conditions a high complication rate of hepatic artery catheters.

All this literature on conversion therapy emphasizes the possibility to pursue the NED state even under conditions that are initially prohibitive.

2.1.2 Extra-hepatic disease

Lung, peritoneum, nodes, and other sites can be affected by metastases by CRC as well. Under exceptional circumstances (single lesion, very long RFS, very benign clinical course, sensitivity to disease control by systemic therapy) these disease sites could be suitable for surgery or loco-regional treatment leading to the NED state. For this reason, what has always been a contraindication to surgery, now, in an era where 50% of patients live longer than 30 months, may indeed be considered for a potentially radical approach. It goes without saying that under these conditions the chances of recurrence are extremely high; hence the need for efficacious systemic treatment to control disseminated microscopic metastases.

Recent data report a median survival time of 16 months in patients with NED surgical outcome, including 50% of patients with liver metastases only[20]. The prognosis of R0 patients shows large variations depending on selection criteria and on the treatment used to achieve the R0 status, with reported median RFS ranging from 8 to 16-18 months[21],[22]. However, most of these estimates derive from uncontrolled studies in highly selected groups of patients.

2.2 Overall Rationale of the study

International guidelines recommend perioperative or adjuvant chemotherapy with FOLFOX/CAPOX in stage IV colorectal cancer patients rendered NED by means of surgery or locoregional treatments. The recommendation is based on previous studies that show a DFS and OS trend in favour of chemotherapy versus no further treatment. These studies lack statistical significance mainly due to the difficulty in accruing patients in this setting. Our innovative design should make it possible to gather data on survival in this prohibitive setting. In addition, it may prove the efficacy of novel treatments (REGO+DURVA) in this setting, potentially establishing a new standard of care for these patients.

To date, the introduction of new effective drugs, improvements in surgical and locoregional techniques and supportive care have led to a median overall survival of over 30 months in patients with metastatic disease. Thanks to this survival prolongation, medical oncologists and patients are more and more attracted by the possibility to reach a NED state not only under the classical favourable condition of a single or double liver metastases, but also under the less favourable conditions of multiple metastases even at different sites and even after 2 or 3 lines of treatment, whenever the clinical course allows. Therefore, this population of stage IV NED patients is growing.

Previous studies showed that median RFS ranges from 8 to 16-18 months in R0 patients, but up to 90% of these patients eventually relapse: hence, there is a unmet clinical need for effective systemic treatment to reduce the chances of recurrence in stage IV NED patients.

After curative resection, international guidelines suggest regimens like FOLFOX, CAPOX, capecitabine or 5-FU/leucovorin alone as potential “adjuvant” therapy, but

no standard treatments have been established and active surveillance with no treatment is the standard of care, especially if the patient has received prior chemotherapy as it will be the case for most of our patient population.

A phase Ib trial (EPOC1603) tested safety and toxicity profile of Regorafenib combined with CPI (Nivolumab) in gastric and colorectal cancer. The rather promising results of the phase II study has been presented to the ASCO 2019 Annual Meeting, suggesting the activity of Regorafenib in combination with immune-checkpoint inhibitors.
In addition, Regorafenib with Durvalumab has proved to be safe in a recent French study in neuroendocrine tumors.
Durvalumab and Tremelimumab showed to prolong median overall survival by 2.5 months compared with best supportive care alone in patients with advanced treatment-refractory colorectal cancer (phase II Canadian Cancer Trials Group (CCTG) CO.26 study). However, no data are available about the role of Durvalumab as adjuvant therapy together with a TKI like Regorafenib in CRC.
Given the promising results of these drugs in the metastatic setting, the main objective of this study is to evaluate the efficacy (DFS) of Regorafenib plus Durvalumab versus control in the adjuvant setting for stage IV NED CRC patients.

Feasibility: need for crossover

Any trial randomizing active treatments vs a no –treatment-control arm presents feasibility problems. In this setting, where the large majority of patients will relapse within a few months, randomizing to an inactive control vs the possibility of receiving entirely innovative treatments will constitute a prohibitive feasibility obstacle.

This may be overcome by offering the most innovative treatment (Regorafenib + Durvalumab) to patients randomized to control whenever they relapse. This will also provide an opportunity for the conduct of a “satellite” phase IIa trial among a patient population that should present very good conditions and with a not too bulky disease load.

2.3 The different ways to reach the NED state

2.3.1 **Surgery**.

Based on current evidence[23], a number of concepts are widely accepted:

a. the primary aim of treatment is achieving long term RFS following resectability;

b. assessment of resectability should be performed with high quality cross-sectional imaging, staging the liver with magnetic resonance imaging and/or abdominal computed tomography (CT), depending on local expertise, staging extrahepatic disease with thoracic and pelvic CT, and in selected cases fluorodeoxyglucose positron emission tomography with ultrasound (preferably contrast-enhanced ultrasound) for intraoperative staging;
c. optimal first-line chemotherapy –doublet or triplet chemotherapy regimens combined with targeted therapy– is advisable in potentially resectable patients;
d. in this situation, at least four courses of first-line chemotherapy should be given, with assessment of tumor response every 2 months;
e. response assessed by RECIST criteria [24] (conventional chemotherapy) or non-size-based morphological changes (antiangiogenic agents) is clearly correlated with outcomes; no imaging technique is currently able to diagnose accurately complete pathological response;
f. duration of chemotherapy should be as short as possible and resection achieved as soon as technically possible in the absence of tumor progression;
g. number of metastases or patient age should not be an absolute contraindication to surgery combined with chemotherapy;
h. for synchronous metastases, it is not advisable to undertake major hepatic surgery during surgery for removal of the primary CRC; the reverse surgical approach (liver first) produces as good an outcome as the conventional approach in selected cases;
i. for patients with resectable CRC liver metastases, perioperative chemotherapy may be associated with modest improved RFS;
j. whether initially resectable or unresectable, cure is possible after complete resection of the metastases and MDT treatment is essential for improved clinical outcome and survival [23].

The surgical approach to limited liver metastases has produced a 40 and 20 % OS at 5 and 10 years and a DFS of 20 and 12% at the same long terms, respectively[6].

2.3.2 Radiotherapy

Radiofrequency and liver-directed treatment could be listed among other non-conventional approaches to obtain NED status. Nonetheless, numerical data about complete response are so far unavailable with these techniques despite growing evidence for their efficacy[25],[26],[27],[28]. A retrospective analysis from the MD Anderson indicated that the RFS and OS of resected stage IV are better than the figures obtained through RFA[29],[30],[31].

2.3.3 Others

In most patients with colorectal metastases chemotherapy is the primary option with progression delaying or tumor shrinking intent. The achievement of NED status by means of complete response to chemotherapy has become more and more frequent recently thanks to the use of new antineoplastic agents. Recent clinical trials in metastatic colorectal cancer have shown complete response rates ranging from 4 to 7%[20].

2.4 Definition of NED state

For the purpose of this trial, NED state is defined as follows:

1. **NED following surgery**: complete resection of all visible lesions (R-0 or R-1) and no evidence of disease elsewhere. In case of uncertain lesions, potentially related to the colorectal neoplastic disease, PET scan can be used and, if used, it should be negative. Postoperative CEA must be within normal limits.
2. **NED following RFA (radio frequency ablation)**: there is no formal definition of complete ablation (technically effective ablation). The literature refers to the concept of an ablation defect completely covering the target lesion assessed by CT scan within 4 to 8 weeks since the procedure[32]·[33]. From a pragmatic point of view, RFA is accepted as a procedure with radical intent when at the baseline CT scan done after the procedure and before randomization, no living tissue is detected in the ablated area (less than 6% chances of local relapses with this method in case of lesions below 4 cm in diameter and less than 3% chances of relapses for lesions smaller than 3 cm[34]. CEA level post procedure must be within normal limits.
3. **NED following stereotactic RT**: no formal definition of potentially radical outcome on imaging is available following this procedure. However, one, two and three years LC rate is reported to be 97%, 92% and 83% for doses higher than 60cGy[35]. Patients receiving 60 or more cGy and no other signs of disease, including CEA level post stereotactic RT must be within normal limits.
4. **NED following chemotherapy**: this is the case of complete response defined as the complete disappearance of any lesion and the normalization of tumor markers.

2.5 The problem of high rate of relapses dominates the stage IV NED condition.

Despite the improved possibility of reaching the NED state in metastatic CRC, it must be remembered that more than 80% of these patients eventually recur and die of their disease. Therefore, any systemic treatment aimed at reducing the

chances of recurrence of stage IV patients who reached the NED state should be considered.

2.6 Why adjuvant therapy of stage IV should work.

The classical paradigm of cancer treatment is that whatever works in the advanced setting (useful clinical responses, prolonged PFS or OS) should work with curative intent when used as adjuvant therapy. This paradigm has held up in CRC: Fluoropyrimidines affording a 6 month gain in the advanced setting, produce an additional cure rate of about 10% when used adjuvantly in stage III. Based upon this paradigm the benefit of adjuvant chemotherapy in the setting of stage IV NED is expected to be even higher, considering the 90% chances of relapsing of these patients.

2.7 But adjuvant therapy of stage IV does not work too well.

The efficacy of pure adjuvant CT is debatable: FU affords a borderline significant benefit in OS compared to surgery alone [36] (absolute delta 7% at 5 years) and FOLFIRI produced a numerically better OS that was not statistically significant compared to FU alone [37]. FOLFOX has not been studied (the NSABP trial C09 was discontinued for lack of accrual), although FOLFOX/CAPOX remain the most commonly employed regimen in clinical practice around the world. In the light of these marginal results obtained by the adjuvant strategies, “neoadjuvant CT” of resectable metastases has been investigated within the frame of a “perioperative strategy” i.e, preoperative CT, then surgery, then CT after surgery. The EORTC produced the only randomized phase III study available (BOS study), that failed to demonstrate a OS advantage of the interventional strategy as compared to surgery alone[38].

2.8 The challenge of running adjuvant trials in stage IV NED patients.

No prospective randomized adjuvant trial of systemic therapy has ever been completed in this setting. The failure in conducting and completing this kind of trial can be ascribed to different causes. First, a randomized trial with experimental treatments versus a control arm with no treatment at all is usually less attractive to patients. However, the possibility to crossover to REGODURVA in the control arm upon progression will improve the feasibility. Second, patients can achieve the NED state by different therapeutic approaches (surgery upfront or after induction chemotherapy, radiofrequency, chemotherapy alone). Thus, the definition of clear and simple eligibility criteria is prohibitive. In this perspective, the trial internal consistency is opposed to its feasibility and conducting.

2.9 Regorafenib and immune-checkpoints inhibitors

Regorafenib is approved treatments for previously treated mCRC patients. It is an oral multi-kinase inhibitor which targets angiogenic, stromal and oncogenic receptor tyrosine kinase (RTK) administered in numerous countries worldwide, including the United States and European Union.

It was found to exhibit potent inhibitory activity against angiogenic and stromal receptor tyrosine kinases (RTKs) VEGFR 1–3, tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE2), fibroblast growth factor receptor 1 (FGFR1), and platelet derived growth factor receptor beta (PDGFR-β), in addition to oncogenic RTKs RET and KIT, and intracellular signaling kinases c-RAF/RAF-1 and BRAF.

It was approved based on a Phase III trial (CORRECT trial) that showed an improvement of OS compared to best supportive care of 1.4 months (6.4 versus 5 months, hazard ratio [HR] 0.77, 95% CI 0.64-0.94) and a PFS of 0.2 months (HR 0.49, mPFS 1.9 versus 1.7 months) (Grothey et al. 2013). These results were later confirmed by a smaller Phase III, randomized, double-blind, placebo-controlled trial conducted in Asia (CONCUR) (Li et al. 2015).

As the approved dose of regorafenib (160 mg daily for 21 days of every 28-day cycle) may be too high for many patients it was conducted the phase II ReDOS trail. It demonstrated that a weekly dose escalating strategy (starting with 80 mg daily, escalating weekly in the absence of treatment-related toxicity to a target of 160 mg daily) allows more patients to continue therapy beyond the first response assessment compared with starting at 160 mg per day. In a preliminary report, presented at the 2018 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, median overall survival also trended better in the dose escalation cohort (9 versus 5.9 months), and toxicity was more favorable. (Bekali-Saab T et al. 2018)

2.9.1 Regorafenib after curative therapy for CRC

Regorafenib have been largely studied in clinical trials as a palliative treatment for metastatic colorectal cancer, showing a good efficacy and safety profile.
To date, a few studies have been conducted for the adjuvant or NED settings and unfortunately no data are available.
All the following trials withdraw for low accrual: a trial for stage IIIC adjuvant CRC (NCT02425683) randomized patients to Regorafenib or placebo after FOLFOX; the COAST trial (NCT01939223) randomized patients to Regorafenib or placebo after obtaining NED status; patients who have received peri-operative multimodal treatment for locally advanced rectal cancer were randomized to Regorafenib versus observation (NCT02287727).

2.9.2 Combination of Regorafenib and immune check-points inhibitors for mCRC

Interesting preliminal results of the REGONIVO trial have been presented in the poster session of the 2019 ASCO annual meeting. Fifty heavely pre-treated pts (25 Gastric Cancer; 25 CRC) were given the combination of nivolumab and regorafenib. An objective tumor response was observed in 19 patients (38%), including 7 MSS CRC and 1 MSI-H CRC. A response rates of 29% was observed in patients with MSS CRC.
We are now waiting for results of two ongoing trials which combine Pembrolizumab + Regorafenib (ongoing **NCT03657641**) and Nivolumab + Regorafenib (NCT03712943).

2.9.3 Immune checkpoints inhibitors for CRC

Immune checkpoint blockade has been an area of active investigation in gastrointestinal cancers.
Initial trials lead to disappointing results of PD-1 and PD-L1 blockade in unselected patients with colorectal cancer. Some results are here reported in the table.

Phase	Regimen	Patient population	Results
I	Nivolumab (anti-PD-1 antibody)	Advanced solid tumours, including CRC	Of 19 patients, no objective responses were observed
I	BMS-936559 (anti-PD-L1 antibody)	Advanced solid tumours, including CRC	Of 18 patients, no objective responses were observed
I	Atezolizumab (anti-PD-L1 antibody)	Advanced solid tumours, including CRC	Of 4 patients, one achieved a partial response
Ib	Atezolizumab (anti-PD-L1 antibody) + Bevacizumab +/– FOLFOX	Metastatic CRC (chemotherapy naïve and refractory)	ORR: 7 % in the refractory cohort (atezolizumab + bevacizumab), 48 % in the chemotherapy naïve cohort (atezolizumab + bevacizumab + FOLFOX)

The approved use of immune checkpoints for CRC are currently restricted to a specific subgroup of patients (i.e. Microsatellite instability (MSI) or Mismatch Repair deficient (dMMR). This subtype, observed in approximately in 5% of mCRC, is characterized by dense immune cell infiltration, probably due to the accumulation of somatic mutations as a result from inactivation of the DNA mismatch repair system.

In the study of Le DT et al. (NEJM, 2015), which lead to the FDA approval of Pembrolizumab for agnostic dMMR tumors, there were 10 patients with dMMR mCRC. Four (40 %) patients achieved objective responses and 5 (50 %) patients had stable disease. In contrast, no patient with pMMR colorectal cancer had an objective response and only 2 patients (11 %) experienced disease stabilization. PFS at 20 weeks was 78 % in the dMMR colorectal cancer cohort and 11% in the pMMR colorectal cancer group.

Based on these results, the clinical activity of pembrolizumab is currently being evaluated in a larger, single arm phase II (NCT02460198) and a randomized phase III trial (NCT02563002) for patients with metastatic dMMR colorectal cancer as first line treatment versus standards of care. In addition, a phase II trial of durvalumab in dMMR colorectal cancer is currently enrolling patients (NCT02227667).

The interim analysis of CheckMate-132 included 56 patients with dMMR metastatic colorectal cancer, treated with nivolumab or nivolumab and ipilimumab. The ORR was 27 % for the Nivolumab group and 15 % for the combination group. Despite the higher response rate in the monotherapy group, the combination was superior with regard to PFS and OS. The 4-month PFS was 55 % for the Nivolumab group and 80 % for the Nivolumab+Ipilimumab group, while the 5-month OS was 75 % and 100 % respectively.

The Canadian Cancer Clinical Trials Group (CCCTG) evaluate in the CO.26 trial the addition of the immune checkpoint doublet durvalumab + tremelimumab to best supportive care in unselected refractory mCRC. The study was presented at the ASCO GI 2019 symposium and demonstrated a median OS of 6.6 months compared with 4.1 months with supportive care alone (hazard ratio [HR], 0.72; 90% CI, 0.54-0.97; P = .07). However, median progression-free survival (PFS) did not significantly differ between arms (1.8 months vs. 1.9 months; HR, 1.01; 90% CI, 0.76-1.34; P = .97).

An ongoing Phase Ib/II trial (NCT03202758) will evaluate the safety, tolerability and immunological activity of durvalumab (MEDI4736) (anti-PD-L1) plus tremelimumab (anti-CTLA-4) combined with FOLFOX in patients with metastatic colorectal cancer.

Little is known for early stage disease. In the first neoadjuvant study (Chalabi M et al., presented at ESMO 2018 annual meeting) to test ipilimumab plus nivolumab in early-stage dMMR and pMMR colon cancers, 19 patients with resectable, early-stage colon cancer were treated with ipilimumab at 1 mg/kg on day 1 and nivolumab at 3 mg/kg on days 1 and 15. Patients then underwent surgery within a planned maximum of 6 weeks. Seven patients had dMMR tumors (1 patient had a double tumor) and major pathological responses (<10% residual vital tumor) were observed in 100% (7/7) of them, with 4 (57%) complete responses.

As far as we know, no trials have been conducted with Durvalumab or any other immune check point in the adjuvant setting.

2.9.4 Durvalumab

Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of programmed cell death ligand 1 (PD-L1) with the PD-1 and CD80. It is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the Ig G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma receptors involved in triggering effector function.
It works as a checkpoint inhibitor, blocking a signal that would have prevented activated T cells from attacking the cancer, thus allowing the immune system to clear the cancer.

It is indicated as monotherapy for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumors express PD-L1 on ≥ 1% of tumor cells and whose disease has not progressed following platinum-based chemoradiation therapy.

2.9.5 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 diarrhoea, 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.

2.9.5.1 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, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions, and infections/serious infections.
For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB.
Further information on these risks can be found in the current version of the durvalumab IB.
In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 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
A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

2.9.6 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 (Ng et al 2006, Wang et al 2009, Zhang et al 2012, Narwal et al 2013) 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 (Wang et al 2009) . 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 (Zhang et al 2012).

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.

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 refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics

Durvalumab has recently been approved by FDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma who either have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
As regards colorectal cancer a monotherapy with CPI have not demonstrated clinically meaningful efficacy in the majority of mCRC, the MSS mCRC cohort, which are cold tumors with a low mutational burden.
However, in the small percentage of MSI mCRC (5%) they are proving outstanding results. In fact, two works were published recently by Overman et al, the first one with Nivolumab (Overman et al) and the second one with Nivolumab and Ipilimumab in combination (Overman et al). These studies showed an ORR of 31% and 55% and a 1y-PFS of 50% and 71%, respectively.

2.10 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 (Stewart et al 2015). *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al 2015). 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 0. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

2.11 Rationale for Regorafenib dose in combination with Durvalumab

Regorafenib will be administered at a dose of 90 mg orally, once daily (q.d.) for 3 weeks in a 4-week cycle. Durvalumab will be administered intravenously (i.v.) at a dose of 1500 mg every 4 weeks (Q4W).

The dose of regorafenib is lower than the dose currently approved in CRC and other indications. The selection of this dose is based on the recently published REGONIVO trial as well as data from other ongoing trials, as explained below. REGONIVO was a phase Ib trial that enrolled 50 patients with pre-treated metastatic gastric and colorectal cancer. Patients received (during the dose expansion phase), 80-120 mg of regorafenib in combination with nivolumab. The 80 mg dose had a manageable safety profile and encouraging antitumor activity (objective tumor response 40%) in patients with heavily pretreated disease. Based on these promising results, the Rego-Nivo combination is being tested in a number of ongoing clinical trials, including an industry-sponsored phase II trial in patients with mismatch repair-proficient advanced colorectal cancer and two phase II trials in unresectable HCC.

Based on data from the combination of regorafenib and nivolumab in the REGONIVO trial, the combination of regorafenib and pembrolizumab in an ongoing HCC trial, as well as ongoing data from a phase II regorafenib + nivolumab trial in colorectal cancer (Bayer - data on file), a few observations are noted:

- A starting dose of 120 mg of regorafenib cannot be sustained in the majority of patients, predominantly due to rash.

- A starting dose of 80 mg is more tolerable and certain patients can maintain therapy at this dose as well as escalate to 120 mg; however approximately 25% of Western patients require further dose reduction.

It is therefore not clear whether additional efficacy beyond that seen with an 80 mg starting dose could be observed, this suggests that the optimal dose of regorafenib in combination with a PD-(L)1 inhibitor may lie between 80 and 120 mg.

Since there is no pharmacodynamic marker for the regorafenib activity in combination with a PD-(L)1 inhibitor, empirically one can conclude that an intermediate dose closer to 80 mg would have a lower likelihood of eliciting toxicity. However, concerns regarding unrealized efficacy may remain. Conversely, a dose closer to 120 mg may elicit toxicity, leading to higher rates of discontinuation.

A further consideration is that some patients treated with 80 mg of regorafenib still require dose reductions and with 40 mg tablets, a 50% dose reduction is drastic and not considered usual practice.

Based on PK and PD data from the phase I dose escalation trial (11650), regorafenib exposure in the range expected for a dose of 40 mg had less of an impact on levels of sVEGFR2 as compared to exposure associated with doses ≥ 60 mg. Since VEGFR inhibition is one of the proposed mechanisms for the beneficial effect of regorafenib and PD-(L)1 inhibitor combination therapy, this is relevant to consider.

Dosing regorafenib in combination using a lower strength tablet would allow flexibility to achieve a starting dose between 80 and 120 mg and have a more gradual dose reduction if needed.

In order to provide maximum flexibility to attain an optimal dose, with the current information, 30 mg tablets are optimal. A starting dose of 90 mg (3 tabs) in combination therapy is recommended. Should an initial dose reduction be required, the first dose reduction would be to 60 mg (2 tablets), which is a more conventional 30% reduction and is also expected to provide regorafenib exposure in a pharmacologically active range.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is:

- To investigate the efficacy of Regorafenib plus Durvalumab versus control arm as adjuvant treatment in stage IV CRC patients rendered Disease-Free after completion of standard treatment according to local practices.

3.1.1 Primary Endpoint

The primary endpoint is Disease-Free Survival (DFS) defined according to Punt, 2007 (Table 4)[60]. In addition to the Punt definition, one the following will be considered DFS event as well :

a) Appearance of any imaging or clinical new sign of disease
b) Two consecutive (time gap will be decided by the clinical investigator but it should not be longer than 30 days) increases in CEA levels above upper limit level.

3.1.2 Treatment at progression

Since progression marks the achievement of the primary endpoint, the treatment upon progression is left to investigator clinical judgment.

In the control arm (observation) crossover to regorafenib plus durvalumab is allowed.

Table 4. Contribution of nine different events to the definition of six endpoints in adjuvant studies with cancer patients

	Endpoint [a]					
Event	DFS	RFS	TTR	TTF	CSS	OS
Loco-regional recurrence	E	E	E	E	I	I
Distant metastases	E	E	E	E	I	I
Second primary, same cancer	E	I	I	E	I	I
Second primary, other cancer	E	I	I	E	I	I
Death from same cancer	E	E	E	E	E	E
Death from other cancer	E	E	C	E	C	E
Non-cancer-related death	E	E	C	C	C	E
Treatment-related death	E	E	C	E	C	E
Loss to follow-up	C	C	C	C	C	C

(Consensus agreement, from: Punt, 2007).

[a] DFS = disease-free survival; RFS = relapse-free survival; TTR = time to recurrence; TTF = time to treatment failure; CSS = cancer specific survival; OS = overall survival;
E = event; **C** = censor; **I** = ignore

To the purpose of this trial a **loco-regional recurrence or systemic recurrence** is defined as follows:

CT positive or CT uncertain with elevated CEA and positive PET scan.

3.2 Secondary Objectives

The secondary objectives of this study are:

- to assess the short-term effects of adjuvant regorafenib plus durvalumab on DFS
- to assess the effect of adjuvant regorafenib plus durvalumab on all causes mortality.
- to investigate potential correlation between molecular and biological markers and survival outcomes(progression and death) in patients treated with adjuvant regorafenib plus durvalumab.
- to assess toxicity correlated to study treatment
- to assess the treatment compliance

3.2.1 Secondary Endpoints

The secondary endpoints are:

- 18 months Disease-Free Survival (DFS)
- Overall Survival (OS)
- Compliance to the experimental treatment.

3.2.2 Exploratory Objectives

- Correlation between ctDNA and survival outcomes (progression and death) in patients treated with adjuvant regorafenib plus durvalumab.
- Explore the potential prognostic and predictive value of Next-generation sequencing analyses, Tumour DNA methylation analyses, Gene expression analyses, CMS subgrouping analyses, Immune signature analyses and the correlation with the survival outcomes in mCRC NED patients enrolled in this trial.

3.3 Endpoints definition

3.3.1 Disease-free survival

The primary study endpoint is DFS as defined in Section 3.1.1 and computed for each patient from the day of randomization to the day of occurrence of first event

of interest or last follow up clinical examination. If no event (relapse or death) has been observed, the patient is censored at the date of the last follow up.

Patients who discontinue treatment prior to documented disease relapse including those who initiate non-protocol therapy prior to relapse, will be followed up for disease progression and death and will be censored at the time of therapy change.

3.3.2 Overall survival

Defined as time from the date of randomization until death from any cause. If no event (death) has been observed, the patient is censored at the date of last follow up.

3.3.3 Toxicity

Toxicity / adverse events classified according to NCI CTCAE version 5.0 [61] .

3.3.4 Compliance to the experimental treatment

Defined as the ratio between the actual and expected number of Durvalumab+Regorafenib administrations in each patient.

4 INVESTIGATIONAL PLAN

4.1 Description and Justification of the Trial Design and Plan

This project is a randomized, open-label, multicenter study. All eligible patients, after completion of locoregional treatment to render them disease free, will be randomized to experimental treatment (adjuvant regorafenib plus durvalumab) or no further treatment (observation). Randomization is 1:1. Patients randomized to the experimental arm will receive up to 1 year of regorafenib + durvalumab. Patients randomized to the control arm will receive no further treatment. Patients in the control arm will be offered the possibility to crossover to regorafenib plus durvalumab upon relapse.

4.1.1 Justification of a no treatment control group

The use of an untreated control group (i.e., no further treatment) is acceptable when patients in the control group are managed as per SoC, and patients are informed of the possibility of being randomized to no further treatment.

Standard of care “treatment” for CRC patients after resection surgery and chemotherapy is observation. The possibility of randomization to no further treatment will be clearly documented in the Informed Consent Form (ICF).

4.1.2 Justification of an open label design

The primary study endpoint is Disease-Free Survival (DFS) (Section 3.1). The open label design (lack of masking) is justified by the need of up to 1-year placebo injections and placebo pills, which are not felt ethically justifiable.

4.1.3 Justification of DFS as primary study endpoint

The choice of DFS as the primary study endpoint is justified by

a) the intrinsic clinical relevance of living without relapse and,
b) the demonstration of its validity as a surrogate endpoint of overall survival (OS)[62].

4.2 Determination of Sample Size

The study is set up as an exploratory phase 2B trial with sufficient patient numbers to broadly explore the differences between the experimental arm regimen and the control group.

The randomization plan is 1 to 1. Patients will be stratified by centre.

The main aim of this study is to estimate the effect of the experimental arm relative to control group on the endpoint of interest: disease-free survival.

In view of the treatment setting, disease-free survival is considered as the most sensitive clinical endpoint.

To achieve 90% power at a 0.05 two-sided significance level to detect a 40% fall in DFS event rate (corresponding to a median increase from 6 to 10 months), 172 patients have to be accrued and followed up for at least 2 years in order to achieve the requested 164 events (recurrences or deaths). Assuming an attrition rate of approximately 5%, a total of 182 patients (91 per arm) have to be randomized. The primary efficacy endpoint will be evaluated on the ITT population.

A log-rank test will be used to assess disease-free survival and overall survival. A Cox proportional hazards model will be used to calculate HRs and 95% CIs). Sensitivity analysis of disease-free survival will be also done with a restricted mean survival time approach that does not assume the proportional hazards model, as outlined by Anderson and colleagues.

For patients in the control group after progression, a cross-over is allowed. A descriptive summary of the duration of this crossover treatment (overall and from the time of initial progression) will be done. The proportions of patients achieving an objective response or disease control will be compared with a logistic regression model adjusted for relevant covariates. Effect on survival of regorafenib plus durvalumab regimen within this crossover part of the study will be analysed by means of proportional hazard time dependent analysis. Median progression-free survival will be calculated with the reverse Kaplan-Meier method.

All statistical testing is two-sided at the nominal 5% significance level, with no adjustment for multiplicity. All patients who receive at least one regorafenib plus durvalumab dose will be included in the safety analysis.

A data-monitoring committee will be appointed to assess the trial data periodically to ensure patient safety and the integrity of the trial.

4.3 Study plan

Approximately 182 patients, >18 years of age, with Stage IV CRC and no evidence of disease (NED) will be enrolled. Randomization will be 1:1.

Prior to enrolment, all patients will have received standard of care (SoC) treatment for Stage IV CRC (locoregional), and will have to be NED.

Treatment schedules and safety and efficacy assessments will be the same for all patients, regardless of treatment group.

All patients will undergo assessments (Section 6.2) to confirm compliance with inclusion and exclusion criteria, after that they will sign informed consent. Patients who will be randomized to the experimental treatment group will receive up to 1 year of regorafenib plus durvalumab.

Run-in phase: The combination of an immune-checkpoint inhibitor plus TKI anti-angiogenic agents has been extensively investigated in several trials (phase II and III) in different types of tumors, with no evidence of new safety signals. Although specific data are not available on the combination of durvalumab and regorafenib, we would not expect major toxicity issues.

Therefore, a run-in phase will be conducted on the first 4 patients randomized to the experimental arm using a starting dose of 60 mg/die of Regorafenib (and fixed 1500 mg of Durvalumab), to be escalated after 2 months to 90 mg/die if < 2 patients report serious adverse events (SAE). If Regorafenib 90 mg/die is well tolerated for other 2 months (< 2 patients with SAE) the run-in phase will be closed with the dose of 90 mg/die. In case of > 2 patients report SAE with 90 mg/die, additional 4 patients will be enrolled and treated with the same dose of Regorafenib (90 mg/die) and if < 2 of them report SAE the run-in will be closed at 90 mg/die. Conversely, if > 2 patients report SAE the dose of Regorafenib will be reduced again to 60 mg/die and the run-in will be closed with Regorafenib 60 mg/die.

If during the first part of the run-in > 2 patients report SAE with Regorafenib 60 mg/die, additional 4 patients will be treated with Regorafenib 30 mg/die for 2 months and, in case of > 2 patients with SAE, the trial will be revised. In case of good tolerance of Regorafenib 30 mg/die (< 2 patients with SAE), additional 4 patients will be enrolled and treated with Regorafenib 60 mg/die: if > 2 patients will report SAE the run-in phase will be closed with Regorafenib 30 mg/die, instead if Regorafenib 60 mg/die will be well tolerated (< 2 SAE) this will be the final dose of the run-in phase.

(see Flowchart in Appendix 4)

The first regorafenib plus durvalumab cycle will be administered on Day 1.

The timing of visits, assessments and procedures is detailed in Section 8 and in Table 1, Table 2, and Table 3, respectively.

4.4 Study Duration, End of Trial and Dates

The study duration for each patient will be dependent on patient survival and/or on the occurrence of unacceptable toxicities. Given that the accrual period is 2 years and follow-up is 2 year, the maximum active study period for each patient range from 24 months to 48 months after randomization.

5 PLANNED STATISTICAL METHODS

All trial data must be recorded in the eCRF. The data will be recorded as soon as possible after they are generated. All sections of each eCRF must be completed. Only the Investigator can electronically sign the eCRF for assurance of exactitude and completeness of each page.

5.1 Analysis populations

- **Intention-to-treat population (ITT)**: The ITT population will include all randomized patients. Patients will be analyzed in the arm they were allocated by randomization.
- **Per protocol population (PP)**: All patients of the ITT population who do not have any major deviation from eligibility criteria and have started their allocated treatment (at least one dose of the study drug).
- **Safety population (SP)**: All patients of the ITT population, who have received at least one dose of the study drug. Patients will be analyzed in the treatment they actually received.

5.2 Statistical methods

5.2.1 Time to event endpoints

The analyses of the primary and secondary time to event endpoints (DFS and OS) will be performed on all patients according to the intention to treat principle.

5.2.2 Estimates and confidence intervals

Estimates of the event-free rates at a fixed time points, namely 1, 3 and 5 years will be obtained using the Kaplan Meier technique and (1- α) CI will be calculated by Greenwood's estimation of the standard deviation. Estimates of hazard ratios and their (1-α) CI will be obtained by Cox regression.

Kaplan Meier Curves will be drawn for both the experimental and control arms on the same plot.

Follow-up time will be estimated based on the reverse Kaplan Meier method for both groups

5.2.3 Inference: Test statistics for comparisons

A log-rank test will be used to compare the experimental versus the control arms for the time to event endpoints.

5.2.4 Toxicity

Analyses for toxicity will be based on the safety population. For each patient and for each type of toxicity, the worst grade of toxicity/adverse events observed over the whole treatment period according to CTCAE version 5 will be presented and used for the analyses. Two sets of statistical analyses will be performed to compare toxicity in the two treatment groups. In the first set the whole pattern of toxicity (all grades) will be considered for each item; analysis will be done by a linear rank test. In the second set toxicity will be defined as severe (mostly including grade 3 or higher) and not severe (mostly including grades up to 2) and analysis will be performed by chi-square or the Fisher's exact test, as appropriate.

5.2.5 Interim analyses

For the primary endpoint of efficacy an interim analysis for futility is planned when approximately 40% of patients will be accrued and evaluated for endpoint. A conditional power analysis will be considered and trial will be stopped if, under the assumption that the results distribution of future data under the current trend and under alternative hypothesis, the probability of detect a statistically significant result will be <20%.

5.2.6 Pre-planned multivariate analysis, exploratory subgroup analyses and analyses of DFS

As a sensitivity analysis aimed at confirming the results of the primary analysis while adjusting for any imbalance in baseline factor, a multivariate Cox PH model will be fitted to the data with treatment assigned at random, routine prognostic factors including gender, age and CEA at randomization, number of metastatic lesions (1vs >1, or as continuous), size of metastatic lesions, number of metastatic sites (1vs >1, or as continuous), time from primary resection to metastatic detection (<6 mos vs >=6 mos, or as continuous), R0 vs R1 resections, RFS since removal of primary, molecular determinants such as RAS, BRAF status and therapy used to achieve the NED status, as covariates. The results of this analysis will be used to confirm those of the primary analysis, and any difference in the results of the two analyses will be mentioned in the presentation of the trial results, but in no case they will be used to overrule the conclusions drawn based on the results of the primary analysis.

Subgroup analyses will be carried out for all prognostic factors considered in the Cox model by including in the model the appropriate treatment-by-factor interaction terms, one at a time, and evaluating the change in the log-likelihood. The results of these analyses will be presented with the standard Forrest plots with stratum-specific hazard ratios and p-values for interaction, but they will be considered and presented as merely exploratory, hypothesis-generating, analyses. Proportional hazards assumption will be checked using the method described by Grambsch & Therneau [64]. If the data clearly do not follow proportional hazards, medical

explanations should be identified and alternative statistical methods will be explored.

The same univariate and multivariate analyses will be replicated for Overall Survival.

5.2.7 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarised by treatment group and overall. These assessments will include other relevant parameters such as blood pressure measurements and medical history. By-treatment summaries will serve to identify any imbalances between the treatment groups at baseline. Summary tables will be provided for the ITT and the PP populations by means of descriptive statistics and frequency tables where appropriate.

6 SUBJECT SELECTION CRITERIA

6.1 Study Population

This study plans to enrol 182 patients, ≥ 18 years of age, with Stage IV CRC and no evidence of disease (NED state, see Section 2.4 for the definition of NED), who comply with all inclusion and exclusion criteria and who provide written consent to participate in the study.

The patients will be enrolled at approximately 25-40 study facilities in Italy.

6.2 Inclusion Criteria

To be enrolled in this study each patient must meet all of the following criteria at the time of randomization:

1. Signed ICF, after oral as well as written information. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations
2. Age ≥ 18 years at time of study entry
3. Body weight >30 kg
4. Histologically confirmed diagnosis of colorectal adenocarcinoma;
5. Patients must be in NED after completion of any treatments for stage IV CRC, including resections, RFA; RT with or without neoadjuvant/adjuvant therapies or CR after chemotherapy;
6. Patients must be randomized within 10 weeks since the achievement of the NED state. Those who have also received adjuvant therapy following the locoregional treatment are still eligible, provided they are randomized within 4 weeks since the last chemotherapy cycle;
7. NED state ascertained by means of CT scan and/or PET scan and/or MRI scan;
8. ECOG Performance Status ≤ 1;
9. Life expectancy of at least 12 weeks
10. CEA within normal limits;
11. No residual toxicity from previous chemotherapy;
12. Women of childbearing potential must use safe contraception.
13. Adequate normal organ and marrow function as defined below:

Haemoglobin ≥9.0 g/dL

Absolute neutrophil count (ANC) ≥1.5 × 10^9 /L

- Platelet count ≥100 × 10^9/L

Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN).

This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology), who will be allowed only in consultation with their physician.

Serum Creatinine ≤ 1.5 x ULN o measured creatinine clearance (CL) >40 mL/min or Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

AST (SGOT)/ALT (SGPT) ≤2.5 x ULN, o ≤ 5 x ULN in the presence of liver metastases

14. 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.

6.3 Exclusion Criteria

1. Participation in another clinical study with an investigational product during the last 4 weeks.
2. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study
3. Prior randomisation or treatment in a previous durvalumab clinical study regardless of treatment arm assignment.
4. Patients with microsatellite instability (MSI) or DNA Mismatch Repair Deficiency (dMMR) are not allowed.
5. Any form of systemic disease that, in the opinion of the Investigator, would make the subject unsuitable for the study (including autoimmunity) or would prevent compliance with the study protocol;
6. 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
    a. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
    b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.

7. Any concurrent chemotherapy, 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.
8. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
9. History of allogenic organ transplantation.
10. 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:
    a. Patients with vitiligo or alopecia
    b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    c. Any chronic skin condition that does not require systemic therapy
    d. Patients without active disease in the last 5 years may be included but only after consultation with the study physician
    e. Patients with celiac disease controlled by diet alone
11. 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
12. History of another primary malignancy except for
    f. Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence
    g. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    h. Adequately treated carcinoma in situ without evidence of disease
13. History of leptomeningeal carcinomatosis
14. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart)
15. History of active primary immunodeficiency
16. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C. 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. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

17. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
    d. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
    e. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
    f. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)
18. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.
19. 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 durvalumab monotherapy.
20. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
21. Any condition that, in the opinion of the investigator, would interfere with evaluation of the study drug or interpretation of patient safety or study results.

6.4 Withdrawal of patients from study treatment and/or study

6.4.1 Permanent discontinuation of Durvalumab or Regorafenib

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, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This 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 modify follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

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 the SoAs).

Patients who permanently discontinue drug for reasons other than objective RECIST disease progression should continue to have RECIST scans performed every 12 weeks ± 1 week for the first year (relative to the date of randomization), and then every 16 weeks ± 1 week in the second year and then every 24 weeks ± 1 week thereafter until RECIST 1.1-defined radiological PD or death (whichever comes first) as defined the SoAs.

If a patient is discontinued for RECIST 1.1-defined progression, then the patient should have 1 additional follow-up scan performed preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD.
All patients will be followed for survival until the end of the study.
Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in the SoAs as an alternative.
Patients who have permanently discontinued from further receipt of IP will need to be discontinued from the IVRS/IWRS.

6.4.2 Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up."
Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol. In order to support key end points of DFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow up."

- Lost to Follow up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable CRF modules will be updated.)

- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status. (The applicable CRF modules will be updated.)

6.4.3 Withdrawal of consent

Patients are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment. Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study. If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- All further participation in the study including any further follow up (eg, survival contact telephone calls)
- Withdrawal to the use of any samples

7 STUDY TREATMENT

Control arm

Patients in the control arm upon relapse will be treated with either standard treatment or regorafenib + durvalumab.

7.1 Treatment Administered

Patients randomized and assigned to experimental arm will receive Regorafenib + durvalumab. Treatment will begin only after the patient has been randomized to the Treatment Group. Regorafenib 90 mg will be administered orally once daily for the first 21 days of each 28-day cycle, up to 1 year. Durvalumab (1500mg q4W IV infusion) will be administered every four weeks up to 1 year.

7.1.1 Run-in phase

Run-in phase: The combination of an immune-checkpoint inhibitor plus TKI anti-angiogenic agents has been extensively investigated in several trials (phase II and III) in different types of tumors, with no evidence of new safety signals. Although specific data are not available on the combination of durvalumab and regorafenib, we would not expect major toxicity issues.

Therefore, a run-in phase will be conducted on the first 4 patients randomized to the experimental arm using a starting dose of 60 mg/die of Regorafenib (and fixed 1500 mg of Durvalumab), to be escalated after 2 months to 90 mg/die if < 2 patients report serious adverse events (SAE). If Regorafenib 90 mg/die is well tolerated for other 2 months (< 2 patients with SAE) the run-in phase will be closed with the dose of 90 mg/die. In case of > 2 patients report SAE with 90 mg/die, additional 4 patients will be enrolled and treated with the same dose of Regorafenib (90 mg/die) and if < 2 of them report SAE the run-in will be closed at 90 mg/die. Conversely, if > 2 patients report SAE the dose of Regorafenib will be reduced again to 60 mg/die and the run-in will be closed with Regorafenib 60 mg/die.

If during the first part of the run-in > 2 patients report SAE with Regorafenib 60 mg/die, additional 4 patients will be treated with Regorafenib 30 mg/die for 2 months and, in case of > 2 patients with SAE, the trial will be revised. In case of good tolerance of Regorafenib 30 mg/die (< 2 patients with SAE), additional 4 patients will be enrolled and treated with Regorafenib 60 mg/die: if > 2 patients will report SAE the run-in phase will be closed with Regorafenib 30 mg/die, instead if Regorafenib 60 mg/die will be well tolerated (< 2 SAE) this will be the final dose of the run-in phase.

(see Flowchart in Appendix 4)

7.2 Dose interruption or reduction

In case of adverse events, dose interruption or reduction are at the investigator's discretion based on local clinical practice.

If an adverse event is attributed to only one drug (i.e., regorafenib or durvalumab), the investigator's discretion will be used to determine what drug dose should be reduced or withheld.

Table 5. Dose reduction levels

Drug	Dose levels		
	Starting dose	-1	-2
Durvalumab	1500mg	-	-
Regorafenib	90mg	60 mg	30 mg

7.3 Durvalumab Dosage and Administration

Durvalumab will be used in the commercially available formulation.
Patients randomized to REGO-DURVA arm will receive Durvalumab at the dose level of 1500mg (60 minutes intravenous injection infusion) every 4 weeks.

Premedications are not recommended for the first dose of Durvalumab.

The study investigator may interrupt or delay Durvalumab administration according to adverse events to ensure patient safety and tolerability. Guidelines for treatment delay or discontinuation are provided in Appendix 3.
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; it has a pH of 6.0 and density of 1.054 g/mL. The nominal fill label-claim volume is 10.0 mL.

Durvalumab is a sterile, clear to opalescent, colorless to slightly yellow solution, free from visible particles.

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

Any overdose or incorrect administration of Durvalumab should be noted on the Durvalumab Administration eCRF. Adverse events associated with an overdose or

incorrect administration of Durvalumab should be recorded on the Adverse Event eCRF.

7.3.1 Study drug preparation

Patients in the durvalumab treatment group will receive 1500 mg durvalumab via IV infusion Q4W for up to a maximum of 12 months (up to 12 doses/cycles), confirmed disease progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion. If a patient's weight falls to 30 kg or below (≤30 kg) the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W.

7.3.2 Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should must not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hrs

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 30.0 mL (i.e. 1500 mg) of durvalumab (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.
If patient 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.

Standard infusion time is 1 hour, however if there are interruptions, In the event that there are interruptions during infusion, the total allowed infusion time should must not exceed 8 hours at room temperature.

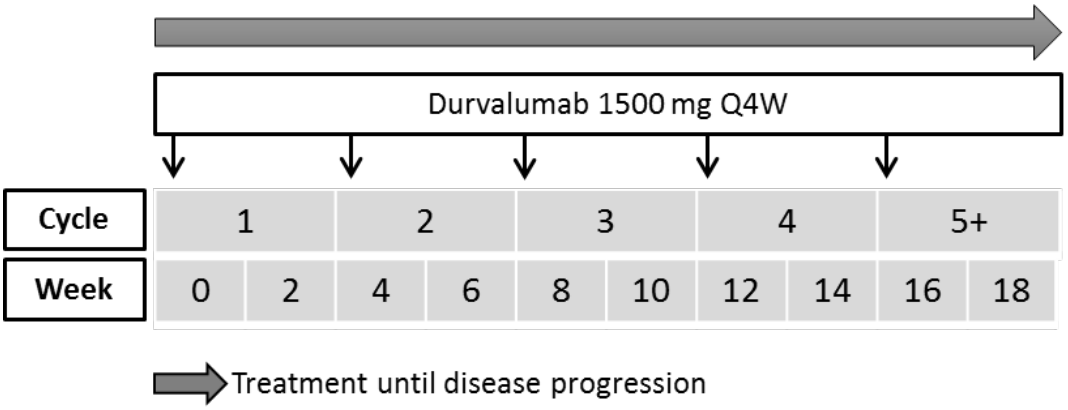
Do not co-administer other drugs through the same infusion line.

The IV line will be flushed 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 or

complete the infusion according to institutional policy to ensure the full dose is administered.
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.

Figure 1. Durvalumab Dosing Schedule



7.4 Dose-limiting toxicities (DLTs)

A DLT is defined as the occurrence of an adverse event (AE) that is at least possibly related to the investigational product (IP) or investigational regimen (IR), with two exceptions: any grade of vitiligo or alopecia will not qualify as a DLT. AEs that are at least possibly related to durvalumab- and/or tremelimumab-containing regimens shall be assessed as DLTs if they meet any of the following criteria:

Hematologic toxicity:
- Grade ≥3 neutropenia complicated by fever >38.3°C
- Grade 4 neutropenia (lasting more than 7 days)
- Grade ≥3 thrombocytopenia with significant bleeding
- Grade 4 thrombocytopenia (regardless of duration)
- Grade 4 anemia (regardless of duration)

Non-hematologic toxicity:
- Any Grade 4 non-immune-mediated AE
- Any Grade 4 immune-mediated AE, excluding endocrinopathies
- Any Grade 3 non-immune mediated AE that does not resolve to ≤Grade 1 or baseline within 30 days with optimal medical management
- Any Grade 3 immune-mediated AE – excluding diarrhea/colitis, pneumonitis, hepatitis, rash, neurotoxicity, myocarditis, myositis/polymyositis, endocrinopathies and nephritis – that does not resolve to ≤Grade 1 or baseline within 30 days after onset of the event despite optimal medical management including systemic corticosteroids

- Grade 3 diarrhea or colitis that does not resolve to ≤Grade 1 within 14 days [*both* immune- *and* non-immune-mediated indicated here; the same is the case if not specified in remaining bullet points below]
- Grade 3 non-infectious pneumonitis
- Grade 2 noninfectious pneumonitis that does not resolve to ≤Grade 1 within 3 days of the initiation of maximal supportive care
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3×ULN with concurrent increase in total bilirubin (TBL) ≥2×ULN without evidence of cholestasis or alternative explanations (e.g., viral hepatitis, disease progression in the liver; i.e., “Hy’s Law”)
- ALT or AST >8×ULN or TBL>5×ULN
- Grade 3 immune-mediated rash that does not resolve to ≤Grade 1 or baseline within 30 days
- Grade 2 rash covering > 30% BSA that does not resolve to ≤Grade 1 or baseline within 30 days
- Any grade of immune-mediated rash with bullous formation
- Grade 3 immune-mediated neurotoxicity (excluding Guillain-Barre and myasthenia gravis) that does not resolve to ≤Grade 1 within 30 days
- Grade 2 or 3 immune-mediated peripheral neuromotor syndrome (such as Guillain-Barre and myasthenia gravis) that does not resolve to ≤Grade 1 within 30 days or that exhibits signs of respiratory insufficiency or autonomic instability
- Grade 3 immune-mediated myocarditis
- Any symptomatic immune-mediated myocarditis that does not become asymptomatic within 3 days of initiating optimal medical management including systemic corticosteroids
- Grade 2 or 3 immune-mediated myositis/polymyositis that does not resolve to Grade ≤1 within 30 days of initiating optimal medical management including systemic corticosteroids or that exhibits signs of respiratory insufficiency regardless of optimal medical management
- Immune-mediated increase in creatinine >3×ULN, or >3×baseline for patients with a baseline creatinine elevated above ULN

The period for evaluating DLTs will be from the time of first administration of durvalumab until the complete resolution of the treatment-related toxicity.

7.4.1 Management of toxicity

The following general guidance should be followed for management of toxicities:

1. Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
2. If the symptoms promptly resolve with supportive care, consideration should be given to continuing study drug along with appropriate continuing

supportive care. If medically appropriate, dose modifications are permitted (see below).
3. All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which study drug should be permanently discontinued (see Appendix 3). Following the first infusion of study drug, subsequent administration of study drug can be modified based on toxicities observed as described in Appendix 3. All toxicities will be graded according to NCI CTCAE Version 5.0.
Dose reductions are not permitted for durvalumab.
Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in the Toxicity Management Guidelines (TMGs) (see Appendix 3).

Dose modifications will not be required for AEs that are clearly not attributed to study drug (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant. Dosing may continue despite concurrent vitiligo of any AE grade. Based on the mechanism of action of Durvalumab leading to T cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab and nivolumab including immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies (Brahmer et al 2010, Hodi et al 2010). Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate aetiology (eg, infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

- Management of irAEs may require administration of immunosuppressive medications (and/or hormone replacement therapy for endocrinopathies). Resolution of irAEs managed in this manner in the timeframes specified is acceptable.
- Pneumonitis may be immune-related or as a result of late toxicity to radiotherapy. Either way study drug modifications detailed in this table should be followed.

AE Adverse event; irAE Immune-related adverse event; ULN Upper limit of normal.

7.4.2 Infusion-related reaction

In the event of a ≤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 ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (eg, 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. As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

7.4.3 Pneumonitis

Pneumonitis has been reported in association with use of anti-PD-L1/anti-PD-1 antibodies (Brahmer et al 2012). It is also seen in 5% to 15% of patients irradiated for breast, lung, and mediastinal tumours. The risk of developing radiation pneumonitis is directly related to the volume of irradiated lung, the amount of radiation given, and the use of concurrent chemotherapy. Additional risk factors include co-morbid lung disease, poor baseline pulmonary function testing, and low performance status. Symptoms of radiation pneumonitis, including low-grade fever, congestion, dry cough, pleuritic chest pain, and a sensation of chest fullness, usually develop 1 to 3 months after completion of radiation therapy. Diagnosis is difficult, often complicated by co-morbid conditions and radiation injury to adjacent structures (eg, oesophagus, pericardium). Prednisone, in dosages of at least 50 to 60 mg per day for 1 week followed by an extended taper, has been shown to abate symptoms and improve lung function. Bronchodilators and supplemental oxygen may be necessary.

7.4.4 Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 use (Brahmer et al 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of monoclonal antibodies can be caused by various mechanisms, including acute

anaphylactic (IgE-mediated) and anaphylactoid reactions against the monoclonal antibody, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnoea, cyanosis, respiratory failure, urticaria, pruritis, angioedema, hypotonia, urticaria, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

7.4.5 Hepatic Function Abnormalities (Hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1 (Brahmer et al 2012). Inflammatory hepatitis has been reported in 3% to 9% of patients treated with anti-CTLA-4 monoclonal antibodies (eg, ipilimumab). The clinical manifestations of ipilimumab-treated patients included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin. Cases where a patient shows AST or ALT ≥3 x ULN or total bilirubin ≥2 x ULN may need to be reported as SAEs.

7.5 Administration, dose delay, reduction or interruption for Regorafenib

Regorafenib tablets should be taken as follows:

- Once a day, approximately at the same time every day (the recommendation is to have at least a 20 hour interval between doses).
- With approximately 240 mL (8 fluid ounces) of water, after a light meal that contains less than 30% fat. Some examples of low-fat meals are:
    - Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces (240 mL) of skim milk (approximately 319 calories and 8.2 g of fat).
    - One cup of cereal (i.e. Special K), 8 ounces (240 mL) of skim milk, one piece of toast with jam (no butter or marmalade), apple juice and one cup of coffee or tea (2 g fat, 17 g protein, 93 g of carbohydrate, 520 calories).
- Tablets must not be chewed
- If a dose of regorafenib is missed, the missed dose should be skipped (vomited tablets cannot be made up), and the next dose should be taken at the regular time. The subsequent dose of regorafenib should not be doubled. The Investigator should be informed if the dose of regorafenib taken exceeded the scheduled dose.

7.5.1 Regorafenib Dose Levels

Dose Level	Daily Dose	Daily Dose	Daily Dose
Dose level patient is currently receiving	90 mg	60 mg	30 mg
Dose level -1	60 mg	30 mg	Not permitted*
Dose level -2	30 mg	Not permitted*	Not permitted*
* If a dose reduction is required to manage a regorafenib-related AE, then regorafenib must be discontinued.			

Recommended dose modification for toxicities except hand-foot-skin reaction, 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 ≤ 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(Grade 3) recurs, institute permanent dose reduction.
Grade 4	Delay until ≤ 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 should be permanently discontinued unless subject is deriving clinical benefit.

If greater than 2 dose level reductions are required, regorafenib will be discontinued and the rest of the study follow up may be continued. The following tables outline dose adjustments for toxicities related to regorafenib except hand-foot skin reaction, hypertension and liver function test abnormalities.

The table above outlines dose adjustments for hematologic and non-hematologic toxicities related to regorafenib except PPES and hypertension. 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.

Regorafenib Dose Modification Guidance, Non-Immune Toxicities: Hand-Foot Skin Reaction Related to Regorafenib Only

CTCAE v5.0 Grade	Occurrence	Recommended Management
G1	Any	• Maintain dose level and immediately institute supportive measures for symptomatic relief.
G2	1st occurrence	• Consider decreasing dose by 1 dose level and immediately institute supportive measures. • If no improvement, interrupt therapy for a minimum of 7 days, until toxicity resolves to G0-1.[a, b]
	No improvement within 7 days or 2nd occurrence	• Interrupt therapy until toxicity resolves to G0-1.[b] • When resuming treatment, treat at reduced dose level.[a]
	3rd occurrence	• Interrupt therapy until toxicity resolves to G0-1.[b] • When resuming treatment, decrease dose by 1 dose level.
	4th occurrence	• Discontinue permanently.
G3	1st occurrence	• Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to G0-1. • When resuming treatment, decrease dose by 1 dose level.
	2nd occurrence	• Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to G0-1. • When resuming treatment, decrease dose by 1 additional dose level.
	3rd occurrence	Discontinue permanently.

Abbreviations: CTCAE=common terminology criteria for adverse events; G=Grade
If reductions are required resulting in a daily dose of less than 30 mg of regorafenib, regorafenib will be permanently discontinued.
Footnotes:

a) If toxicity returns to G0-1 after dose reduction, dose re-escalation is not permitted.
b) If there is no recovery after a 4-week delay (28 days) (including the 1 week drug holiday), treatment with regorafenib will be discontinued permanently.

Regorafenib Dose Modification Guidance, Non-Immune Toxicities: Hypertension

CTCAE v5.0 Grade	Suggested regorafenib dose modification
Specific guidance for Hypertension	
G1	• No change. Consider increased BP monitoring.
G2	• If symptomatic, hold until symptoms resolve. At restart, continue at the same dose level.
G3	• Hold until diastolic BP < 100 mm Hg, and if symptomatic, until symptoms resolve. At restart, continue at the same dose level. • If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level. • If G3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level.
G4	• Discontinue permanently.
Abbreviations: BP=blood pressure; CTCAE=common terminology criteria for adverse events; G=Grade; Hg=mercury If reductions are required resulting in a daily dose of less than 30 mg of regorafenib, regorafenib will be permanently discontinued. If BP remains controlled for at least one full cycle, dose re-escalation is permitted at the Investigator's discretion. Patients requiring a delay of > 4 weeks (28 days) (including the 1 week drug holiday) should discontinue regorafenib treatment. However, continuation of regorafenib may be considered if, in the Investigator's opinion, the patient may continue to benefit from the regorafenib treatment, and after consultation with the Medical Monitor.	

Regorafenib Dose Modification Guidance, Non-Immune Toxicities: Liver Function Test Abnormalities[a]

Increases in AST/ALT and/or bilirubin	1st occurrence	Restart	Recurrence
AST and/or ALT ≤ to 5 x ULN, with normal AST and/or ALT at baseline	**Continue dosing**, with weekly monitoring of liver function until transaminases return to < 3 x ULN (< or equal to G1) or baseline.		
AST and/or ALT > 5 x ULN	**Interrupt dosing**, with weekly monitoring of liver function until transaminases return to < 3 x ULN or baseline.	If the potential to reinitiate regorafenib is considered to outweigh the risk of hepatotoxicity: reduce 1 dose level and measures serum transaminases weekly for at least 4 weeks.	Discontinue permanently
AST and/or ALT > 20 x ULN	**Discontinue permanently** and measure serum transaminases weekly until resolution.		

AST and/or ALT > 3 x ULN with concurrent total bilirubin > 2 x ULN	**Discontinue permanently** and measure serum transaminases weekly until resolution. **Exception:** participants with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.		
Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal; G=Grade If reductions are required resulting in a daily dose of less than 30 mg of regorafenib, regorafenib will be permanently discontinued. Footnote: a) If all values remain stable for 2 full cycles, dose re-escalation may be considered at the discretion of the Investigator. After re-escalation AST, ALT, bilirubin should be checked 2×/week for 2 weeks, followed by weekly assessments for at least 4 weeks.			

7.6 Method of Assigning Patients to Treatment Groups

Randomization, according to a 1:1 ratio, will be performed using centre as stratification variable.

7.6.1 Method of collection of Patients Data

Data collection will be granted electronically through the internet (remote data entry, RDE) to data managers and clinical investigators at each clinical site using a safe internet based procedure, providing the best and most secure on line data entry process and a daily backup of all collected data. RDE will be done via connection only after the identification via individual user name and password.

For each clinical site, individual user names and passwords will be granted to the principal investigator and to qualified delegated staff members by GISCAD upon reception of a delegation log form dated and signed by all the staff members involved in the trial and the documentation of the affirmative decision of the IEC that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set by the IEC, the institution, GCP, and the applicable regulatory requirements (ICH E6).

7.7 Prior and Concomitant Therapies

All relevant medications administered within 4 weeks prior to the randomization visit are to be recorded as prior medications; medications administered from the time of signing the ICF are to be recorded as concomitant medications. Both prior and concomitant medications are to be documented in the eCRF.

7.8 Prohibited Therapies

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])
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	Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs. • Use in patients with contrast allergies. • Use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

Patients in any arm who take prohibited medications will be considered protocol violators and thus excluded from the present study.

7.9 Treatment Compliance

The details of each administration of study treatment will be documented in the eCRF.

8 STUDY VISITS AND PROCEDURES

The timing of all assessments and procedures is detailed in Section 8.1; details of procedures and assessments to be done are provided in Section 8.2; Schedules of Events for pre-randomization, treatment periods and long term follow-up are provided in Table 1, Table 2 and Table 3.

Any procedures other than those indicated will be considered SoC of the facility, and not part of the study. Data from any CEA/CA 19-9 analyses or CT scans done as part of SoC procedures should be collected and recorded in the eCRF.

For all treatment arms

Tumor efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of randomization (not the date of therapy).

All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc. required for dosing should be performed within 3 days prior to dosing.

For durvalumab + regorafenib combination arms

Patients may delay dosing under certain circumstances.

- Dosing may be delayed per Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible
- Dosing_intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST). Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-lives of durvalumab (see current Investigator Brochure for durvalumab).

Standard of Care Arm:

Patients may delay and subsequently resume dosing per local standard clinical practice.

If dosing must be delayed for reasons other than treatment-related toxicity, dosing will occur as soon as feasible.

8.1 Study Visits

8.1.1 Screening

Screening, to verify inclusion and exclusion criteria, will include:

1. obtaining written informed consent from patient or legally authorised representative (Section 8.2.1.1)
2. Review of eligibility criteria
3. documentation of demographics and medical history (Section 8.2.1.2)
4. Complete physical examination (Section 8.2.2.1)
5. vital signs (Section 8.2.2.2)
6. ECOG performance status (Section 8.2.2.3)
7. 12-lead electrocardiogram (ECG; Section 8.2.2.4)
8. clinical chemistry, coagulation profile and haematology (Section 8.2.2.45)
9. CEA and CA 19-9 analysis, backup plasma sample (Section 8.2.3.2)
10. pregnancy test (serum or urine) for female patients of child-bearing potential (Section 8.2.1.3); patients with positive results will be discontinued from the study with no further study procedures performed
11. CT/MRI/PET scan of chest and abdomen with tumor measurement and evaluation by RECIST 1.1 criteria (Section 8.2.3.3)
12. documentation of prior and concomitant medications (Section 7.7)
13. Histological confirmation

Patients who meet the inclusion/exclusion criteria (Section 6) will be randomized to one of the following:

1. Treatment arm (Regorafenib + Durvalumab)
2. Control arm

8.1.2 Treatment Phase: Table 2 and 3.

Patients allocated to regorafenib + durvalumab arm will undergo visits every week for the first cycle, every 2 weeks for the second cycle, and monthly thereafter.

Patients allocated to the control group will undergo visits every 12 weeks.

If at any time a relapse is confirmed, the patient will discontinue treatment. Patients in the control arm will be offered to crossover to regorafenib plus durvalumab.

All visits have a window of ± 7 days.

- Patients allocated to Treatment arms will undergo the following procedures and assessments:

  At each visit:

1. Limited physical examination
2. vital signs
3. ECOG performance status
4. Weight
5. Clinical chemistry and haematology (CBC + differential platelet count; creatinine; total bilirubin; AST; ALT; alkaline phosphatase; LDH; albumin; glucose; potassium; sodium; calcium)
6. administration of therapy (regorafenib plus durvalumab at Day 1 of every cycle)
7. documentation of AEs/SAEs
8. documentation of concomitant medications and procedures (at Day 1 of every cycle)
9. CEA and CA19-9 analysis and CT/MRI/PET scan as per baseline assessment: every 12 weeks. From day 1 (± 7 days).

- Patients allocated to no further treatment (Control Group) will undergo the following procedures and assessments:

  at each visit (every 12 weeks.)

  1. physical examination
  2. vital signs
  3. ECOG performance status
  4. Weight
  5. pregnancy test (serum or urine) for female patients of child-bearing potential
  6. Clinical chemistry and haematology (CBC + differential platelet count; creatinine; total bilirubin; AST; ALT; alkaline phosphatase; LDH; albumin; glucose; potassium; sodium; calcium)
  7. documentation of AEs/SAEs
  8. documentation of concomitant medications and procedures
  9. CEA and CA 19-9 analysis
  10. CT/MRI/PET scan as per baseline assessment

8.1.3 End of treatment

End of treatment is defined as the last planned dosing visit within the 12-month dosing period. For patients who discontinue durvalumab prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ±7 days of the end of

treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

Assessments for patients who have completed the treatment and achieved disease control, or have discontinued durvalumab due to toxicity in the absence of confirmed progressive disease:

1. Prior/concomitant medications
2. Complete physical examination
3. Vital signs
4. ECOG performance status
5. 12 - lead ECG
6. Tumor imaging/response assessment
7. Clinical chemistry and haematology (CBC + differential platelet count; creatinine; total bilirubin; AST; ALT; alkaline phosphatase; LDH; albumin; glucose; potassium; sodium; calcium)
8. Documentation of AEs/SAEs

8.1.4 Follow-up

During the early follow-up phase (Month 13-Month 24, Table 2 and 3) all patients will undergo the following visits every 3 months.

During the late follow-up phase (Month 25 to Month 60) all patients will undergo the following visits every 4-6 months.

1. Safety assessments
2. Physical examination
3. Vital signs
4. Eastern Cooperative Oncology Group [ECOG] performance status
5. CT/MRI/PET scan as per Investigator's choice
6. CEA and CA 19-9 analysis
7. Clinical chemistry and haematology (CBC + differential platelet count; creatinine; total bilirubin; AST; ALT; alkaline phosphatase; LDH; albumin; glucose; potassium; sodium; calcium; amylase; lipase)
8. Concomitant medications
9. For patients with documented relapse: visit (according to SoC) or telephone contact to document OS.

8.2 Study Procedures

All study related investigations are to be performed by the Investigator or medically qualified study personnel delegated by the Investigator. The Investigator is considered responsible for the overall treatment of the patient.

All procedures will be carried out at the times indicated in Table 1, Table 2, and Table 3 and in Section 8.1.

8.2.1 Enrolment Procedures

8.2.1.1 Informed consent

Before inclusion into the study, each patient will be informed, both verbally and in writing, about the nature of the study, the anticipated risks and discomfort associated with the study and also about the right to discontinue participation in the study at any time.

Prior to participation in the study, each patient will have signed the written ICF which has been approved by the Independent Ethics Committee (IEC).

No study activities may take place until the informed consent documents have been signed.

8.2.1.2 Demographics and medical history

All relevant hospital records are to be made available to the Investigator prior to randomization. Medical history includes details of: any neoadjuvant or adjuvant chemotherapy; surgical or other procedure; tissue samples and documentation relating to tumour assessment; and prior antitumoral drugs.

8.2.1.3 Pregnancy test

A serum or urine pregnancy test will be administered to all female patients of childbearing potential, defined as follows:

- Premenopausal women capable of becoming pregnant, including women on oral, injectable or mechanical contraception.

If the result of the pregnancy test is positive, the patient will be withdrawn from the study prior to administration of study treatment.

Female patients who become pregnant during the study or within 6 months after receiving the last administration of study treatment will be followed through birth or termination of the pregnancy. The Investigator or designee must report all pregnancies to the Study Contact for Reporting Serious Adverse Events (Section 9.2) immediately after becoming aware of the event.

8.2.2 Safety Assessments

8.2.2.1 Physical examination

Physical examinations will include height (at screening), weight, and a general assessment of overall body systems (cardiovascular, respiratory, gastrointestinal, etc.).

8.2.2.2 Vital signs

Assessment of vital signs includes systolic and diastolic blood pressure, heart rate, body temperature and respiratory rate. Body temperature should be measured using the same methodology at each assessment and it should be measured in decimals.

8.2.2.3 Eastern Cooperative Oncology Group performance status

The ECOG performance status is a standardised set of scales and criteria used to assess how a patient's disease is progressing, how the disease affects the daily living abilities of the patient and to determine appropriate treatment and prognosis. The assessment is provided in Appendix 1.

8.2.2.4 Electrocardiogram

Perform a 12-lead resting electrocardiogram (ECG) before the begin of the treatment, at the end-of-treatment and if clinically indicated. Patients should be in a supine position for at least 10 min before recording. ECG tracings will be reviewed by a qualified physician for assessment of QT interval as well as signs of qualitative abnormalities, including evaluation of rhythm, ST segment morphology, T wave morphology, and presence/absence of U wave.

The original ECG tracing will be maintained in the source documentation of each patient.

8.2.2.5 Clinical chemistry, coagulation and hematology

The Investigator must review the laboratory assessments (initialled and dated) within 24 hours after the receipt of results. Out of range values will be interpreted by the Investigator with a comment of “not clinically significant” (NCS) or “clinically significant” (CS). Clinically significant abnormal laboratory values must be repeated at the appropriate clinical follow-up arranged by the Investigator and documented on the lab report until the lab value has stabilised or has returned to a clinically acceptable range (regardless of relationship to study treatment). Any laboratory value that remains abnormal and is judged to be clinically significant will be followed according to accepted medical standards for 30 days or until resolution of the abnormality.

Procedure does not have to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (i.e. first day of dosing).

All haematology, coagulation and blood chemistry samples will be processed at the local laboratory according to institutional procedures. Blood samples will be collected for the following analyses:

Chemistry

- albumin
- total bilirubin
- alkaline phosphatase (ALP)
- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- LDH
- glucose
- sodium
- potassium
- chloride
- magnesium
- urea
- calcium
- creatinine
- total protein
- amylase
- lipase

Coagulation Profile

- aPTT
- PT
- INR

Haematology profile (complete blood count [CBC])

- red blood cell (RBC) count
- white blood cell (WBC) count and differential (neutrophils, eosinophils, limphocytes, monocytes, basophils)
- haemoglobin (Hgb)
- haematocrit (Hct)
- platelet count

A Plasma sample will be stored for potential future research for which specific experimental plan and informed consent form will be developed

8.2.2.6 Adverse events (AEs)

After informed consent is obtained, AEs will be recorded continuously through the study conduct, and managed as outlined in Section 9 and according to the Safety Management Plan developed for this study. Events that occur prior to initiation of study treatment will be assessed as “not related” to study medication; AEs that occur after the first administration of study medication will be assessed as treatment-emergent AEs (TEAEs).

Adverse events will be categorised based on severity; relationship to study treatment and seriousness and according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

8.2.3 Efficacy Assessments

8.2.3.1 Relapse

Any of the following events will be considered as relapse: loco-regional recurrence (as defined in Section 3.3.1), distant metastases, death from same cancer or death from other cancer, non-cancer-related death, and treatment-related death.

A positive CT/MRI/PET scan (appearance of a lesion) will be considered evidence of relapse. Two consecutive increases in CEA levels above upper limit level (time gap decided by the clinical investigator).

Confirmation of progression guidelines are set for the following reasons:

- for patient management and treatment decisions
- in the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiologic progression, also known as RECIST 1.1 modified for confirmation of progression
- when scans are evaluated by Investigator and by BICR, to reduce informative censoring by Investigator assessments (Investigator assesses PD at a time-point earlier than does BICR).

Confirmed objective disease progression refers to either of the following scenarios: 1. clinical progression/deterioration followed by a radiologic verification scan (PD by RECIST 1.1); or 2. in the absence of significant clinical deterioration, radiologic PD by RECIST 1.1 followed by a second radiologic confirmation scan with PD assessed according to the specific confirmation of progression criteria listed below. RECIST 1.1 modified for confirmation of progression refers to the second scenario above. The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of RECIST 1.1 PD.

Immediate prior radiologic progression would be considered confirmed if any the following criteria are met in the confirmatory scan:

- ≥20% increase in the sum diameters of target lesions (TLs) compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir,
- and/or significant progression (worsening) of non-target lesions (NTLs) and/or of pre-existing new lesions at the confirmatory scan time-point

compared with the immediate prior time-point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point),

- and/or additional new unequivocal lesions at the confirmatory scan time-point.

NOTE: In order to have confirmed objective disease progression, there should be two consecutive assessments meeting the PD definition: the first PD by RECIST 1.1 and the second PD using the confirmation of progression criteria (above). If the first assessment fulfilling the PD definition by RECIST 1.1 is not confirmed, continue with assessments until the next PD by RECIST 1.1, which in turn will need its own immediate subsequent confirmation scan. In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression.

If the confirmation scan confirms progression, then the date of the prior scan with PD should be declared as the date of progression.

If progression is not confirmed, in the absence of significant clinical deterioration, then the patient should continue study drug and on-treatment assessments until the next PD which will also require a follow-up confirmation scan. If the first PD is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, then the patient should still continue to be followed until confirmed objective disease progression.

8.2.3.2 Carcinoembryonic antigen and CA 19-9

Blood will be collected for assessment of CEA and CA 19-9 as markers of potential relapse of CRC. Samples will be analysed at the local laboratory.

Data from CEA and CA 19-9 analyses done at any times other than those specified for this study, i.e., done as part of SoC of the facility, will be collected for the eCRF.

8.2.3.3 Computed tomography and magnetic resonance imaging

CT/MRI/PET scans will be done to detect relapse, as specified by the objectives and endpoints of the study, and to confirm a diagnosis of relapse at any time during the study (Section 3.3.1).

While scans will be done as per SoC of the facility, minimal standards for CT/MRI/PET procedures will be provided. Data from CT/MRI/PET scans done at any times other than those specified for this study, i.e., done as part of SoC of the facility, will be collected for the eCRF.

8.3 Appropriateness of Measurements

All measurements will be carried out according to standard methodologies and to ensure patient safety. The methods used in this study are commonly regarded as reliable and valid, and relevant to the indication. The design of this study is a design for the assessment of efficacy, safety, and tolerability in a Phase IIb study, including use of the ECOG Performance Scale. CT/MRI/PET scans and CEA/CA 19-9 have been included for the purposes of this study and the timing is that patients would be undergoing CT/MRI/PET scans and CEA/CA 19-9 as part of SoC treatment and follow-up of NED CRC patients.

9 ADVERSE EVENT ASSESSMENTS

The criteria outlined in this section will be used to evaluate each patient before, during, and after treatment to determine the safety associated with the patient's treatment and study procedures. The safety of the investigational treatments will be assessed by evaluating the nature and frequency of Adverse Events (AEs). Details of the management of Serious Adverse Events (SAEs) will be further documented in the Safety Management Plan developed for this study.

Clinical laboratory tests

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Other safety assessments

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix 1) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters, etc.) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.
The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

9.1 Definitions

9.1.1 Adverse Events (AEs)

According to the International Conference of Harmonization (ICH), an AE is any untoward medical occurrence in a clinical investigation subject (patient) administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the investigational product. Pre-existing conditions which worsen during a study are to be considered as AEs.

An AE that occurs after signing informed consent but prior to the first administration of study treatment will be considered not related to study treatment.

9.1.2 Definition of adverse events 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 regards to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- Hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, 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
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Intestinal Perforations

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

- Pericarditis
- 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 aetiology are also considered AESIs.

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 (please see 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.

9.1.3 Serious Adverse Event (SAEs)

A SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfils at least one of the following criteria:

- ✓ is fatal (results in death)[1] ;
- ✓ is Life-Threatening[2] ;
- ✓ required in-patient hospitalization or prolongation of existing hospitalization;
- ✓ results in persistent or significant disability/incapacity;
- ✓ is a congenital anomaly/birth defect;
- ✓ is medically significant or requires intervention to prevent one or other of the outcomes listed above. Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

Adverse Events (AEs) for malignant tumours 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 tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression

[1] Death is an outcome, not an event. The term sudden death should be used only when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably.

[2] the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death if had it been more severe

occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill 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 tumours, 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.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (i.e., it is not the tumour 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 tumour under study). Malignant tumours 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 tumour.

Hospitalisation will **not be considered a SAE** for the following cases:

- hospitalisation or prolongation of hospitalisation for a procedure required by the study Protocol
- hospitalisation or prolongation of hospitalisation is part of a routine procedure followed by the study site
- hospitalisations or prolongation of hospitalisation due to merely diagnostic reasons, planned surgery, planned chemotherapy.

Merely the introduction of a patient in the emergency room does not fulfil the criteria “hospitalisation” without subsequent admission.

Medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that are not immediately life-threatening or do not result in death or hospitalisation.

9.1.4 Adverse Drug Reaction (ADR)

All AE related to the medicinal (investigational) product at any dose should be an ADR.

An ADR, the nature or severity of which is not consistent with the applicable product information is an Unexpected adverse drug reaction.

9.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

When an SAE is recognized as unexpected and its correlation with the investigational product cannot reasonably be excluded, it is classified as Suspected Unexpected Serious Adverse Reaction (SUSAR).

9.1.6 Classification of AEs

ALL AE will be classified on the basis of its intensity and relatedness to study treatments. The relationship between an AE and the study treatments will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions:

9.1.6.1 Intensity

Intensity of all AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events v 5.0 (CTCAE v 5.0; most recent sub-version), on a five-point scale (Grade 1 to 5) and reported in detail on the CRF.

AEs not listed on the CTCAE should be graded as follows:

Table 6. Grading of AEs not listed on the CTCAE

CTC Grade Equivalent to:	
Grade 1 (Mild)	Mild Discomfort noticed but no disruption of normal daily activity
Grade 2 (Moderate)	Moderate Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
Grade 3 (Severe)	Severe Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall wellbeing or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk
Grade 4 (Life threatening)	Life threatening/disabling. An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival
Grade 5 (Death)	AE resulting in death

9.1.7 Trial Relationship to Study Drug

The investigator will evaluate the relationship of the adverse events to the study product based on the following definitions:

Table 7. AEs Relatedness to the study chemotherapy

Definite/Certain (yes)	are terms applied to an adverse events which have a timely relationship to the study drug and no alternative etiology is present. The adverse event must have occurred within a reasonable temporal sequence of the chemotherapy administration, must not be reasonably explained, and must follow a known pattern of response
Probable (yes)	means that the adverse event has a timely relation to the study drug and a potential alternative etiology is not apparent (i.e., fever or malaise when no other symptoms suggestive of an illness are present)
Possible (yes)	means that the adverse event has a timely relation to the study drug; however, a potential alternative etiology exists, which may be responsible for the symptom (i.e., fever or malaise when other symptoms are present that suggest another etiology such as upper respiratory infection)
Unrelated/Unlikely (No)	means that the adverse event is applied to those adverse events for which evidence exists that the symptom is definitely related to an etiology other than the study drug (i.e., car accident, or a symptom suggestive of another illness that is not accepted to have a possible relatedness to chemotherapy).

9.1.8 Follow-up of Adverse Event

The Investigator must continue to monitor the following events until they resolve or until the Investigator assesses them as chronic or stable: 1) all SAEs; 2) any non-serious events assessed as possibly, probably, or definitely related to the study treatment; and 3) any SAEs or AEs that lead to study withdrawal. This follow up will be extended through the end of the study.

9.1.9 Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the CRF.

9.2 Reporting of Adverse Events

AEs: At each study visit the Investigator, will determine whether any AEs have occurred. Any AEs will be reported in the patient's medical record and on the AE eCRF page and each will be classified according to the criteria above. Adverse event reporting for each patient starts when the patient signs the Informed Consent

Form (ICF). Any pre-existing conditions that are detected as part of the initial pre-randomization procedures will need to be reported in the medical history and not as an AE. However, pre-existing conditions that worsen after enrolment should be reported as an AE.

SAEs: AEs and SAEs will be collected from the time of the patient signing the informed consent form until the follow-up period is completed (90 days after the last dose of durvalumab). If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

During the course of the study, all AEs and SAEs should be proactively followed up for each patient for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient has discontinued study drug or the study has completed.

The Sponsor retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

9.3 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix 1 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

9.4 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.

9.5 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page of eCRF.
- The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF.

- A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to Sponsor Safety Desk

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be reported as SAE term. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term “sudden death” should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death later becomes available (e.g. after autopsy), “sudden death” should be replaced by the established cause of death.

9.6 Reporting of serious adverse events to Sponsor

To ensure patient safety, all SAEs, regardless of suspected causality, occurring from the time of enrolment must be immediately reported to Sponsor, and always within 24 hours of learning of its occurrence.

All identified SAEs must be recorded and described on the appropriate SAE form of the eCRF. All forms must be dated and signed by the responsible investigator or sub-investigator and sent by email or fax within 24 hours of the initial observation of the event to the Sponsor safety desk:

Laboratory of Methodology for Clinical Research

Istituto di Ricerche Farmacologiche Mario Negri IRCCS

Study Safety Desk

Email: safetydesk.rc@marionegri.it

Fax: + 39 02 3571800

Any new or additional significant information regarding an SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information.

New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- A new serious criterion met or worsening of severity
- Significant new diagnostic test results

- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Once an SAE is detected, it should be followed until its resolution or until it is judged to be permanent. Follow-up information is sent to the same contact(s) to whom the initial SAE report form was sent, accessing the original SAE report form and completing the section dedicated to follow-up reporting.

The repetition of the same SAE after its resolution should be reported as a second separate event.

9.7 Other events requiring reporting

9.7.1 Overdose

An overdose is defined as a patient receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study patient with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose.

9.7.2 Hepatic function abnormality

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 criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study patient will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient must be interrupted immediately. Follow-up

investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor.

9.7.3 Reporting of SUSARs to the Competent Authorities / Independent Ethics Committees

All SUSAR will be notified by Sponsor or its delegated to Competent Authority, investigators and Ethics Committees in the manner and time provided by law.

In accordance with Community Legislation, Regulation 726/2004 and Directive 2001/83/EC (and subsequent amendments) and Agenzia Italiana del Farmaco (AIFA) determination 20/09/2012:*"Adozione delle linee guida CT-3 (giugno 2011 della C.E. di attuazione della Direttiva 2001/20/CE, delle linee guida ICH E2F (settembre 2011)",* all SUSAR will be sent electronically to EudraVigilance by the Sponsor or designee. Competent Authority (AIFA) will be aware of the SUSAR through EudraVigilance.

9.7.4 Immediate Reactogenicity

Immediate reactions occurring within the first 15 minutes after administration of the study drug and treatment of the reactions will be reported in the patient's medical record and on the treatment eCRF page (i.e., hives, difficulty breathing, anaphylaxis and other severe reactions) and observations and treatment recorded. Reactions fulfilling the criteria for a SAE should be reported as such.

9.7.5 Relapse of Underlying Malignancy

Loco-regional and distant metastasis of the underlying malignancy and death from same malignancy (see RFS definition, Table 4) are not reported as AE/SAEs.

Second primary, other cancer; death from other cancer; non-cancer-related death; treatment-related death are reported as AE/SAEs.

9.7.6 Laboratory Test abnormalities

Laboratory test results will be recorded on the laboratory results form of the eCRF.

Any laboratory result abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE page in the eCRF:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

This applies to any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after the first dose of study medication, which falls outside the laboratory reference range and meets the clinical significance criteria.

9.7.6.1 Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the CRF.

9.8 Pregnancy

A female patient must immediately inform the investigator and must stop taking study product if she becomes pregnant during the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the sponsor within 1 day, i.e., immediately, but no later than 24 hours of when he or she becomes aware of it.

The sponsor will work with the Investigator to ensure that all relevant information is provided within 1 to 5 calendar days.

The same timelines apply when outcome information is available.

The investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. **Pregnancy will not be considered an SAE.**

Pregnancies occurring up to 6 months after the completion of the study medication must also be reported to the investigator.

Pregnancy occurring in the partner of a male patient participating in the study should be reported to the investigator and the Sponsor. The partner should be counseled, the risks of continuing the pregnancy discussed, as well as the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with

local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

9.9 Review of Serious Adverse Event

The Investigator, the Data Safety Manager, and Ospedale Policlinico S. Martino IRCCS will review each SAE report and evaluate the relationship of the SAE to study treatment. Based on the assessment of the SAE, a decision will be made concerning the need for further action (e.g., report single SAEs to the IDMSC). The primary consideration governing further action is whether new findings affect the safety of patients participating in the clinical study.

Further actions that may be required includes the following:

- modification of the Protocol
- discontinuation or suspension of the study
- modification of the existing consent form and informing current study participants of new findings (Section 10.3)
- updating of the IB.

9.10 Protocol Deviations Due to an Emergency or an Adverse Event

In the case of a clinical emergency or medically important AE, significant departure from the Protocol procedures may be necessary in the judgment of the Investigator. Such Protocol deviations will be determined as allowable on a case-by-case basis. The Investigator or designee must contact the Sponsor as soon as possible to discuss the circumstances of Protocol deviation and the Sponsor will decide whether the patient should continue to participate in the study. All Protocol deviations and the reasons for such deviations must be noted in the site's regulatory documents and monitoring reports.

10 ETHICAL CONSIDERATIONS/PROTECTION OF HUMAN SUBJECTS

10.1 Independent Ethics Committee Approval

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.

This protocol and the informed consent document will be reviewed and approved by the IRB or IEC responsible for oversight of the study. Any patient materials or advertisements used during the trial also be reviewed and approved by the IEC/IRB.

The approval letter, signed by the Chair of the IEC/IRB, must specify name, location and composition of the committee, the date of the approval, the documents approved, the Investigator's name, the Protocol version, date and title.

Approval of both the protocol and the informed consent form (ICF) must be obtained before any subject is enrolled.

Any amendment to the protocol and the ICF will require review and approval by the IRB before the changes are implemented in the study except where necessary to eliminate apparent immediate hazards to participants.

10.2 Patient protection

The trial will be conducted in accordance with the latest version of the Declaration of Helsinki[67], ICH Guideline on Good Clinical Practice (ICH-GCP (E6)[68] and in accordance with the protocol and applicable European and local regulatory requirements regarding ethical committee review, informed consent, and other statutes and regulations regarding the protection of the rights and welfare participants participating in the study.

10.3 Informed consent process

Patients will sign the informed consent document prior to any study-related assessments or procedures.

Extensive discussion of risks and possible benefits of study participation will be provided to patients. The investigator or designee will explain the research study to the patients and how personal health information may be used and disclosed in research. A consent form describing in detail the study procedures and risks will be given to the patient. Patients will be given the opportunity to think about it prior to agreeing to participate and to discuss the study with their families and their family physician. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

Patients will be encouraged and will have the opportunity to have their questions answered before and after consenting to participate. They may withdraw consent at any time throughout the course of the study without giving a reason.

The consent process will be documented in the clinical or research record.

Consent forms will be provided in duplicate (the original will be kept by the investigator and a copy given to the trial participant).

10.4 Subject Confidentiality

Trial participant confidentiality will be strictly protected by the trial investigators, involved staff, the sponsor(s) and associates following the protocol. This pertains to all personal information relating to participants including clinical information and results of laboratory testing of biological samples. A unique trial participant ID number will be assigned to participant to be used through the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, the patient's ID will also be reported on all case report forms.

Identifiable information of trial participants will not be disclosed without prior written consent of the participant. However, in the case of safety and quality monitoring, the trial monitor or other authorized representatives of Ospedale Policlinico S. Martino IRCCS may access all documents and records maintained by the investigator at the trial sites.

In case of data transfer, Ospedale Policlinico S. Martino IRCCS will maintain high standards of confidentiality and protection of patient personal data.

11 ADMINISTRATIVE RESPONSIBILITIES

11.1 Trial insurance

A clinical trial insurance has been taken out according to the Italian laws. An insurance certificate will be made available to the participating sites at the time of study initiation.

12 REFERENCE LIST

[1] F. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, "GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from http://globocan.iarc.fr." 2013.

[2] Bray F, Ferlay J, Soerjomataram I, et al. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 68 (6), 394-424 Nov 2018

[3] R. Adam, D. G. Haller, G. Poston, J.-L. Raoul, J.-P. Spano, J. Tabernero, and E. Van Cutsem, "Toward optimized front-line therapeutic strategies in patients with metastatic colorectal cancer--an expert review from the International Congress on Anti-Cancer Treatment (ICACT) 2009.," *Ann. Oncol.*, vol. 21, no. 8, pp. 1579–84, Aug. 2010.

[4] R. Giacchi, M. Sebastiani, and F. Lungarotti, "[Natural history of synchronous hepatic metastases from a non-treated colorectal cancer].," *J. Chir. (Paris).*, vol. 125, no. 6–7, pp. 419–23.

[5] Lenz H, Niedzwiecki D, Innocenti F, Blanke C, Mahony MR, et al "CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (MFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients with expanded RAS analyses untreated metastatic adenocarcinoma of the colon or rectum." 2014.

[6] "LiverMetSurvey Sanofi-Aventis." [Online]. Available: http://www.livermetsurvey.org/. [Accessed: 07-Nov-2014].

[7] H. Bismuth, R. Adam, F. Lévi, C. Farabos, F. Waechter, D. Castaing, P. Majno, and L. Engerran, "Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy.," *Ann. Surg.*, vol. 224, no. 4, pp. 509–20; discussion 520–2, Oct. 1996.

[8] R. Adam, V. Delvart, G. Pascal, A. Valeanu, D. Castaing, D. Azoulay, S. Giacchetti, B. Paule, F. Kunstlinger, O. Ghémard, F. Levi, and H. Bismuth, "Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival.," *Ann. Surg.*, vol. 240, no. 4, pp. 644–57; discussion 657–8, Oct. 2004.

[9] S. R. Alberts, W. L. Horvath, W. C. Sternfeld, R. M. Goldberg, M. R. Mahoney, S. R. Dakhil, R. Levitt, K. Rowland, S. Nair, D. J. Sargent, and J. H. Donohue, "Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study.," *J. Clin. Oncol.*, vol. 23, no. 36, pp. 9243–9, Dec. 2005.

[10] C. Tournigand, T. André, E. Achille, G. Lledo, M. Flesh, D. Mery-Mignard, E. Quinaux, C. Couteau, M. Buyse, G. Ganem, B. Landi, P. Colin, C. Louvet, and A. de Gramont, "FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study.," *J. Clin. Oncol.*, vol. 22, no. 2, pp. 229–37, Jan. 2004.

[11] A. Falcone, S. Ricci, I. Brunetti, E. Pfanner, G. Allegrini, C. Barbara, L. Crinò, G. Benedetti, W. Evangelista, L. Fanchini, E. Cortesi, V. Picone, S. Vitello, S. Chiara, C. Granetto, G. Porcile, L. Fioretto, C. Orlandini, M. Andreuccetti, and G. Masi, "Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil,

leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nor," *J. Clin. Oncol.*, vol. 25, no. 13, pp. 1670–6, May 2007.

[12] A. Falcone, C. Cremolini, G. Masi, S. Lonardi, V. Zagonel, L. Salvatore, P. Trenta, G. Tomasello, M. Ronzoni, L. Ciuffreda, A. Zaniboni, G. Tonini, A. Buonadonna, C. Valsuani, S. Chiara, C. Carlomagno, C. Boni, L. Marcucci, L. Boni, and F. Loupakis, "FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group.," *ASCO Meet. Abstr.*, vol. 31, no. 15_suppl, p. 3505, May 2013.

[13] J. Souglakos, N. Androulakis, K. Syrigos, A. Polyzos, N. Ziras, A. Athanasiadis, S. Kakolyris, S. Tsousis, C. Kouroussis, L. Vamvakas, A. Kalykaki, G. Samonis, D. Mavroudis, and V. Georgoulias, "FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncolog," *Br. J. Cancer*, vol. 94, no. 6, pp. 798–805, Mar. 2006.

[14] R. Adam, J. Bridgewater, I. Chau, P. G. Alfonso, M. Rivoire, S. Lasserre, D. Waterkamp, and T. Gruenberger, "Randomised, Phase 2 Study (Olivia) Of Bevacizumab Plus Mfolfox6 or Folfoxiri in Patients With Initially Unresectable Colorectal Cancer Liver Metastases," *Ann. Oncol.*, vol. 24, no. suppl 4, pp. iv21–iv21, Jun. 2013.

[15] G. Folprecht, T. Gruenberger, W. O. Bechstein, H.-R. Raab, F. Lordick, J. T. Hartmann, H. Lang, A. Frilling, J. Stoehlmacher, J. Weitz, R. Konopke, C. Stroszczynski, T. Liersch, D. Ockert, T. Herrmann, E. Goekkurt, F. Parisi, and C.-H. Köhne, "Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial.," *Lancet. Oncol.*, vol. 11, no. 1, pp. 38–47, Jan. 2010.

[16] C. Bokemeyer, I. Bondarenko, A. Makhson, J. T. Hartmann, J. Aparicio, F. de Braud, S. Donea, H. Ludwig, G. Schuch, C. Stroh, A. H. Loos, A. Zubel, and P. Koralewski, "Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer.," *J. Clin. Oncol.*, vol. 27, no. 5, pp. 663–71, Feb. 2009.

[17] E. Van Cutsem, C.-H. Köhne, E. Hitre, J. Zaluski, C.-R. Chang Chien, A. Makhson, G. D'Haens, T. Pintér, R. Lim, G. Bodoky, J. K. Roh, G. Folprecht, P. Ruff, C. Stroh, S. Tejpar, M. Schlichting, J. Nippgen, and P. Rougier, "Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer.," *N. Engl. J. Med.*, vol. 360, no. 14, pp. 1408–17, Apr. 2009.

[18] L. B. Saltz, S. Clarke, E. Díaz-Rubio, W. Scheithauer, A. Figer, R. Wong, S. Koski, M. Lichinitser, T.-S. Yang, F. Rivera, F. Couture, F. Sirzén, and J. Cassidy, "Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study.," *J. Clin. Oncol.*, vol. 26, no. 12, pp. 2013–9, Apr. 2008.

[19] N. E. Kemeny, F. D. H. Melendez, M. Capanu, P. B. Paty, Y. Fong, L. H. Schwartz, W. R. Jarnagin, D. Patel, and M. D'Angelica, "Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma.," *J. Clin. Oncol.*, vol. 27, no. 21, pp. 3465–71, Jul. 2009.

[20] A. P. Venook, D. Niedzwiecki, H.-J. Lenz, F. Innocenti, M. R. Mahoney, B. H. O'Neil, J. E. Shaw, B. N. Polite, H. S. Hochster, J. N. Atkins, R. M. Goldberg, R. J. Mayer, R. L. Schilsky, M. M. Bertagnolli, C. D. Blanke, and S. and E. Cancer and Leukemia Group B (Alliance), "CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or re," *ASCO Meet. Abstr.*, vol. 32, no. 18_suppl, p. LBA3, Jun. 2014.
[21] et al Lam VW, Spiro C, Laurence JM, "A Systematic Review of Clinical Response and Survival Outcomes of Downsizing Systemic Chemotherapy and Rescue Liver Surgery in Patients with Initially Unresectable Colorectal Liver Metastases," *Ann Surg Oncol*, vol. 19, pp. 1292–1301, 2012.
[22] B. C. Venook A, Niedzwiecki D, B. O. Innocenti F, M Mahoney, H. H. J Shaw, B Polite, R. S. R Goldberg, R Mayer, H. L. M Bertagnolli, and 2014 SWOG, for the ALLIANCE and SWOG. ESMO, "CALGB/SWOG 80405: Patients undergoing surgery as part of treatment strategy." 2014.
[23] R. Adam, E. Avisar, A. Ariche, S. Giachetti, D. Azoulay, D. Castaing, F. Kunstlinger, F. Levi, and F. Bismuth, "Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal.," *Ann. Surg. Oncol.*, vol. 8, no. 4, pp. 347–53, May 2001.
[24] F. Grossi, "RECIST in the pocket." Elsevier Srl, Milano, 2009.
[25] G. Fiorentini, C. Aliberti, M. Tilli, L. Mulazzani, F. Graziano, P. Giordani, A. Mambrini, F. Montagnani, P. Alessandroni, V. Catalano, and P. Coschiera, "Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study.," *Anticancer Res.*, vol. 32, no. 4, pp. 1387–95, Apr. 2012.
[26] A. Hendlisz, M. Van den Eynde, M. Peeters, G. Maleux, B. Lambert, J. Vannoote, K. De Keukeleire, C. Verslype, L. Defreyne, E. Van Cutsem, P. Delatte, T. Delaunoit, N. Personeni, M. Paesmans, J.-L. Van Laethem, and P. Flamen, "Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy.," *J. Clin. Oncol.*, vol. 28, no. 23, pp. 3687–94, Aug. 2010.
[27] M. Hoyer, H. Roed, A. Traberg Hansen, L. Ohlhuis, J. Petersen, H. Nellemann, A. Kiil Berthelsen, C. Grau, S. Aage Engelholm, and H. Von der Maase, "Phase II study on stereotactic body radiotherapy of colorectal metastases.," *Acta Oncol.*, vol. 45, no. 7, pp. 823–30, Jan. 2006.
[28] T. Ruers, C. Punt, F. Van Coevorden, J. P. E. N. Pierie, I. Borel-Rinkes, J. A. Ledermann, G. Poston, W. Bechstein, M. A. Lentz, M. Mauer, E. Van Cutsem, M. P. Lutz, and B. Nordlinger, "Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004).," *Ann. Oncol.*, vol. 23, no. 10, pp. 2619–26, Oct. 2012.
[29] E. K. Abdalla, J.-N. Vauthey, L. M. Ellis, V. Ellis, R. Pollock, K. R. Broglio, K. Hess, and S. A. Curley, "Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for

colorectal liver metastases.," *Ann. Surg.*, vol. 239, no. 6, pp. 818–25; discussion 825–7, Jun. 2004.
[30] R. M. Goldberg, D. J. Sargent, R. F. Morton, E. Green, H. K. Sanoff, H. McLeod, and J. Buckner, "NCCTG Study N9741: leveraging learning from an NCI Cooperative Group phase III trial.," *Oncologist*, vol. 14, no. 10, pp. 970–8, Oct. 2009.
[31] V. Heinemann, L. F. von Weikersthal, T. Decker, A. Kiani, U. Vehling-Kaiser, S.-E. Al-Batran, T. Heintges, C. Lerchenmüller, C. Kahl, G. Seipelt, F. Kullmann, M. Stauch, W. Scheithauer, J. Hielscher, M. Scholz, S. Müller, H. Link, N. Niederle, A. Rost, H.-G. Höffkes, M. Moehler, R. U. Lindig, D. P. Modest, L. Rossius, T. Kirchner, A. Jung, and S. Stintzing, "FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial.," *Lancet Oncol.*, vol. 15, no. 10, pp. 1065–75, Jul. 2014.
[32] X. Wang, C. T. Sofocleous, J. P. Erinjeri, E. N. Petre, M. Gonen, K. G. Do, K. T. Brown, A. M. Covey, L. A. Brody, W. Alago, R. H. Thornton, N. E. Kemeny, and S. B. Solomon, "Margin size is an independent predictor of local tumor progression after ablation of colon cancer liver metastases.," *Cardiovasc. Intervent. Radiol.*, vol. 36, no. 1, pp. 166–75, Feb. 2013.
[33] S. N. Goldberg, C. J. Grassi, J. F. Cardella, J. W. Charboneau, G. D. Dodd, D. E. Dupuy, D. Gervais, A. R. Gillams, R. A. Kane, F. T. Lee, T. Livraghi, J. McGahan, D. A. Phillips, H. Rhim, and S. G. Silverman, "Image-guided tumor ablation: standardization of terminology and reporting criteria.," *J. Vasc. Interv. Radiol.*, vol. 16, no. 6, pp. 765–78, Jun. 2005.
[34] E. Tanis, B. Nordlinger, M. Mauer, H. Sorbye, F. van Coevorden, T. Gruenberger, P. M. Schlag, C. J. A. Punt, J. Ledermann, and T. J. M. Ruers, "Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983.," *Eur. J. Cancer*, vol. 50, no. 5, pp. 912–9, Mar. 2014.
[35] T. Comito, L. Cozzi, E. Clerici, M. C. Campisi, R. L. E. Liardo, P. Navarria, A. Ascolese, A. Tozzi, C. Iftode, F. De Rose, E. Villa, N. Personeni, L. Rimassa, A. Santoro, A. Fogliata, P. Mancosu, S. Tomatis, and M. Scorsetti, "Stereotactic Ablative Radiotherapy (SABR) in inoperable oligometastatic disease from colorectal cancer: a safe and effective approach.," *BMC Cancer*, vol. 14, p. 619, Jan. 2014.
[36] E. Mitry, A. L. A. Fields, H. Bleiberg, R. Labianca, G. Portier, D. Tu, D. Nitti, V. Torri, D. Elias, C. O'Callaghan, B. Langer, G. Martignoni, O. Bouché, F. Lazorthes, E. Van Cutsem, L. Bedenne, M. J. Moore, and P. Rougier, "Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials.," *J. Clin. Oncol.*, vol. 26, no. 30, pp. 4906–11, Oct. 2008.
[37] M. Ychou, W. Hohenberger, S. Thezenas, M. Navarro, J. Maurel, C. Bokemeyer, E. Shacham-Shmueli, F. Rivera, C. Kwok-Keung Choi, and A. Santoro, "A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer.," *Ann. Oncol.*, vol. 20, no. 12, pp. 1964–70, Dec. 2009.
[38] B. Nordlinger, H. Sorbye, B. Glimelius, G. J. Poston, P. M. Schlag, P. Rougier, W. O. Bechstein, J. N. Primrose, E. T. Walpole, M. Finch-Jones, D.

Jaeck, D. Mirza, R. W. Parks, L. Collette, M. Praet, U. Bethe, E. Van Cutsem, W. Scheithauer, and T. Gruenberger, “Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial.,” *Lancet*, vol. 371, no. 9617, pp. 1007–16, Mar. 2008.

[39] F. S. Hodi, S. J. O’Day, D. F. McDermott, R. W. Weber, J. A. Sosman, J. B. Haanen, R. Gonzalez, C. Robert, D. Schadendorf, J. C. Hassel, W. Akerley, A. J. M. van den Eertwegh, J. Lutzky, P. Lorigan, J. M. Vaubel, G. P. Linette, D. Hogg, C. H. Ottensmeier, C. Lebbé, C. Peschel, I. Quirt, J. I. Clark, J. D. Wolchok, J. S. Weber, J. Tian, M. J. Yellin, G. M. Nichol, A. Hoos, and W. J. Urba, “Improved survival with ipilimumab in patients with metastatic melanoma.,” *N. Engl. J. Med.*, vol. 363, no. 8, pp. 711–23, Aug. 2010.

[40] F. Pagès, A. Kirilovsky, B. Mlecnik, M. Asslaber, M. Tosolini, G. Bindea, C. Lagorce, P. Wind, F. Marliot, P. Bruneval, K. Zatloukal, Z. Trajanoski, A. Berger, W.-H. Fridman, and J. Galon, “In situ cytotoxic and memory T cells predict outcome in patients with early-stage colorectal cancer.,” *J. Clin. Oncol.*, vol. 27, no. 35, pp. 5944–51, Dec. 2009.

[41] R. Yamanaka, T. Abe, N. Yajima, N. Tsuchiya, J. Homma, T. Kobayashi, M. Narita, M. Takahashi, and R. Tanaka, “Vaccination of recurrent glioma patients with tumour lysate-pulsed dendritic cells elicits immune responses: results of a clinical phase I/II trial.,” *Br. J. Cancer*, vol. 89, no. 7, pp. 1172–9, Oct. 2003.

[42] L. Höltl, R. Ramoner, C. Zelle-Rieser, H. Gander, T. Putz, C. Papesh, W. Nussbaumer, C. Falkensammer, G. Bartsch, and M. Thurnher, “Allogeneic dendritic cell vaccination against metastatic renal cell carcinoma with or without cyclophosphamide.,” *Cancer Immunol. Immunother.*, vol. 54, no. 7, pp. 663–70, Jul. 2005.

[43] J. Bubenik, “Cytokine gene-modified vaccines in the therapy of cancer.,” *Pharmacol. Ther.*, vol. 69, no. 1, pp. 1–14, Jan. 1996.

[44] R. I. Tepper and J. J. Mulé, “Experimental and clinical studies of cytokine gene-modified tumor cells.,” *Hum. Gene Ther.*, vol. 5, no. 2, pp. 153–64, Feb. 1994.

[45] S. A. Rosenberg, J. C. Yang, D. J. Schwartzentruber, P. Hwu, F. M. Marincola, S. L. Topalian, N. P. Restifo, M. E. Dudley, S. L. Schwarz, P. J. Spiess, J. R. Wunderlich, M. R. Parkhurst, Y. Kawakami, C. A. Seipp, J. H. Einhorn, and D. E. White, “Immunologic and therapeutic evaluation of a synthetic peptide vaccine for the treatment of patients with metastatic melanoma.,” *Nat. Med.*, vol. 4, no. 3, pp. 321–7, Mar. 1998.

[46] T. Felzmann, H. Gadner, and W. Holter, “Dendritic cells as adjuvants in antitumor immune therapy.,” *Onkologie*, vol. 25, no. 5, pp. 456–64, Oct. 2002.

[47] D. N. Hart, “Dendritic cells and their emerging clinical applications.,” *Pathology*, vol. 33, no. 4, pp. 479–92, Nov. 2001.

[48] A. Razzaque, E. Dye, and R. K. Puri, “Characterization of tumor vaccines during product development.,” *Vaccine*, vol. 19, no. 6, pp. 644–7, Nov. 2000.

[49] S. K. Burgdorf, A. Fischer, M. H. Claesson, A. F. Kirkin, K. N. Dzhandzhugazyan, and J. Rosenberg, “Vaccination with melanoma lysate-pulsed dendritic cells, of patients with advanced colorectal carcinoma: report from a phase I study.,” *J. Exp. Clin. Cancer Res.*, vol. 25, no. 2, pp. 201–6, Jun. 2006.

[50] S. K. Burgdorf, A. Fischer, P. S. Myschetzky, S. B. Munksgaard, M.-B. Zocca, M. H. Claesson, and J. Rosenberg, “Clinical responses in patients with advanced colorectal cancer to a dendritic cell based vaccine.,” *Oncol. Rep.*, vol. 20, no. 6, pp. 1305–11, Dec. 2008.
[51] H. C. Toh, W.-W. Wang, W. K. Chia, P. Kvistborg, L. Sun, K. Teo, Y. P. Phoon, Y. Soe, S. H. Tan, S. W. Hee, K. F. Foo, S. Ong, W. H. Koo, M.-B. Zocca, and M. H. Claesson, “Clinical Benefit of Allogeneic Melanoma Cell Lysate-Pulsed Autologous Dendritic Cell Vaccine in MAGE-Positive Colorectal Cancer Patients.,” *Clin. Cancer Res.*, vol. 15, no. 24, pp. 7726–7736, Dec. 2009.
[52] M. A. Morse, R. E. Coleman, G. Akabani, N. Niehaus, D. Coleman, and H. K. Lyerly, “Migration of human dendritic cells after injection in patients with metastatic malignancies.,” *Cancer Res.*, vol. 59, no. 1, pp. 56–8, Jan. 1999.
[53] L. Fong, D. Brockstedt, C. Benike, L. Wu, and E. G. Engleman, “Dendritic cells injected via different routes induce immunity in cancer patients.,” *J. Immunol.*, vol. 166, no. 6, pp. 4254–9, Mar. 2001.
[54] B. Thurner, I. Haendle, C. Röder, D. Dieckmann, P. Keikavoussi, H. Jonuleit, A. Bender, C. Maczek, D. Schreiner, P. von den Driesch, E. B. Bröcker, R. M. Steinman, A. Enk, E. Kämpgen, and G. Schuler, “Vaccination with mage-3A1 peptide-pulsed mature, monocyte-derived dendritic cells expands specific cytotoxic T cells and induces regression of some metastases in advanced stage IV melanoma.,” *J. Exp. Med.*, vol. 190, no. 11, pp. 1669–78, Dec. 1999.
[55] M. V Dhodapkar, R. M. Steinman, M. Sapp, H. Desai, C. Fossella, J. Krasovsky, S. M. Donahoe, P. R. Dunbar, V. Cerundolo, D. F. Nixon, and N. Bhardwaj, “Rapid generation of broad T-cell immunity in humans after a single injection of mature dendritic cells.,” *J. Clin. Invest.*, vol. 104, no. 2, pp. 173–80, Jul. 1999.
[56] F. O. Nestle, S. Alijagic, M. Gilliet, Y. Sun, S. Grabbe, R. Dummer, G. Burg, and D. Schadendorf, “Vaccination of melanoma patients with peptide- or tumor lysate-pulsed dendritic cells.,” *Nat. Med.*, vol. 4, no. 3, pp. 328–32, Mar. 1998.
[57] P. K. Srivastava, “Immunotherapy of human cancer: lessons from mice.,” *Nat. Immunol.*, vol. 1, no. 5, pp. 363–6, Nov. 2000.
[58] L. Höltl, C. Zelle-Rieser, H. Gander, C. Papesh, R. Ramoner, G. Bartsch, H. Rogatsch, A. L. Barsoum, J. H. Coggin, and M. Thurnher, “Immunotherapy of metastatic renal cell carcinoma with tumor lysate-pulsed autologous dendritic cells.,” *Clin. Cancer Res.*, vol. 8, no. 11, pp. 3369–76, Nov. 2002.
[59] A. Mackensen, B. Herbst, J. L. Chen, G. Köhler, C. Noppen, W. Herr, G. C. Spagnoli, V. Cerundolo, and A. Lindemann, “Phase I study in melanoma patients of a vaccine with peptide-pulsed dendritic cells generated in vitro from CD34(+) hematopoietic progenitor cells.,” *Int. J. Cancer*, vol. 86, no. 3, pp. 385–92, May 2000.
[60] C. J. A. Punt, M. Buyse, C.-H. Köhne, P. Hohenberger, R. Labianca, H. J. Schmoll, L. Påhlman, A. Sobrero, and J.-Y. Douillard, “Endpoints in adjuvant treatment trials: a systematic review of the literature in colon cancer and proposed definitions for future trials.,” *J. Natl. Cancer Inst.*, vol. 99, no. 13, pp. 998–1003, Jul. 2007.

[61] N. C. I. U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES, National Institutes of Health, “Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.” 2017.
[62] D. J. Sargent, H. S. Wieand, D. G. Haller, R. Gray, J. K. Benedetti, M. Buyse, R. Labianca, J. F. Seitz, C. J. O’Callaghan, G. Francini, A. Grothey, M. O’Connell, P. J. Catalano, C. D. Blanke, D. Kerr, E. Green, N. Wolmark, T. Andre, R. M. Goldberg, and A. De Gramont, “Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials.,” *J. Clin. Oncol.*, vol. 23, no. 34, pp. 8664–70, Dec. 2005.
[63] J. D. Elashoff, “nQuery Advisor® Version 7.0. Statistical Solutions (2012), nTerim 2.0, Statistical Solutions, Cork, Ireland.” 2012.
[64] P. M. GRAMBSCH and T. M. THERNEAU, “Proportional hazards tests and diagnostics based on weighted residuals,” *Biometrika*, vol. 81, no. 3, pp. 515–526, Sep. 1994.
[65] C. L. Meinert, *Clinical Trials: Design, Conduct and Analysis*. 1986.

Appendix 1 Eastern Cooperative Oncology Group (ECOG) Performace Status Scale

Grade	Description
0	Fully active, able to carry all predisease performance without restriction
1	Restricted in phisically strenous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or a chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 2 Response Evaluation Criteria In Solid Tumors

	RECIST 1.1
Lesion measurement	
Imaging modality	CT, PET/CT, MRI and chest radiography
Definition of measurable lesions	CT: 10 mm Clinical: 10 mm (must be measurable with calipers)
Lymph node	CT: >= 15 mm short axis for target >= 10 or < 15 mm for non-taget < 10 mm is non-pathological
Method of measurement	Longest diameter in the axial plane
No. lesions to be measured	5 lesions (2 per organ)
Response evaluation	
Complete response (CR)	Disappearance of all lesions and pathological lymph nodes
Partial response (PR)	>= 30% decrease in the sum of the longest diameter
Stable disease (SD)	Neither PR nor PD
Progressive Disease (PD)	>= 20% increase smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions

APPENDIX 3. DOSING MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES FOR DURVALUMAB (V. 17 OCT 2019, CTCAE V5.0)

17 October 2019, CTCAE version 5.0

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 MEDI4736 alone, tremelimumab alone, or MEDI4736 + tremelimumab in combination, or MEDI4736 +/- 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 issued in CTCAE version as specified in the clinical study protocol. This Annex to Protocol presents the dated version of the TMGs issued in CTCAE version 5.0.

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 for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions 17 October 2019 Version (CTCAE v5.0)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications		Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** of the start of the immune-mediated adverse event (imAE) • Grade 3 recurrence of a previously experienced treatment-related imAE following resumption of dosing		It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (e.g., infliximab; also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids.
Grade 1	No dose modification	
Grade 2	Hold study drug/study regimen dose until Grade 2 resolution toGrade ≤1. 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. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent.	
Grade 3	Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.	
Grade 4	Permanently discontinue study drug/study regimen.	

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions 17 October 2019 Version (CTCAE v5.0)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
Note: For asymptomatic amylase or lipase levels of >2X ULN, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	– With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures 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 CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	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 (radiographic changes only):** – 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. – Consider Pulmonary and Infectious Disease consults.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or

			anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)[a] – Consider Pulmonary and Infectious Disease consults. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Disease consults; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Diarrhea/Colitis **Large intestine perforation/Intestine perforation**	**Any Grade**	**General Guidance**	**For Any Grade:** – 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 a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – 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 event, including perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only; intervention not indicated)	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), and loperamide. Use probiotics as per treating physician's clinical judgment.
Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day; limiting instrumental ADL) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: invasive intervention not indicated)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**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 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Grade 3 or 4 (Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day; limiting self care ADL; Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, fever; ileus; peritoneal signs; Grade 4 Colitis: life-threatening consequences, urgent intervention indicated) (Grade 3 Perforation: invasive intervention indicated; Grade 4 Perforation: life-threatening consequences; urgent intervention indicated)	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **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 . – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Grade**	**General Guidance**	**For Any Grade** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 **(**AST or ALT >ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baseline if baseline abnormal; and/or TB >ULN and ≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal)	• No dose modifications. • If it worsens, then treat as Grade 2.	– Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5×ULN and ≤3.0×ULN if baseline normal, >1.5-3.0×baseline if baseline abnormal)	• Hold study drug/study regimen dose until resolution to Grade≤1. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade≤1, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to ≤Grade 1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Grade 3 (AST or ALT >5.0×ULN and ≤20×ULN if baseline normal, >5-20× baseline if baseline abnormal; and/or TB >3.0×ULN and ≤10.0×ULN if baseline normal, >3.0-10.0× baseline if baseline abnormal)	For elevations in transaminases ≤8×ULN, or elevations in TB ≤5×ULN: • Hold study drug/study regimen dose until resolution to Grade≤1 • Resume study drug/study regimen if elevations downgrade to Grade≤1 within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade≤1 within 14 days. For elevations in transaminases >8×ULN or elevations in bilirubin >5×ULN, permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Request Hepatology consult, and perform abdominal workup and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Grade 4 (AST or ALT >20×ULN if baseline normal, >20×baseline if baseline abnormal; and/or TB >10×ULN if baseline normal, >10.0×baseline if baseline abnormal)	Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3×ULN + bilirubin >2×ULN without initial findings of cholestasis [i.e., elevated alkaline P04] and in the absence of any alternative cause).[b]	

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** 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**	**Any Elevations of AST, ALT, or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Isolated AST or ALT >ULN and ≤5.0×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 **Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN 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.	– 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 study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline **Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN 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 within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days 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 1-2 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, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**Same as above (except would recommend obtaining liver biopsy early)**

If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >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×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >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**	**General Guidance**	**For Any Grade:** – Consult with 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, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.

Grade 1 (serum creatinine >ULN to 1.5×ULN)	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. – If baseline serum creatinine is elevated above normal, and there is a rise to > 1 to 1.5 × baseline, consider following recommendations in this row.
Grade 2 (serum creatinine >1.5 to 3.0×baseline; >1.5 to 3.0×ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**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 (>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, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
Grade 3 or 4 (Grade 3: serum creatinine	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated.

	>3.0×baseline; >3.0 to 6.0×ULN) (Grade 4: serum creatinine >6.0×ULN)		– 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, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Rash or Dermatitis (including Pemphigoid)	**Any Grade** (refer to NCI CTCAE v 5.0 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain Dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. If > 30% body surface area is involved, consider initiation of systemic steroids promptly. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.

	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4 (or life-threatening):** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (or life-threatening):** – Consult Dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – 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.
Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning 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	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, 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 (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.

	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v5.0 for defining the CTC 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 Neurology consult as appropriate. –

	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above. – Treat mild signs/symptoms as Grade 1 (e.g. loss of deep tendon reflexes or paresthesia)
	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. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – 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 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
	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. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain Neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** – 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. – 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 Neurology consult. – 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 (Guillain-Barre [GB]: mild symptoms) (Myasthenia gravis [MG]: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology consult.
Grade 2 (GB: moderate symptoms; limiting instrumental ADL)	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	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology consult

(MG: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL)	within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	– Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o 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. o 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. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 3 or 4 (Grade 3 GB: severe symptoms; limiting self care ADL; Grade 4 GB: life-threatening consequences; urgent intervention indicated; intubation) (Grade 3 MG: severe or medically significant	**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 or autonomic instability.	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain Neurology consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG.

	but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL; Grade 4 MG: life-threatening consequences; urgent intervention indicated)	**For Grade 4:** Permanently discontinue study drug/study regimen.	○ 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. *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** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – 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). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, 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. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)

Grade 1 (asymptomatic or mild symptoms*; clinical or diagnostic observations only; intervention not indicated) *Treat myocarditis with mild symptoms as Grade 2.	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
Grade 2, 3 or 4 (Grade 2: Symptoms with moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms*) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)) * Consider "new onset of symptoms" as referring to patients with prior episode of myocarditis.	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, 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 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – 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 study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein 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. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1 (mild pain)	- 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. – Consider, as necessary, discussing with the study physician.

Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	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.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – 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 along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 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 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Grade 3 or 4 (Grade 3: pain associated with severe weakness; limiting self-care ADLs Grade 4: life-threatening consequences; urgent intervention indicated)	**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 4:** - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – 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 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). 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. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

[a]ASCO Educational Book 2015 “Managing Immune Checkpoint Blocking Antibody Side Effects” by Michael Postow MD.
[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.
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.

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	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 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 standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

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

Non–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	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 ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤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 Study Physician."
AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

Appendix 4. Run in phase