Clinical Trial Protocol MS 100070-0028

Title: **CAVE (*C*etuximab-*AVE*lumab) mCRC: A single arm phase IIclinical study of the combination of avelumab plus cetuximab in pre-treated RAS wild type metastatic colorectal cancer patients.**

Short Trial Name: **CAVE mCRC**

EudraCT Number **2017-004392-32**

Coordinating Investigator: Fortunato Ciardiello

Sponsor: **Dipartimento di internistica clinica e sperimentale "Flaviano Magrassi"Università degli studi della Campania "Luigi Vanvitelli"**

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1. Synopsis

Title	CAVE (Cetuximab-AVElumab) mCRC: A single arm phase II clinical study of the combination of avelumab plus cetuximab in pre-treated RAS wild type metastatic colorectal cancer patients.
Short name trial	CAVE mCRC
EudraCTnumber	2017-004392-32
Sponsor	Dipartimento di internistica clinica e sperimentale "Flaviano Magrassi" Università degli studi della Campania "Luigi Vanvitelli"
Phase	PhaseII
Trial Centers/Countries	The study will be conducted in nine centers in Italy 1. Oncologia Medica, Università degli Studi della Campania "L. Vanvitelli", PI: Prof. Fortunato Ciardiello 2. Oncologia Medica, Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione Giovanni Pascale" – IRCCS, Napoli, PI: Dr Antonio Avallone. 3. Oncologia Medica, Azienda Ospedaliera Universitaria, Università di Pisa. PI: Prof Alfredo Falcone 4. Oncologia Medica, Ospedale Casa Sollievo della Sofferenza - San Giovanni Rotondo (FG). PI: Dr Evaristo Maiello 5. Oncologia Medica, Nuovo Ospedale Garibaldi, Nesima, Catania. PI: Dr Roberto Bordonaro 6. Oncologia Medica,Campus Biomedico , Roma. PI: Prof Daniele Santini 7. Oncologia Medica, ASL Pescara. PI: Dr Carlo Garufi 8. Oncologia Medica,Istituto Nazionale dei Tumori di Milano. PI: Prof Filippo De Braud 9. Oncologia Medica, IRCCS Santa Maria Nuova. PI: Dr Carmine Pinto 10. Onco-Ematologia, Azienda Ospedaliera di Rilievo Nazionale "S.G. Moscati" Avellino. PI: Dr Gridelli Cesare
Planned Trial period (first enrollment-last subject out)	36 months
Trial objectives	The primary objective of the study is to evaluate the efficacy (OS) of avelumab and cetuximab combinedin pre-treated RAS wild type metastatic colorectal cancer patients

	Secondaryobjectivewill be: • To demonstrate superiority with regard to the objective response rate (ORR) of avelumab and cetuximab combined in pre-treated RAS wild type metastatic colorectal cancer patients. • To demonstrate superiority with regard to progression free survival (PFS) of avelumab and cetuximab combined in pre-treated RAS wild type metastatic colorectal cancer patients. • To determine the safety and tolerability of avelumab and cetuximab combinedin pre-treated RAS wild type metastatic colorectal cancer patients.
Trial design and plan	This isa non-profit phase II, open-label, single-arm study of cetuximab plus avelumabin patients with RAS WT mCRC treated in first line with chemotherapy in combination with an anti-EGFR drug that have had a clinical benefit (complete or partial response)from treatment. Tumor measurements by computed tomography (CT) scan or magnetic resonance imaging (MRI) will be performed every 8 weeks from the beginning of treatment to determine response to treatment. Response will be evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Treatment will continue until disease progression, significant clinical deterioration, unacceptable toxicity, any criterion for withdrawal from the trial or trial drug is fulfilled. Treatment may continue past the initial determination of disease progression per RECIST 1.1 if the subject's performance status has remained stable, and if in the opinion of the Investigator, the subject will benefit from continued treatment and if other criteria are fulfilled as outlined in the protocol.
Plannednumber of subjects	75patients
Schedule of visits and assessments	**Screening/Baseline Assessments (day -28 from starting treatment)** <u>Screening procedures will include the following:</u> - Signing of the informed consent - Collection of tumor tissue when available. Tumor tissue can be archival or resulting from a screening biopsy of the subject if no archival tissue is available (biopsies are only to be obtained from safely accessible tumor tissue/sites). - Recording of the demographic information, complete medical history, and baseline medical condition - A physical examination including vital signs, body weight, and height, 12-lead electrocardiogram (ECG), and a determination of the Eastern Cooperative Oncology Group Performance Status (ECOG PS)

	- Oftalmological assessment - AE and concomitant medication assessments - Safety laboratory assessments including free T4 and TSH - Tumor evaluation by CT scan or MRI (a bone scan should be done at Screening as clinically indicated) - Serum β-human chorionic gonadotropin (β-HCG) pregnancy test for females of childbearing potential - Blood samples for hepatitis B virus (HBV) and hepatitis C virus (HCV) testing (local laboratory) <u>Treatment phase</u> Treatment phase begins the day of first infusion and ends when a decision is made to stop the trial drugs by the Investigator or when consent is withdrawn by the subject. Visits will take place every week (-1/+1 days) <u>The main assessments are as follows:</u> • Tumor responses will be assessed every 8 weeks from starting treatment, per RECIST 1.1 while on trial. • Vital signs will be collected prior to each trial drugs administration. Administration of trial drugs will take place only after relevant results have been checked by a medically qualified person. • Blood chemistry and hematology assessments: must be performed at baseline, every two weeks prior to each avelumabplus cetuximab dose, at end of treatment visit and at 30 days post-treatment safety follow-up. • Urine pregnancy test for women of childbearing potential must be performed at baseline and least every month during treatment. • Free T4 and TSH must be performed at baseline and at least every 8 weeks during treatment and at end of treatment or 30 days post-treatment safety follow-up (if not performed in the previous 8 weeks). • AEs and concomitant medications will be documented at each visit Avelumab treatment will be administered by IV infusion once everytwo weeks whereas cetuximab treatment will be administrated by IV infusion once everyweekuntil disease progression, significant clinical deterioration (clinical progression), discontinuation for unacceptable toxicity, or withdrawal of consent. Note: Treatment may continue past the initial determination of disease progression per RECIST 1.1 if the subject's ECOG PS has remained stable, and if in the opinion of the Investigator, the subject will benefit from continued treatment and if other

	criteria are fulfilled as outlined in the protocol, that is, no new symptoms or worsening of existing symptoms and no decrease in performance score. <u>Extended safety follow-up</u> • Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days after the last dose of avelumab administration. • The extended safety follow-up beyond 30 days after last avelumab administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call. <u>Discontinuation visit</u> Any subject who experiences an AE that mandates discontinuation of trial treatment should have a Discontinuation visit within 7 days of the decision to discontinue trial treatment. <u>Follow-up phase</u> The Follow-up phase starts when the decision has been made to stop trial drug treatment. Subjects will have - an End-of-Treatment visit at 28 days (± 5 days) after the last administration of trial treatment or before the start of any other antineoplastic therapy, and - a Safety Follow-up visit 12 weeks (± 2 weeks) after the last administration of trial treatment. After the End-of-Treatment visit only treatment related AEs have to be documented until the Safety Follow-up visit, defined as 12 weeks (± 2 weeks) after the last trial treatment administration. Subjects with a serious AE (SAE) ongoing at the Safety follow-up visit must be followed up by the Investigator until stabilization or until outcome is known, unless the subject is documented as “lost to follow-up.” Subjects who discontinue the trial treatment for reasons other than disease progression according to RECIST 1.1 will be followed up every 6 weeks (± 5 days) for radiographic assessment until disease progression, lost to follow-up, or withdrawal of informed consent.

	After the End-of-Treatment visit, subjects will be followed quarterly (that is, every 3 months ± 1 week) for survival (including assessment of any further tumor therapy). The survival follow-up will continue a maximum of 2 years after the last subject receives the last dose of avelumab and cetuximab. Subject-reported outcomes questionnaires will be assessed at the Early Discontinuation/End-of-Treatment visit.
Diagnosis and main inclusion and exclusion criteria	**Inclusion Criteria** For inclusion in the trial, all of the following inclusion criteria must be fulfilled: 1. Signed written informed consent before any trial-related procedure is undertaken that is not part of the standard patient management 2. Male or female subjects aged ≥ 18 years 3.Histologically proven diagnosis of colorectal adenocarcinoma. 4.Diagnosis of metastatic disease 5. RAS (NRAS and KRAS exon 2,3 and 4) wild-type in tissue at initial diagnosis. 6. Efficacy of a first line therapy containing an anti-EGFR agent (panitumumab or cetuximab) with a major response achieved (complete or partial response). 7. A second line therapy. 8. More than 4 months from last dose of anti-EGFR agent administered in first line treatment before randomization. 9.Measurable disease according to RECIST criteria v1.1 10 ECOG PS of 0 to 1 at trial entry 11. Estimated life expectancy of more than 12 weeks 12. Adequate hematological function defined by white blood cell (WBC) count ≥ 2.5 × 10^9/L with absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, lymphocyte count ≥ 0.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, and hemoglobin ≥ 9 g/dL (may have been transfused) 13. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range and AST and alanine aminotransferase (ALT) levels ≤ 2.5 × ULN for all subjects or AST and ALT levels ≤ 5 x ULN (for subjects with documented metastatic disease to the liver). 14. Adequate renal function defined by an estimated creatinine clearance > 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method) 15. Effective contraception for both male and female subjects if the risk of conception exists (Note: The effects of the trial drug on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use effective contraception, defined as 2 barrier methods, or 1 barrier method with a spermicide, an intrauterine device, or use of oral female contraceptive. Should a woman become

	pregnant or suspect she is pregnant while she or her partner is participating in this trial, the treating physician should be informed immediately.) Highly effective contraception for both male and female subjects throughout the study and for at least 30 days after last avelumab treatment administration if the risk of conception exists. 16. No prior immunotherapy **Exclusion Criteria** Subjects are not eligible for this trial if they fulfill any of the following exclusion criteria: 1.Any contraindication to cetuximab and/or avelumab. 2.Past or current history of malignancies other than colorectal carcinoma, except for curatively treated basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix. 3.Pregnancy 4.Breastfeeding 5.Participation in a clinical study or experimental drug treatment within 30 days. 6.Subjects receiving immunosuppressive agents (such as steroids) for any reason should be tapered off these drugs before initiation of the trial treatment, with the exception of: -subjects with adrenal insufficiency, who may continue corticosteroids at physiologic replacement dose, equivalent to ≤ 10 mg prednisone daily -intranasal, inhaled, topical steroids, -local steroid injection (e.g., intra-articular injection) -Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent -Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication) 7.All subjects with brain metastases, except those meeting the following criteria: -Brain metastases have been treated locally, and -No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable) 8.Prior organ transplantation, including allogeneic stem-cell transplantation 9.Significant acute or chronic infections including, among others: -Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome -Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-

	HCV antibody screening test positive) 10.Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent: -Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible -Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or equivalent prednisone per day. -Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable. -Active infection requiring systemic therapy. 11.Previous or ongoing administration of systemic steroids for the management of an acute allergic phenomenon is acceptable as long as it is anticipated that the administration of steroids will be completed in 14 days, or that the daily dose after 14 days will be ≤ 10 mg per day of equivalent prednisone. 12.Known severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade ≥ 3), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more feauters of partially controlled asthma). 13.History of hypersensitivity to Polysorbate 80 that led to unacceptable toxicity requiring treatment cessation 14. Persisting toxicity related to prior therapy of Grade > 1 NCI-CTCAE v 4.03. 15. Known alcohol or drug abuse. 16.Clinically significant (that is active) cardioavscular disease: cerebral vascular accident/stroke (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, comgestive heart failure (New York Heart Association Classification Class≥II), or serious uncontrolled cardiac arrhytmia requiring medication 17.Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study. 18. Any psychiatric condition that would prohibit the understanding or rendering of informed consent.

	19.Vaccination within 4 weeks of the first dose of avelumab and cetuximab and while on treatment is prohibited except for administration of inactivated vaccine (i.e. inactivated influenza vaccine) 20. Legal incapacity or limited legal capacity.
Investigational Medicinal Product: dose/mode of administration/dosing schedule	Avelumab will be administered as a 1-hour IV infusion at 10 mg/kg once every 2-week treatment cycle. Cetuximab will be administered at 1st dose at 400 mg/m^2 by i.v.infusionover 120 minutes, after avelumab infusion. The 2nd dose and subsequent doses will be peroformed at 250 mg/ m^2 by i.v.infusionover 60 minutes, every week and after avelumab infusion every two weeks. NB: Dilution is not required, but is possible in NaCl 0.9% only, via infusion pump or gravity drip. <u>Special Precautions for Administration:</u> • Premedication: In order to mitigate infusion related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to the infusions of avelumab and cetuximab is mandatory (for example, 25 50 mg diphenhydramine and 500 650 mg paracetamol IV or oral). This may be modified based on local treatment standards and guidelines, as appropriate. • Setting: Avelumaband cetuximab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access and must be in place for use in the treatment of potential infusion-related reactions. • Observation period: Following avelumab infusions, patients must be observed for 30 minutes post infusion for potential infusion related reactions. The dose of avelumaband cetuximab will be calculated based on the weight and body surface, respectively, of the subject determined on the day prior to or the day of each drug administration. Infusion of avelumab will be stopped in case of Grade ≥ 2 infusion-related, allergic, or hypersensitivity reactions (according to NCI-CTCAE v 4.03). If the subject experiences an infusion-related reaction of Grade 2, the infusion rate of the subsequent administration of

	avelumab or cetuximab will be reduced by 50%. If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, the subject must discontinue avelumab or cetuximab. If the subject has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, the infusion should be stopped and the subject should be removed from treatment.
Planned treatment duration per subject	Subjects will receive trial treatment until progressive disease (PD) per RECIST 1.1, significant clinical deterioration (clinical progression), unacceptable toxicity, withdrawal of consent, or if any criterion for withdrawal from the trial or trial treatment is fulfilled. Treatment may continue past the initial determination of disease progression per RECIST 1.1 if the subject's ECOG PS has remained stable, and if in the opinion of the Investigator, the subject will benefit from continued treatment and if other criteria are fulfilled as outlined in the protocol, that is, no new symptoms or worsening of existing symptoms and no decrease in performance score. Subjects receiving avelumab plus cetuximab who have experienced a CR should be treated for a maximum of 24 months after confirmation, at the discretion of the Investigator.If the Investigator believes that a subject may benefit from treatment beyond 24 months, it may be permissible after discussion with the Sponsor. In case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment is allowed at the discretion of the Investigator and agreement of the Medical Monitor. In order to be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial therapy. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol.
Primaryendpoint	The primary endpoint for the trial is OS time, defined as the interval from enrollment to death for every cause.
Secondary/exploratoryendpoints	Secondaryendpointswill be: • The overall response rate (ORR) according to RECIST 1.1 • Progression free survival (PFS) according to RECIST 1.1 • The safety profile of the trial drugs as measured by the incidence of AEs, SAEs, clinical laboratory assessments, vital signs, physical examination, ECG parameters, and ECOG PS.
Exploratoryendpoints	Exploratoryendpoints are • Duration of response of cetuximab plus avelumabaccording to RECIST 1.1 • Quantification PD-L1 expression levels in tumor cells

	and cells of the tumor microenvironment at baseline with their relation to selected clinical response parameters • EGFR expression levels in tumor cells as candidate predictive biomarker with their relation to selected clinical response parameters • Molecular, cellular, and soluble markers in peripheral blood and/or tumor tissue that may be relevant to the mechanism of action of, or response/resistance to avelumab and cetuximab
Statistical methods (includes sample size calculation)	To determine the potential efficacy on OS of the combination of avelumab and cetuximab we have considered the median OS that is obtained in third line in mCRC patients treated with standard third line therapy (CORRECT, RECOURSE). The current study aims to demonstrate a median OS of 11.0months (alternative hypothesis) by experimental combination for comparison with historical median OS 8.0(null hypothesis) with standard third line treatment, which correspond to an improvement of OS at 6 months from 35% to 46%. It was estimated that we would need to enroll 66 patients to achieve with a 1-sided 5% level test in this single stage, single arm trial. The accrual period will be of 18 months and the total duration of the stud will be of 36 months. Considering a potential drop-out of approximately 15% of patients a total of 75 patients will be recruited.

2. Sponsor, Investigators, and Trial Administrative Structure

The Sponsor of thisclinical trial with avelumaband cetuximab is the Dipartimento di internistica clinica e sperimentale “Flaviano Magrassi” Università degli studi della Campania “Luigi Vanvitelli”

2.1 Investigational Sites

The trial will be conducted in Italy in 9 Centers.

3. Background Information

3.1 Metastatic colorectal cancer

Colorectal cancer (CRC) is considered the third most commonly diagnosed cancer in males and the second in females worldwide, with an estimated 1.4 million new cases in 2012. In the same year, CRC was responsible for 693900 deaths, making it the fourth leading cause of cancer-related death in men and the third in women(1). Although the advances in screening and medical treatments have led a trend in reduction of both incidence and mortality, almost 20% of patients present metastases at the time of diagnosis, and approximately 35% of patients will subsequently develop a metastatic disease(2). The prognosis of patients with metastatic colorectal cancer (mCRC) has improved over the last 20 years, thanks to the introduction of active chemotherapy drugs and target therapies, such as fluropyrimidines, oxaliplatin, irinotecan, TAS-102, and of targeted drugs, such as bevacizumab, cetuximab, panitumumab, aflibercept, ramucirumab and regorafenib that led to an increase in median overall survival (OS) from 6 mo, with the only best supportive care (BSC), to approximately 30 mo(3,4).

The Epidermal Growth Factor Receptor (EGFR) targeted therapy with the monoclonal antibodies cetuximab or panitumumab represents a major step forward in the treatment of RAS wild type (WT) metastatic colorectal cancer (mCRC), given the relevant efficacy in terms of progression-free survival (PFS), overall survival (OS), response rate (RR), as well as quality of life (QoL), observed in several phase III clinical trials among different lines of treatment. However, the clinical benefit observed with these agents is limited to only a subset of patients and responses are often transient due to the development of various mechanisms of resistance. Several studies have provided new insights into molecular basis of EGFR inhibitors resistance and have identified mutations in KRAS, NRAS, BRAF and EGFR extracellular domain (ECD) as well as the amplification of ERBB2 and MET, as biomarkers of both primary and/or acquired resistance to these drugs. Unraveling the biology underlying the complex mechanisms of resistance have been useful for developing rational combination therapies in order to revert or overcome resistance. Rechallenge with an alternative anti-EGFRmonoclonal antibody (MoAb) after failure with an agent of the same family has been proposed as strategy to overcome drug resistance. However, panitumumab, as single agent, has demonstrated to provide minimal benefit in patients with KRAS WT mCRC who have experienced progression to cetuximab as prior therapy (5,6). The hypotheses that pre-existing sensitive subclones may emerge after treatment breaks with anti-EGFRmoAb has led the design of several clinical trials prospectively evaluating the rechallenge with anti-EGFRmoAbs in the third-line setting after a response to afirst-line therapy with anti-EGFR drugs (7). The immune system has a crucial role in modulating response to monoclonal antibody therapy in cancer, with novel agents inducing potent cytotoxicity and combinations with immune checkpoint inhibitors worth exploring in the anti-EGFR resistance setting. Avelumab is a fully human anti-PD-L1 IgG1 monoclonal antibody. By inhibiting PD-L1 interactions, avelumab is thought to enable the activation of T-cells and the adaptive immune system. By retaining a native Fc-region, avelumab is thought to potentially engage the innate immune system and induce antibody-dependent cell-

mediated cytotoxicity (ADCC) (8). In preclinical model, Cetuximab stimulates tumor antigen presentation through the formation of immune complexes,wich enhances the induction of tumor specific T cells. In an *in vitro* study using colon cancer cell lines, cetuximab promoted dendritic cell (DC) opsonization of tumor cells, and associated DC maturation with increased expression of MHC class II molecules, CD40, CD80 and CD 86. DCs incubated with tumor cells and cetuximab more effectively primed tumor-specific T cells than DCs that were incubated with tumor cells alone(9). Additionally, cetuximab facilitates NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytoxicity(CDC), wich may further enhance tumor cell killing (10, 11).Cetuximab in combination with avelumab could be a valid therapeutic option for mCRCRAS WT patients that achieved a major response in the first line of therapy to panitumumab or cetuximab as third line rechallenge treatment.

3.2Avelumab

The Investigational Medicinal Product (IMP) for the present trial is avelumab (*avelumab is the proposed International Nonproprietary Name for the anti-PD-L1 monoclonal antibody MSB0010718C), a fully human monoclonal antibody of the immunoglobulin (Ig) G1 isotype. This anti-PD-L1 therapeutic antibody concept is being developed in oncological settings by Merck KGaA, Darmstadt, Germany, and by its subsidiary, EMD Serono R&D, Billerica, MA, USA.

Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD-1. Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells, and therefore is expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the PD-L2 – PD-1 pathway intact to promote peripheral self-tolerance (22). For complete details of the in vitro and nonclinical studies, please refer to the Investigator's Brochure.Avelumab is currently in clinical development with 2 ongoing Phase I studies in subjects with solid tumors and a Phase II trial in subjects with Merkel cell carcinoma:

- Trial EMR100070-001 is "a Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological, and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors." The most frequently reported treatment-related emergent adverse events (TEAEs) observed in subjects during the dose-expansion portion of the trial are presented in Table 1.

Table 1. Most Frequently Reported Treatment-related TEAEs During Dose Expansion

Treatment-emergent Adverse Events Grande ≤2 a Preferred Term (MedDRA)	Subjects (Safety Population, N = 480) N (%)	Treatment-emergent Adverse Events Grade ≥3 a Preferred Term (MedDRA)	Subjects (Safety Population, N = 480) N (%)
Fatigue	97 (20.2%)	Fatigue	5 (1.0%)
Nausea	62 (12.9%)	Anemia	5 (1.0%)
Infusion-related reaction	47 (9.8%)	Infusion-related reaction	4 (0.8%)
Chills	33 (6.9%)	Lipase increase	4 (0.8%)
Diarrhea	33 (6.9%)	GGT increase	4 (0.8%)
Decreased appetite	30 (6.3%)		
Pyrexia	27(5.6%)		
Influenza like illness	25 (5.2%)		
Arthralgia	24 (5.0%)		

MedDRA = Medical Dictionary for Regulatory Activities. a Only treatment-emergent adverse eventsstarted during the on-treatment period are summarized.

Serious Adverse Events

Overall, 176 of the 480 subjects (36.7%) treated during the dose expansion had serious TEAEs. Of these, 22 (4.6%) subjects reported dyspnea, which was the most frequent serious TEAE in this group, followed by 19 subjects (4.0%) reporting disease progression, 12 subjects (2.5%) reporting pleural effusion, 11 subjects (2.3%) reporting pneumonia, and 7 subjects (1.5%) reporting anemia. All other serious TEAEs were each reported in less than 1.5% of subjects. Of the serious TEAEs considered treatment-related by the Investigator (31subjects; 6.5%), the following were reported for 2 or more subjects: infusion-related reaction (4 subjects, 0.8%), pneumonitis (3 subjects, 0.6%), and disease progression, dyspnea, and hypercalcemia (each in 2subjects, 0.4%).

Deaths and withdrew from trial

In total, 134 subjects (27.9%) treated during the dose expansion died up to the cut-off date. Of these, the majority of deaths (101 deaths; 21.0%) were due to disease progression. A further 8deaths (1.7%) were due to TEAEs unrelated to trial treatment, 4 deaths (0.8%) were due to TEAEs related to trial treatment, and the reason for 8 deaths (1.7%) was labeled as other.

The reason for 13 deaths (2.7%) was unknown at the time of the data cut-off. Of the 134 subjects who died, 53subjects (11.0%) died within 30 days of the last administration of trial treatment. Among these deaths, 39 (8.1%) were due to disease progression, 7 (1.5%) were due to TEAEs unrelated to trial treatment, 4(0.8%) were due to TEAEs related to trial treatment, and 3(0.6%) were due to otherreasons. No death of unknown reason was reported in the 30-dayperiod. A total of 80 subjects (16.7%) treated during the dose expansion withdrew permanently from trial treatment due to one or more TEAE. In 25 (6.6%) of these subjects, the TEAEs leading to treatment discontinuation were considered related to trial treatment by the Investigator. These TEAEs were infusion-related reaction (6 withdrawals; 1.6%), GGT increased (3 withdrawals, 0.8%), dyspnea (3 withdrawals; 0.8%), and radiation pneumonitis, aspartate aminotransferase (AST) increased, hepatocellular injury, blood creatine phosphokinase increased, blood pressure increased, pneumonitis, anaphylactic reaction, food allergy, adrenal insufficiency, anemia, hypercalcemia, hyperglycemia, arthralgia, arthritis, myositis, pain, abdominal pain lower, chest discomfort, cramps and ache on back and all over body (not yet coded), encephalopathy, syncope, and flushing (1 withdrawal each; 0.3%). Most of the events of infusion-related reaction and anaphylactic reaction that led to permanent discontinuation of trial treatment (as described above) occurred before implementation of mandatory premedication on 28 January 2014.

Immunorelated (Ir) Adverse Events

A cumulative review revealed 56 cases of potential immune-related AEs of out of 480 subjects (11.7%) treated in the dose expansion part of trial EMR 100070-001 and 4 cases out of 50 subjects (8.0%) treated in the dose escalation part of trial EMR 100070-001.

Of 69 potential irAEs reported, 13 were SAEs (18.8%) and 56 were non-serious AEs (81.1%). In the majority of the cases, there was a plausible temporal association between the event onset and the drug administration. Of these 69 events, 46 events (66.7%) were assessed as treatment- related by the Investigator and 23 events (33.3%) were assessed as not treatment-related by the Investigator. Twenty-six events were assessed as Grade 1, 29 events as Grade 2, 11 events as

Grade 3, 2 events as Grade 4, and 1 event (pneumonitis) as Grade 5 (Please note: two more events of autoimmune hepatitis had a fatal outcome; however, they were assessed as Grade 3 with a consequent fatal liver failure). Based on the irAE cases that have been observed, all trial Investigators have been trained to be made aware of the frequency and severity of the observed events and to proactively administer steroid treatment for any suspicion of irAEs. Of note, irAEs are considered as an identified risk by the Sponsor.

Two suspected unexpected serious adverse reactions (SUSARs; anaphylactic reaction and infusion-related reaction) involving 2 subjects were reported in December 2013 and triggered a cumulative review of serious and non-serious cases of infusion-related reactions / hypersensitivity across the avelumab program. Following evaluation of safety signals, infusion-related reactions / hypersensitivity have been classified as a newly identified risk (previously classified as a potential risk) and a mandatory premedication regimen of a histamine H1 receptor (H1) blockers plus acetaminophen was implemented for all trial subjects as of 28 January 2014.

As of 05 November 2014, 49 (10.2%) of the 480 subjects in the expansion cohorts experienced at least 1 episode of an infusion-related reaction when receiving avelumab monotherapy. Most of the events were Grade 1 (8 subjects, 1.7%) or Grade 2 (36 subjects, 7.5%) in intensity, and Grade 3 (3 subjects, 0.6%) or Grade 4 events (2 subjects, 0.4%) were less frequent. No Grade 5 events were reported. Most of the infusion-related reaction events had an onset after the first (30 subjects, 6.3%) or second (16 subjects, 3.3%) avelumab infusion. In 8 subjects (1.7%), avelumab treatment was discontinued because of infusion-related reaction events.In addition, 1 subject (2.0%) in the dose escalation cohort reported an infusion-related reaction event (Grade 2).In addition to the aforementioned 49 subjects, 1 case of Grade 4 cardiac arrest occurred 1.5 hours after the third infusion of avelumab (10 mg/kg). The subject died due to an anoxic brain injury 7 days later; no autopsy was performed.Starting from 29 January 2014, the Sponsor has implemented a mandatory premedication with H1 blockers plus acetaminophen for all subjects who are to receive avelumab. This premedication procedure was applied to 28 and 440 subjects in the dose escalation and the pooled treatment expansion cohort, respectively. Under this premedication procedure, 33 of 440 subjects (7.5%) in the expansion cohort experienced infusion-related reaction events, with 6 subjects (1.4%) having Grade 1, 26 subjects (5.9%) having Grade 2, and 1 subject (0.2%) having Grade 3 events. No infusion-related reaction events were reported in the 28 subjects in the dose escalation cohort.Guidelines for the management of infusion-related reactions and severe hypersensitivity reaction according to the National Cancer Institute (NCI) are found in Section**5.4**. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf.

Further information about the events described below is available in the current version of the Investigator's Brochure.

- Trial EMR100070-002 is "a Phase I trial to investigate the tolerability, safety, pharmacokinetics, biological, and clinical activity of avelumab in Japanese subjects with metastatic or locally advanced solid tumors, with expansion part in Asian subjects with gastric cancer."

- Trial EMR100070-003 is "a Phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab in subjects with Merkel cell carcinoma."

3.3 Cetuximab

Cetuximab (ERBITUX®) has been approved and is available in the United States, European Union, Switzerland and over fifty countries worldwide. Cetuximab is a targeted therapeutic agent, a chimeric IgG1 monoclonal antibody that specifically binds to the EGFR with high affinity, internalising the receptor and preventing the ligands EGF and TGF-α from interacting with the receptors and thus effectively blocking ligand-induced EGFR phosphorylation (22). In addition, cetuximab has been found to potentiate the effects of chemotherapy and radiotherapy in experimental systems (23, 24).The dose of cetuximab (initial dose 400 mg/m^2 and subsequent weekly doses of 250 mg/m^2) has been found to be generally safe and effective in several studies in major tumor types expressing the EGFR. These included colorectal cancer, squamous cell carcinoma of the head and neck and non-small cell lung cancer, with cetuximab given either in combination with chemotherapy and/or radiotherapy or as monotherapy. The main side effects of cetuximab monotherapy are hypersensitivity and acne-like skin reactions.

3.4 Epidermal growth factor receptor

The EGFR is a transmembrane glycoprotein, which is commonly expressed, in many normal human tissues and solid human tumors (Table 2). It was one of several growth factors and their receptors, which were found to be encoded by proto-oncogenes. It is a member of the tyrosine kinase family of growth factor receptors, and is over-expressed in many human tumor types. The EGFR, when situated in the transmembrane position, has an extracellular domain, which provides a ligand-binding site for epidermal growth factor (EGF) and transforming growth factor alpha (TGFα). The intracellular domain of EGFR is activated upon ligand binding, which triggers the EGF-mediated tyrosine kinase signal transduction pathway and cascades many cellular operations concerning cell growth and division (25).

Analyses performed in vitro, using cell lines with a high degree of EGFR expression have shown a proliferation of cells in culture, probably due to activation via an autocrine pathway. In contrast, EGFR antagonists, which block the ligand-binding site, have been developed in order to inhibit proliferation of EGFR-expressing cells (26-28).

Table 2. Prevalence of EGFR expression in common tumour types

Tumour Type	EGFR Expression
Head and Neck	90 - 100%
Colon	75 – 89%
Prostate	Up to 100%
Pancreatic	Up to 95%
Breast	Up to 91%
Renal	Up to 90%
Cervix	Up to 82%
Non-Small Cell Lung Carcinoma	Up to 80%
Ovarian	Up to 77%
Bladder	Up to 72%
Primary Glioblastoma	Up to 63%

3.5 Cetuximab general safety information

Adverse event data are available for 3339 patients treated with cetuximab alone or in combination with chemotherapy and/or radiation therapy from investigational trials across all indications conducted by ImClone, BMS, Merck KGaA, Investigator sponsored Trials (IST), Cooperative Groups and the National Cancer Institute (NCI). As most of the trials were conducted under different settings and in combination with various cytostatic therapies, adverse reaction rates cannot be validly pooled and quoted as mean rates. Nevertheless, they constitute a basis for identifying approximate adverse event rates associated with the administration of Cetuximab.
Skin reactions may develop in more than 80% of patients and mainly present as acne-like rash and/or, less frequently, as pruritus, dry skin, desquamation, hypertrichosis, or nail disorders (e.g. paronychia). The majority of skin reactions develop within the first three weeks of therapy. They generally resolve, without sequelae, over time following cessation of treatment if the recommended adjustments in dose regimen are followed (29).Approximately 15% of the skin reactions are severe, including single cases of skin necrosis. In the event of Grade 3 or 4 skin reactions the patients should be referred for dermatological advice.
The incidence of radiation dermatitis of any grade was comparable between the treatment groups in a phase 3 SCCHN trial in patients receiving either cetuximab in combination with RT (86%) or RT alone (90%) (30)

Other side effects observed in patients receiving cetuximab monotherapy include asthenia, dyspnoea, mucositis, nausea, pain, fever and headache.
Mild or moderate infusion-related reactions may occur (≥ 1/10) comprising symptoms such as fever, chills, nausea, vomiting, headache, dizziness, or dyspnoea that occur in a close temporal relationship mainly to the first cetuximab infusion (29). They can be managed by slowing the infusion rate of cetuximab and by the continued use of pre- medications for subsequent doses in addition to the mandatory use for the first infusion.

Severe infusion-related reactions may occur (≥ 1/100, < 1/10), in rare cases with fatal outcome. They usually develop during or within 1 hour of the initial cetuximab infusion and may include symptoms such as rapid onset of airway obstruction (bronchospasm, stridor, hoarseness, difficulty in speaking), urticaria, hypotension, or loss of consciousness; in rare cases, angina pectoris, myocardial infarction or cardiac arrest have been observed. Severe infusion reactions (grade 3 or 4) require immediate interruption of the cetuximab infusion and permanent discontinuation from further treatment (29).
A large multinational study of cetuximab plus irinotecan in irinotecan-resistant metastatic colorectal cancer (MABEL) investigated, in a post-hoc analysis, whether the type of prophylactic pre-medication had an impact on the incidence of infusion-related reactions including allergic/hypersensitivity reactions. The incidence of infusion-related reactions was lower in patients who received anti-histamines and corticosteroids as prophylactic medication (9.6%, n=700) compared to patients who received anti-histamines but not corticosteroids (25.6%, n=422). A similar trend was seen in the analysis of the grade 3/4 infusion-related reactions (1% vs. 4.7%). These data suggest that the addition of corticosteroids to antihistamines as prophylactic pre-medication seems to reduce the incidence of infusion-related reactions such as allergic/-hypersensitivity reactions (31).

Progressively decreasing serum magnesium levels have been observed leading to severe hypomagnesaemia in some patients. Hypomagnesaemia is reversible following discontinuation of cetuximab. Depending on severity, other electrolyte disturbances, mainly hypocalcaemia or hypokalaemia, have also been observed. Determination of serum electrolyte levels is recommended

prior to and periodically during cetuximab treatment. Electrolyte repletion is recommended, as appropriate (29).

4. Trial Objectives

4.1 Primary

The primary objective of the study is to evaluate the efficacy (OS) of avelumab and cetuximab combined in pre-treated RAS wild type metastatic colorectal cancer patients

4.2 Secondary objectives

Secondary objectives are as follows:

- To demonstrate superiority with regard to the objective response rate (ORR) of avelumab and cetuximab combined in pre-treated RAS wild type metastatic colorectal cancer patients.
- To demonstrate superiority with regard to progression free survival (PFS) of avelumab and cetuximab combined in pre-treated RAS wild type metastatic colorectal cancer patients.
- To determine the safety and tolerability of avelumab and cetuximab combinedin pre-treated RAS wild type metastatic colorectal cancer patients

4.3 Exploratory objectives

Exploratory objectives are as follows:

- To determine duration of response of cetuximab plus avelumab
- To evaluate PD-L1 expression levels in tumor cells and cells of the tumor microenvironment (for example, infiltrating lymphocytes) as candidate predictive biomarker with their relation to selected clinical response parameters
- To characterize the immunogenicity of cetuximab plus avelumab
- To evaluate EGFR expression levels in tumor cells as candidate predictive biomarker with their relation to selected clinical response parameters
- To explore molecular, cellular, and soluble markers in peripheral blood and/or tumor tissue that may be relevant to the mechanism of action of, or response/resistance to avelumab and cetuximab

4.4 Exploratory endpoints

Exploratory endpoints are

- Duration of response of cetuximab plus avelumab according to RECIST 1.1
- Quantification of PD-L1 expression levels in tumor cells and cells of the tumor microenvironment at baseline with their relation to selected clinical response parameters
- EGFR expression levels in tumor cells as candidate predictive biomarker with their relation to selected clinical response parameters

- Molecular, cellular, and soluble markers in peripheral blood and/or tumor tissue that may be relevant to the mechanism of action of, or response/resistance to avelumab and cetuximab

The exploratory endpoint analyses will be performed on the ITT analysis set.

Duration of response will be analyzed descriptively by treatment arm. The Kaplan-Meier estimate of median time along with its 95% CI, as well as estimates of the survival function at 3, 6, and 12 months will be calculated for duration of response.

5. Investigational Plan

5.1 Overall Trial Design and Plan

This is a non-profit phase II, open-label, single-arm study of cetuximab plus avelumabin patients with RAS WT mCRC treated in first line with chemotherapy in combination with an anti-EGFR drug that have had a clinical benefit (complete or partial response) from treatment.

Approximately 75 subjects are planned to be enrolledin the Phase II to receive avelumab at a dose of 10 mg/kg once every 2 weeks plus cetuximab at a starting dose of 400 mg/m2 by i.v.infusion over 120 minutes at first dose and at the dose of 250 mg/ m2 by i.v.infusion over 60 minutes for subsequent infusions every week.

At the screening, when available, tumor tissue will be collected in order to analize the PD-L1 and EGFR expression by IHC (Appendix I, table 8)
During the Screening, and at progression the following collections will be performed:

- Blood and plasma samples will be collected from all subjects prior to infusion on Day1 (Week 1; Baseline samples for soluble factors may also be collected at Screening, instead of on Day 1 prior to dosing) and at progression (Appendix I, table 8).

Subjects will return to the clinic at regular intervals for assessments. Tumor measurements by computed tomography (CT) scan or magnetic resonance imaging (MRI) will be performed every 8 weeks to determine response to treatment. Response will be evaluated using the RECIST 1.1.

Treatment will continue until

- disease progression
- significant clinical deterioration
- unacceptable toxicity, or
- any criterion for withdrawal from the trial or trial drug is fulfilled (see Section 5.6).

Treatment may continue past the initial determination of disease progression according to RECIST 1.1 if the subject's performance status has remained stable, and if in the opinion of the Investigator, the subject will benefit from continued treatment and if other criteria are fulfilled as outlined in the protocol, that is, no new symptoms or worsening of existing symptoms and no decrease in performance score.

Subjects who have experienced a complete response (CR) should be treated for a maximum of 24 months after confirmation, at the discretion of the Investigator. If the Investigator believes that a subject may benefit from treatment beyond 24 months, it may be permissible. In case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment is allowed at the discretion of the Investigator. In order to be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab plus cetuximab therapy. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Assessments (see Appendix I).

Subjects will attend clinic visits at regular intervals to receive trial treatment and for efficacy and safety assessments (see Section 7.2).

5.2 Trial Endpoints

5.2.1 Primary Endpoints

The primary endpoint for the trial is OS time, defined as the interval from enrollment to death for every cause.

5.2.2 Secondary Endpoints and Exploratory Endpoints

Secondary endpoints will be:

- The overall response rate (ORR) according to RECIST 1.1
- Progression free survival (PFS) according to RECIST 1.1
- Safety endpoints include AEs, assessed throughout the trial and evaluated using the NCI-CTCAE version 4.03 (CTCAE v 4.03), clinical laboratory assessments, vital signs, and electrocardiogram (ECG) parameters.

5.3 Trial Medication Administration and Schedule

The trial Schedule of Assessments is illustrated in Appendix I.

5.3.1 Avelumab

Subjects will receive IV infusion of avelumab (10 mg/kg over 1 hour) once every 2 weeks.

<u>Precautions for Administration:</u>

- Premedication: In order to mitigate infusion related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory (for example, 25 50 mg diphenhydramine and 500 650 mg paracetamol IV or oral). Premedication should be administered for subsequent avelumab infusions based upon clinical judgment and presence/severity of prior infusion reactions. This may be modified based on local treatment standards and guidelines, as appropriate.
- Setting: Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.
- Observation period: Following avelumab infusions, patients must be observed for 30 minutes post infusion for potential infusion related reactions.

The formulation and packaging information of avelumab is provided in Sections 6.1.1 and 6.6, respectively.

5.3.2 Cetuximab

Cetuximab will be administered at 1st dose at 400 mg/m^2 by i.v.infusionover 120 minutes, directly afteravelumab.

The 2nd dose and subsequent doses will be performed at 250 mg/ m^2 by i.v.infusionover60 minutes, every week andafter by avelumab every two weeks.

NB: Dilution is not required, but is possible in NaCl 0.9% only, via infusion pump or gravity drip.

5.4 Dose Modification and Adverse Drug Reactions RequiringTreatment Discontinuation

5.4.1 Dose Modification for Avelumab

The dose of avelumab will be calculated based on the weight of the subject determined on the day prior to or the day of each drug administration.

Each subject will stay on the avelumab assigned dose of 10 mg/kg unless treatment needs to be stopped. There are to be no dose reductions.

Dosing modifications (changes in infusion rate) and dose delays are described in Sections 5.4 and 6.4.

5.4.1.2 Adverse Drug Reactions Requiring Avelumab Discontinuation or Modifications

The following adverse drug reactions (ADRs, see Section 7.9) require permanent treatment discontinuation of avelumab:

- Any Grade 4 ADRs require treatment discontinuation with avelumab except for single laboratory values out of normal range that are unlikely related to trial treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.
- Any Grade 3 ADRs require treatment discontinuation with avelumab except for any of the following:
  - Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
  - Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolves to Grade ≤ 1
  - Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to trial treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management
  - Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
  - Change in Eastern Cooperative Oncology Group Performance Status (ECOG PS) to ≥ 3 that resolves to 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of trial drug administration)

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the

event has not resolved to Grade 1, the subject should permanently discontinue treatment with aavelumab ADR (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).

- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with avelumab has to be permanently discontinued.

5.4.1.3 Infusion-Related Reactions

Infusion-related reactions, hypersensitivity reactions (Grades 1 to 4), tumor lysis syndrome, and irAEs should be handled according to guidelines in Section6.3.

A. Symptoms

- Fever
- Chills
- Rigors
- Diaphoresis
- Headache

B. Management according to Table 3

Table 3.Treatment Modification for Symptoms of Infusion-Related Reactions Caused by Avelumab

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for $\leq$ 24 h.	Temporarily discontinue avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop avelumab infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study avelumab and must not receive any further avelumab treatment.
- If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment.- If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice.	

IV=intravenous, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs.

5.4.1.4 Severe Hypersensitivity Reactions and Flu-Like Symtoms

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

A. Symptoms

- Impaired airway
- Decreased oxygen saturation (<92%)
- Confusion
- Lethargy
- Hypotension
- Pale/clammy skin
- Cyanosis

B. Management

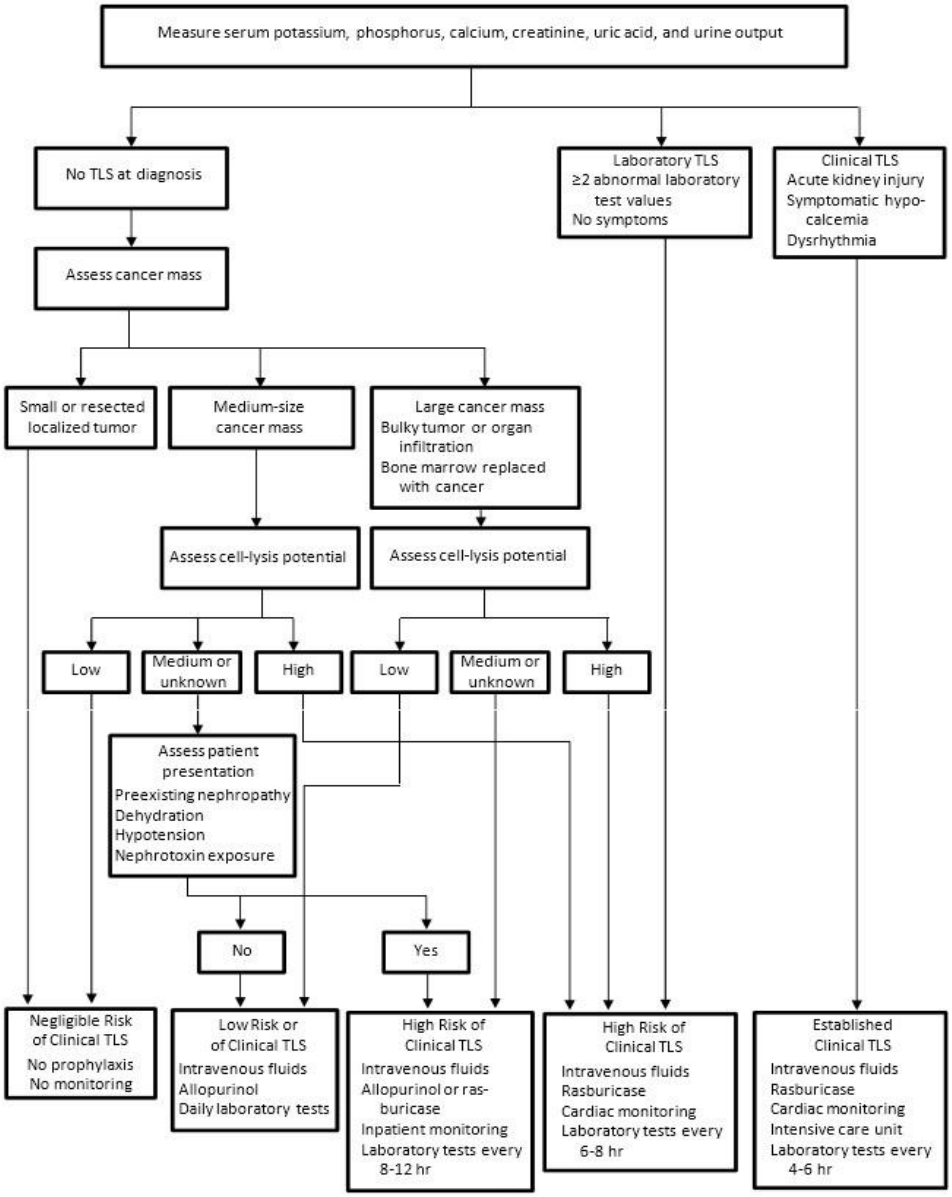
- Epinephrine injection and dexamethasone infusion
- Subject should be placed on monitor immediately
- Alert ICU for possible transfer if required

For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (for example, ibuprofen 600 mg, naproxen sodium 500mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (for example, paracetamol) may be given to subjects at the discretion of the Investigator.

5.4.1.5 TumorLysis Syndrome

Since avelumab can induce ADCC, there is a potential risk of tumor lysis syndrome. Should this occur, subjects should be treated per the local guidelines and the management algorithm published by Howard et al (36) (Figure 1)

Figure 1. Assessment and Initial Management of Tumor Lysis Syndrome



TLS=tumor lysis syndrome.

5.4.1.6 Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, irAEsmayoccur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids

Treatment of irAEs should follow guidelines set forth in the following Table 4

Table 4. Management of Immune-mediated Adverse Reactions

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists> 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).

consequences	Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolatemofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: Resume routine monitoring; resume avelumab therapy. If elevation persists > 5 to 7 days or worsens:

		Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolatemofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

Renal irAEs

Grade of Creatinine Increased (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.

Cardiac irAEs

Myocarditis	Initial Management	Follow-up Management
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is

myocarditis.	Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).

*Local guidelines, or eg. ESC or AHA guidelines
ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines
AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

Endocrine irAEs

Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) : • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1,	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary

	PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for	Permanently discontinue avelumab therapy Specialty consult	

reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**		

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid stimulating hormone; ULN=upper limit of normal.

5.4.2 Dose Modification and Discontinuation for Cetuximab

The dose of Cetuximab will be calculated based on the Body Surface Area of the subject determined on the day prior to or the day of each drug administration. Each subject will stay on the Cetuximab assigned dose unless treatment modification needs to be performed. Dose modifications and dose delays are described in the following Section.

5.4.2.1 Adverse Drug Reaction Requiring Cetuximab Discontinuation or Modifications

5.4.2.1.2 Skin Toxicity

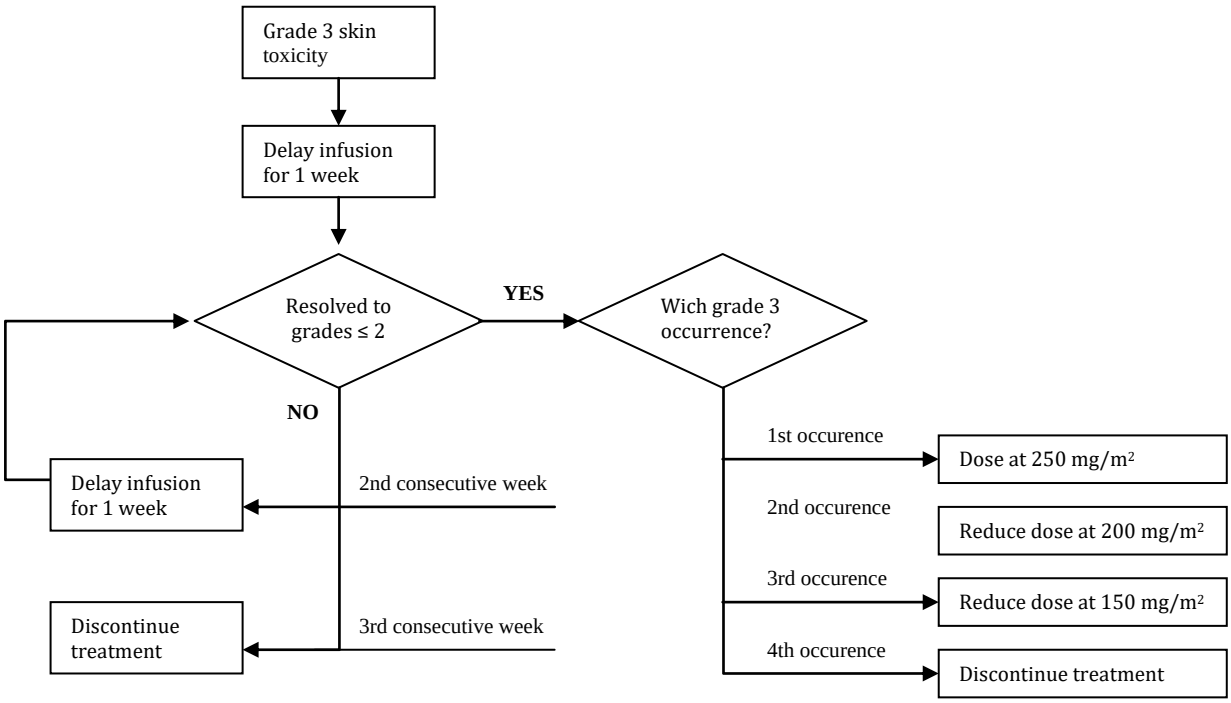
The most common AEs associated with Cetuximab administration are skin reactions, particularly acne-like rash. Skin reactions to Cetuximab may be considered as being in 3 phases. The first, early phase (1-4 weeks) is a moist acneiformphase which is usually responsive to tetracyclines and/or retinoids. Limiting sun exposure may be useful. Drying agents may be of value. The second phase is a dry skin phase, seldom troublesome, which usually responds well to emollients or petroleum jelly.

If started, drying agents should be discontinued. The third phase also included skin fissuring and nail changes. Skin fissures are best treated with cyanoacrylate or other adhesives and strong tape until healed.

If a patient experiences a Grade 3 skin toxicity (as defined in the US National Cancer Institute's - Common Toxicity Criteria - NCI-CTC- Version 3.0), Cetuximab therapy may be deferred for up to two consecutive infusions without changing the dose level. The investigator should also consider concomitant treatment with topical and/or oral antibiotics. Topical corticosteroids are not recommended. If the toxicity resolves to Grade 2 or less by the following treatment period, the treatment may resume.

With the second and third occurrences of a Grade 3 skin toxicity, Cetuximab therapy may again be deferred for up to two consecutive weeks with concomitant dose reductions to 200 mg/m^2 and 150 mg/m^2, respectively. Cetuximab dose reductions are permanent. Patients should discontinue Cetuximab if more than two consecutive infusions are withheld or a fourth occurrence of a Grade 3 skin toxicity occurs despite an appropriate dose reduction (Figure 2).

Figure 2. Treatment adjustment in case of Grade 3 skin toxicity considered to be related to Cetuximab.



5.4.2.1.3 Allergic/Hypersensitivity Reactions

Allergic/hypersensitivity reactions may occur during or following the administration of Cetuximab. Patients must therefore be pretreated with an appropriate antihistamine and acetaminophen before infusions. If should an allergic/hypersensitivity or infusion reaction to Cetuximab occur, then the patient must be treated according to the best available medical practices. Grade 3 or 4 allergic/hypersensitivity reactions require immediate interruption of the Cetuximab infusion, appropriate medical measures and permanent discontinuation of treatment. Patients should be carefully monitored until the complete resolution of all signs and symptoms (Table 5).

Table 5. Treatment adjustment for Cetuximab caused Allergic/Hypersensitivity Reaction

CTC Grade	Treatment
Grade 1 Transient flushing or rash, drug fever <38ºC	Decrease the Cetuximab infusion rate by 50% and monitor closely for any worsening
Grade 2 Rash; flushing; urticaria; dyspnea; drugfever ≥ 38°C	Stop Cetuximab infusion Administer bronchodilators, oxygen etc. as medically indicated Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to grade 1 in severity, and monitor closely for any worsening
Grade 3 or Grade 4 Grade3: Symptomatic bronchospasm, with or without urticaria; parenteral medication(s)indicated;	Stop Cetuximab infusion immediately and disconnect infusion tubing from the patient Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen etc., as

allergy-related edema/angioedema; hypotension Grade 4: Anaphylaxis	medically indicated Patients have to be withdrawn immediately from treatment and must not receive any further Cetuximab treatment

Once a Cetuximab infusion rate has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions. If the patient has a second allergic/hypersensitivity reaction with the slower infusion rate, the infusion should be stopped, and the patient should continue on chemotherapy alone. The patient must not receive any further cetuximab treatment.
If a subject experiences a Grade 3 or 4-allergic/hypersensitivity reaction at any time, Cetuximab should be discontinued.

5.4.2.1.4 Infusion-Related Reactions

Infusion reactions of Grade 1 and 2 severity may be treated with appropriate antihistamines, corticosteroid and by slowing the Cetuximab infusion rate to deliver the volume in 4 hours (but no longer). Infusion reactions of Grade 3 or higher should be managed with appropriate agents, including volume expanders, epinephrine, glucocorticoids and other agents as appropriate. Cetuximab should be immediately and permanentlydiscontinued.

5.4.2.1.5 Other Considerations

A. **Interstitial Pneumonitis**: severe interstitial pneumonitis has been described in subjects treated with the EGFR-pathway targeting therapy gefitinib. To date, no increased risk of interstitial pneumonitis has been identified with Cetuximab. Nevertheless, all subjects must have adequate chest imaging prior to commencing Cetuximab therapy in the study, as a safety precaution in order to document the baseline pulmonary condition. If there are respiratory symptoms at study entry, lung function tests and further diagnostic procedures must also be undertaken in order to diagnose pre-existing pulmonary fibrosis or interstitial pneumonitis. Furthermore, subjects will be regularly questioned about pulmonary symptoms during the study. Should pulmonary symptoms appear or worsen during or after Cetuximab treatment, a detailed description is required and investigators should use their discretion in ordering such diagnostic procedures as are necessary to elicit an accurate diagnosis.

B. **Electrolyte Disturbances**: progressively decreasing serum magnesium levels have been observed leading to severe hypomagnesemia in some patients. Hypomagnesaemia is reversible following discontinuation of cetuximab. Depending on severity, other electrolyte disturbances, mainly hypocalcaemia or hypokalaemia, have also been observed. Determination of serum electrolyte levels is recommended prior to and periodically during Erbitux® treatment. Electrolyterepletionisrecommended, as appropriate.

C. **Other Reasons for Cetuximab Discontinuation**: if a patient develops an intercurrent illness (i.e., infection) that, in the opinion of the investigator mandates interruption of Cetuximab therapy, that intercurrent illness must resolve within a time frame such that no more than two, weekly, infusions are withheld. After the interruption of treatment, the subject will continue with a Cetuximab dose of 250 mg/m² every week at subsequent visits or the last dose before the interruption if there have been previous dose reductions

5.5Selection of Trial Population

Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent following the procedure described in Section 9.2.

5.5.1 Inclusion and Exclusion Criteria

Inclusion Criteria

For inclusion in the trial, all of the following inclusion criteria must be fulfilled:

1. Signed written informed consent before any trial-related procedure is undertaken that is not part of the standard patient management
2. Male or female subjects aged ≥ 18 years
3.Histologically proven diagnosis of colorectal adenocarcinoma.
4.Diagnosis of metastatic disease
5. RAS (NRAS and KRAS exon 2,3 and 4) wild-type in tissue at initial diagnosis.
6. Efficacy of a first line therapy containing an anti-EGFR agent (panitumumab or cetuximab) with a major response achieved (complete or partial response).
7. A second line therapy.
8. More than 4 months from last dose of anti-EGFR agent administered in first line treatment before randomization.
9.Measurable disease according to RECIST criteria v1.1
10 ECOG PS of 0 to 1 at trial entry
11. Estimated life expectancy of more than 12 weeks
12. Adequate hematological function defined by white blood cell (WBC) count ≥ 2.5×10^9/L with absolute neutrophil count (ANC) ≥ 1.5×10^9/L, lymphocyte count ≥ 0.5×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin ≥ 9 g/dL (may have been transfused)
13. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range and AST and alanine aminotransferase (ALT) levels ≤ 2.5 × ULN for all subjects or AST and ALT levels ≤ 5 x ULN (for subjects with documented metastatic disease to the liver).
14. Adequate renal function defined by an estimated creatinine clearance > 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)
15. Effective contraception for both male and female subjects if the risk of conception exists (Note: The effects of the trial drug on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use effective contraception, defined as 2 barrier methods, or 1 barrier method with a spermicide, an intrauterine device, or use of oral female contraceptive. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this trial, the treating physician should be informed immediately.)
Highly effective contraception for both male and female subjects throughout the study and for at least 30 days after last avelumab treatment administration if the risk of conception exists.
16. No prior immunotherapy

Exclusion Criteria

Subjects are not eligible for this trial if they fulfill any of the following exclusion criteria:

1.Any contraindication to cetuximab and/or avelumab.
2.Past or current history of malignancies other than colorectal carcinoma, except for curatively treated basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix.

3.Pregnancy
4.Breastfeeding
5.Participation in a clinical study or experimental drug treatment within 30 days.
6.Subjects receiving immunosuppressive agents (such as steroids) for any reason should be tapered off these drugs before initiation of the trial treatment, with the exception of:
-subjects with adrenal insufficiency, who may continue corticosteroids at physiologic replacement dose, equivalent to ≤ 10 mg prednisone daily
-intranasal, inhaled, topical steroids,
-local steroid injection (e.g., intra-articular injection)
-Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent
-Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)
7.All subjects with brain metastases, except those meeting the following criteria:
-Brain metastases have been treated locally, and
-No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable)
8.Prior organ transplantation, including allogeneic stem-cell transplantation
9.Significant acute or chronic infections including, among others:
-Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome
-Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)
10.Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:
-Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible
-Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or equivalent prednisone per day.
-Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable.
-Active infection requiring systemic therapy.
11.Previous or ongoing administration of systemic steroids for the management of an acute allergic phenomenon is acceptable as long as it is anticipated that the administration of steroids will be completed in 14 days, or that the daily dose after 14 days will be ≤ 10 mg per day of equivalent prednisone.
12.Known severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade ≥ 3), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more feauters of partially controlled asthma).
13.History of hypersensitivity to Polysorbate 80 that led to unacceptable toxicity requiring treatment cessation
14.Persisting toxicity related to prior therapy of Grade > 1 NCI-CTCAE v 4.03.
15. Known alcohol or drug abuse.
16. Clinically significant (that is active) cardioavscular disease: cerebral vascular accident/stroke (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, comgestive heart failure (New York Heart Association Classification Class≥II), or serious uncontrolled cardiac arrhytmia requiring medication

17.Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
18. Any psychiatric condition that would prohibit the understanding or rendering of informed consent.
19. Vaccination within 4 weeks of the first dose of avelumab and cetuximab and while on treatment is prohibited except for administration of inactivated vaccine (i.e. inactivated influenza vaccine)
20. Legal incapacity or limited legal capacity.

5.6Criteria for Subject Withdrawal

5.6.1 Criteria for Withdrawal from Trial Treatment

Subjects will be withdrawn from trial treatment for any of the following reasons:

- PD per RECIST 1.1 (subjects receiving avelumab plus cetuximab treatment may continue past the initial determination of disease progression if the subject's ECOG PS has remained stable, and if in the opinion of the Investigator, the subject will benefit from continued treatment)
- Significant clinical deterioration (clinical progression), defined as new symptoms that are deemed by the Investigator to be clinically significant or significant worsening of existing symptoms
- Unacceptable toxicity
- Withdrawal of consent
- Occurrence of an exclusion criterion, which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor
- Therapeutic failure requiring urgent additional drug (if applicable)
- Occurrence of any Grade ≥ 3 ADRs or repetitive Grade 2 ADRs as defined in Section 5.4
- Occurrence of AEs, resulting in the discontinuation of the trial drug being desired or considered necessary by the Investigator and / or the subject
- Occurrence of pregnancy
- Use of a nonpermitted concomitant drug, as defined in Section 6.4 if considered necessaryby the Investigator or Sponsor
- Noncompliance

5.6.2 Withdrawal from the Trial

Subjects are free to discontinue the trial at any time without giving their reasons.

A subject must be withdrawn in the event of any of the following:

- Withdrawal of the subject's consent
- Participation in any other therapeutic trial during the treatment duration of this trial; however, subjects will continue to be followed for survival

If a subject fails to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case of withdrawal from the trial, the assessments scheduled for the last visit (End-of-Treatment visit) should be performed (see Section 7.3), if possible, with focus on the most relevant assessments. In any case, the appropriate End-of-Treatment electronic case report form (eCRF) visit must be completed. In case of withdrawal, subjects will be asked to continue safety and survival follow-up, which includes the collection of data on survival, subject-reported outcomes and subsequent anticancer therapy.
If a subject is withdrawn prior to progression for any reason, the subject will not be replaced.

5.7 Premature Discontinuation of the Trial

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the trial drug, for example, due to
- evidence of inefficacy of the trial drug,
- occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
- otherunfavorablesafetyfindings.

(Note: Evidence of inefficacy may arise from this trial or from other trials; unfavorable safety findings may arise from clinical or non-clinical examinations, for example, toxicology.)

- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons
- Poor enrollment of subjects making completion of the trial within an acceptable time frame

Unlikely

- Discontinuation of development of the Sponsor's trial drug

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.
The whole trial may be terminated or suspended upon request of Health Authorities.

5.8 Definition of End of Trial

If the trial is not terminated for a reason given in Section 5.8, the survival follow-up will continue until 2 years after the last subject receives the last dose of avelumab plus cetuximab.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

In this trial, the investigational drugs areavelumaband cetuximab.

6.1Description of Investigational Medicinal Product

6.1.1 Avelumab

Avelumab is a sterile, clear, and colorless solution intended for IV administration. It is presented at a concentration of 20 mg/mL in single-use glass vials closed with a rubber stopper and sealed with an aluminum polypropylene flip-off seal.

6.1.2 Cetuximab

Cetuximab (Erbitux®): concentrate for solution is provided in vials of 5 mg/ml (European registered number EU/1/04/281/005, further information on: http://www.emea.europa.eu/)

6.2 Dosage and Administration

6.2.1 Avelumab Dosage and Administration

Subjects will receive an IV infusion of avelumab at a dose of 10 mg/kg (over the duration of 1 hour) following pretreatment with H1 blockers and acetaminophen 30 to 60 minutes prior to each avelumab infusion, once every 2 weeks (refer to Appendix I). Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25 50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). Modifications of the infusion rate due to infusion-related reactions are described in Section 5.4. The dose of avelumab will be calculated based on the weight of the subject determined on the day prior to or the day of each drug administration. Complete blood count and core chemistry samples must be drawn and results reviewed within 48 hours prior to dose administration. Subjects will receive avelumab once every 2 weeks until the criteria in Sections 5.7 through 5.9 are met.

Treatment may continue past the initial determination of disease progression per RECIST 1.1 as long the following criteria are met:

- Investigator-assessed clinical benefit, without any rapid disease progression
- Tolerance of trial drug
- Stable ECOG PS
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).

The decision to continue treatment should be discussed with the Medical Monitor and documented in the trial records.

A radiographic assessment should be performed within 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with avelumab plus cetuximab.

If the Investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Schedule of Assessments (Appendix I).

For subjects who continue avelumab plus cetuximab trial therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD. This includes an increase in the sum of all target lesions and/or the development of new measurable lesions. Treatment should be discontinued permanently upon documentation of further disease progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered nonmeasureable at the time of initial progression may become measureable and therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm).

Additionally, subjects receiving avelumab who have experienced a CR should be treated for a maximum of 24 months after confirmation, at the discretion of the Investigator. If the Investigator believes that a subject may benefit from treatment beyond 24 months, it may be permissible after discussion with the Sponsor. In case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re-initiation of treatment is allowed at the discretion

of the Investigator. In order to be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab therapy. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Assessments (see Appendix I).

6.2.2 Cetuximab Dosage and Administration

Cetuximab will be administered at 1st dose at 400 mg/m^2 by i.v.infusionover 120 minutes, directly afteravelumab.

The 2nd dose and subsequent doses will be performed at 250 mg/ m^2 by i.v.infusionover60 minutes, every week andafter by avelumab every two weeks.

NB: Dilution is not required, but is possible in NaCl 0.9% only, via infusion pump or gravity drip.

6.3 Other Drugs to be Used in the Trial

Subjects will receive pretreatment with H1 blockers and acetaminophen 30 to 60 minutes prior to each avelumab and cetuximab infusion. Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumaband cetuximab is mandatory (for example, 25 50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). This regimen may be modified based on local treatment standards and guidelines as appropriate.

Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available for use in the treatment of infusion-related reactions.

Infusion of avelumab or cetuximab will be stopped in case of Grade ≥ 2 infusion-related, allergic, or anaphylactoid reactions. Following drug infusions, subjects must be observed for 2 hours post infusion for potential infusion-related reactions.

As with all monoclonal antibody therapies, there is a risk of allergic reaction. Avelumaband cetuximab should be administered in a setting that allows for immediate access and administration of therapy for severe allergic/hypersensitivity reactions, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1000 dilution), allergy medications (antihistamines), or equivalents should be available for immediate access.

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Guidelines for management of infusion-related reactions and severe hypersensitivity and flu-like symptoms according to the NCI are found in Sections 5.4.

A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

6.4 Concomitant Medications and Therapies

6.4.1 Permitted Medicines

Any medications (other than those excluded by the clinical trial protocol) that are considered necessary for the subjects' welfare and will not interfere with the trial drug may be given at the Investigator's discretion.

Other drugs to be used for prophylaxis, treatment of hypersensitivity reactions, and treatment of fever or flu-like symptoms are described in Section 5.4.

The Investigator will record all concomitant medications taken by the subject during the trial, from the date of signature of informed consent, in the appropriate section of the eCRF.
Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.
Palliative bone-directed radiotherapy may be administered during the trial. The assessment of PD will be made according to RECIST 1.1 (40) and not based on the necessity for palliative bone directed-radiotherapy.

6.4.2 Nonpermitted Medicines

As stated for the exclusion criteria in Section 5.6.1, subjects must not have had concurrent anticancer treatment (for example, cytoreductive therapy, radiotherapy [with the exception of palliative bone-directed radiotherapy, or radiotherapy administered on superficial lesions], major surgery (excluding prior diagnostic biopsy), concurrent systemic therapy with steroids or other immunosuppressive agents, or use of any investigational drug within 28 days before starting treatment.
In addition, the following treatments must not be administered during the trial:

- Immunotherapy, immunosuppressive drugs (that is, chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of irAEs), or other experimental pharmaceutical products.

- Short-term administration of systemic steroid (that is, for allergic reactions or the management of irAEs is allowed)

- Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor). Exception: Erythropoietin and darbepoietin alpha may be prescribed at the Investigator's discretion
- Bisphosphonate or denosumab treatment is not allowed unless it has been initiated more than 14 days prior to receiving the first administration of study drugs
- Vaccination within 4 weeks of the first dose of study drugs and while on trial is prohibited except for administration of inactivated vaccines (for example,inactivated influenza vaccines)

If the administration of a nonpermitted concomitant drug becomes necessary during the trial, the subject will be withdrawn from trial treatment.
Medications other than those specifically excluded in this trial (see above) may be administered for the management of symptoms associated with the administration of avelumab or cetuximab as required. These might include analgesics, antinausea medications, antihistamines, diuretics, anti-anxiety medications, and medication for pain management, including narcotic agents. Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

6.4.3Other Considerations

The following nondrug therapies must not be administered during the trial (or within 28 days before starting treatment):

- Major surgery (excluding prior diagnostic biopsy)

- Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example,hypericin)
- Subjects should not abuse alcohol or other drugs during the trial

6.5 Investigational Medicinal Products Formulation, Packaging and Storage

6.5.1 Avelumab

Avelumab is formulated as a 20.0 mg/mL solution and is supplied by Merck SeronoKGaAin single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable GMP guidelines. Avelumab will be packed in boxes each containing 1 vial. The information on the trial drugwill be in accordance with approved submission documents.
Avelumab will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature control devices.

The contents of the avelumab vials are sterile and nonpyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

Avelumab drug product must be stored at 2°C to 8°C until use, with a temperature log maintained daily. All medication boxes supplied to each trial site must be stored carefully, safely, and separately from other drugs.
Avelumab drug product stored at room temperature (23°C to 27°C) or at elevated temperatures (38°C to 42°C) for extended periods is subject to degradation. Avelumab must not be frozen. Rough shaking of avelumab must be avoided.

For application in this trial, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection). Avelumab must not be used for any purpose other than the trial.
The administration of trial drug to subjects who have not been enrolled into the trial is not covered by the trial insurance. Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

6.5.2 Cetuximab

Cetuximab will be supplied for the study by Merck SeronoKGaA. Cetuximab will be packed in boxes (with the required details concerning vial number, batch number, retest date, study number) and will be sent to study sites.

All treatment boxes supplied to the study centers must be stored carefully, safely, and separately from other drugs. Cetuximab must be stored under refrigeration at +2ºC to +8ºC. Do not freeze Cetuximab. Rough shaking of Cetuximab must be avoided.
For application in this trial, cetuximab drug product not require dilution but it is possible only with 0.9% saline solution (sodium chloride injection) via infusion pump or gravity drip. Cetuximab must not be used for any purpose other than the trial.
The administration of trial drug to subjects who have not been enrolled into the trial is not covered by the trial insurance. Any unused portion of the solution should be discarded in

biohazard waste disposal with final disposal by accepted local and national standards of incineration.

6.6 Investigational Medicinal Product Accountability

The Investigator is responsible for ensuring accountability for trial drug (avelumab or cetuximab), including reconciliation of drugs and maintenance of drug records.
Upon receipt of trial drug, the Investigator (or designee) will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided by the Sponsor and returning it to the Sponsor. A copy will be retained for the Investigator File.
The dispensing of the trial drug will be carefully recorded on the appropriate drug accountability forms provided by the Sponsor and an accurate accounting will be available for verification by the Sponsor'sl Monitor at each monitoring visit.
Trial drug accountability records will include:

- confirmation of trial drug delivery to the trial site;
- the inventory at the site of trial drug provided by the Sponsor and prepared at the site;
- the use of each dose by each subject;
- the return to the Sponsor or alternative disposition of unused trial drug; and
- dates, quantities, batch numbers, expiry dates and (for trial drug prepared at the site) formulation, as well as the subjects' trial numbers.

The Investigator should maintain records that adequately document

- that the subjects were provided the doses specified by the clinical trial protocol / amendment(s);and
- that all trial drugprovided by the Sponsor was fully reconciled.

Unused trial drug must not be discarded or used for any purpose other than the present trial. Any trial drug that has been dispensed to a subject must not be redispensed to a different subject.
The Sponsor's Monitor will periodically collect the trial drug accountability forms and will check all returns (both unused and used containers) before arranging for their return to the Sponsor or authorizing their destruction by the trial site.
At the conclusion or termination of this trial, trial site personnel and the Clinical Trial Monitor will conduct a final product supply inventory on the Investigational Drug Accountability Forms and all unused containers will be destroyed. Instructions for destruction of product will be provided to the site. The Clinical Trial Monitor will be supplied with a copy for filing of the Investigational Drug Accountability Forms.

This documentation must contain a record of clinical supplies used, unused,and destroyed and shall include information on:

- all administered units,
- all unused units,
- all destroyed units (during the trial),
- all destroyed units at the end of the trial,
- date of destruction(s),
- name and signature of the Investigator/pharmacist.

It must be ensured at each trial site that the trial drugis not used

- after the expiry date, and
- after the retest date unless the trial drugis reanalyzed and its retest date extended.

This is to be closely monitored by the Clinical Trial Monitor.

6.7 Assessment of Investigational Medicinal Product Compliance

In this trial, subjects will receive trial treatment at the investigational site. Well-trained medical staff will monitor and perform the trial drug administration. The information of each trial drug administration including the date, time, and dose of trial drug will be recorded on the eCRF. The Investigator will make sure that the information entered into the eCRF regarding drug administration is accurate for each subject. Any reason for noncompliance should be documented. Noncompliance is defined as a subject missing > 1 infusion of trial treatment for nonmedical reasons. If 1 infusion is missed and the interval between the subsequent infusion and the last administered treatment is longer than 4 weeks for nonmedical reasons, the criteria of insufficient compliance are met as well.

6.8 Treatment of Overdose

An overdose is defined as any dose ≥ 5% than the calculated dose for that particular administration as described in this clinical trial protocol. Any overdose must be recorded in the trial drug section of the eCRF. For monitoring purposes, any case of overdose, whether or not associated with an AE (serious or nonserious), must be reported to the Sponsor's Global Drug Safety department in an expedited manner using the appropriate reporting form (see below). There are no known symptoms of avelumab or cetuximab overdose to date. The Investigator should use his or her clinical judgment when treating an overdose of the trial drug.

6.9 Medical Care of Subjects After End of Treatment

After a subject has stopped trial treatment, usual treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice and depending on the subject's individual medical needs. Upon withdrawal from trial treatment, subjects may receive whatever care they and their physicians agree upon. Subjects will be followed for survival and AEs.

7 Trial Procedures and Assessments

7.1 Screening and Baseline Procedures and Assessments

During the Screening period and before any trial-related investigations and assessments are started, subjects will be asked to sign the ICF. The Screening procedures and Baseline assessments will be completed within 28 days of signing the ICF before start of treatment. Failure to establish eligibility within 28 days would result in screening failure and the subject will be excluded from the trial; however, subjects can be re-entered in the trial based on the Investigator's judgment within 6 weeks of signing the ICF. In this case, a new ICF will be required to be signed by the subject.

The subjects' information that will be documented during Screening includes the demographic information (birth date, sex, and race) and the complete medical history, including the history of mCRC previous and ongoing (concomitant) medications, and Baseline medical condition (the information of concomitant medications and AEs will be monitored throughout the trial treatment period). During Screening, subjects will undergo a physical examination, including recording body height and weight, vital signs, 12-lead ECG, and a determination of the ECOG PS.

The Screening laboratory examination includes hematology, hemostaseology, full serum chemistry (including core chemistry), and full urinalysis (dipstick plus microscopic evaluation). Adrenocorticotropic hormone (ACTH), ANA, ANCA, rheumatoid factor (RF), free thyroxine (T4), and thyroid-stimulating hormone (TSH) will also be assessed at Screening for all subjects. Additionally, HBV surface antigen and anti-HCV tests must be performed at screening to exclude hepatitis infection. If the anti-HCV antibody test is positive, infection should be confirmed by an HCV RNA test.

During Screening, a serum β-human chorionic gonadotropin (β-HCG) pregnancy test will be performed for females of childbearing potential and blood hepatitis B virus and hepatitis C virus will be performed (local laboratory) for all Screening subjects as these conditions are trial entry exclusion criteria.

Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] >40mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, FSH will be drawn at Screening.

The tumor evaluation (type and staging, etc) will be performed using CT scan or MRI (if MRI is used, CT of chest is mandatory) or any other established methods. A brain CT/MRI scan is required at Screening if not performed within 6weeks prior to start treatment. A bone scan should be done at Screening as clinically indicated. The blood samples for soluble factors, and immunogenicity will be collected before or on Day 1 before trial treatment.

7.2 Treatment Period

In this trial, the treatment will be given until PD, significant clinical deterioration (clinical progression), unacceptable toxicity, or any criterion for withdrawal from the trial or trial drug is fulfilled.

Treatment may continue past the initial determination of disease progression per RECIST 1.1 as long the following criteria are met:

- Investigator-assessed clinical benefit, without anyrapid disease progression
- Tolerance of trial drug
- Stable ECOG PS
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).

The decision to continue treatment should be discussed with the Sponsor and documented in the trial records.

A radiographic assessment should be performed within 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical

benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.
If the Investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Schedule of Assessments.
For subjects who continue trial therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD. This includes an increase in the sum of all target lesions and/or the development of new measurable lesions. Treatment should be discontinued permanently upon documentation of further disease progression.
New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15mm). Any new lesion considered nonmeasureable at the time of initial progression may become measureable and therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm).
Additionally, subjects who have experienced a CR should be treated for a maximum of 24months after confirmation, at the discretion of the Investigator. I f the Investigator believes that a subject may benefit from treatment beyond 24months, it may be permissible after discussion with the Sponsor. In case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1re-initiation of treatment is allowed at the discretion of the Investigator. In order to be eligible for re-treatment, the subject must not have experienced any toxicity that led to treatment discontinuation of the initial therapy. Subjects who re-initiate treatment will stay on trial and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Assessments.
While on trial treatment, subjects will be asked to visit the trial site at each cycle. A time window of up to 1 days before or 1 day after the scheduled visit day (-1/+1 days) will be permitted for all trial procedures. In addition, the tumor evaluation has a tumor assessment visiting time window of 5 days prior to the scheduled day(-5 days).

Subjects will receive:

- avelumab by IV infusion following pretreatment with H1 blockers (diphenhydramine 25to 50mg IV, or equivalent), and acetaminophen 500 to 650 mg (oral or IV), once every 2weeks,

  AND

- cetuximab by IV infusion at a dose of 400 mg/m^2 on day 1, then 250 mg/m^2 weekly.

During the treatment period, the following assessments will be performed:

- AEs and concomitant medications will be documented at each trial visit.
- ECOG PS will be assessed at Day 1 (unless the Screening ECOG PS was performed within 3days prior to Day 1) and at each trial visit thereafter.
- Physical examinations will be performed at each visit.
- Vital signs and body weight will be assessed in each visit.

- The laboratory hematology, hemostaseology, full serum chemistry tests and basic urinalysis will be assessed every two weeks before avelumab and cetuximab administration. If the basic urinalysis is abnormal, a full urinalysis should be performed.

- A urine or serum β-HCG pregnancy test will be performed before each administration of the trial drug for females of childbearing potential. Results of the most recent pregnancy test should be available prior to the next dosing of trial drugs.

- Tumor evaluation for all subjects will be performed every 8 weeks for 40 weeks after starting treatment, and every 12 weeks thereafter regardless of any dose delays or treatment, with a tumor assessment visiting time window of 5 days prior to the scheduled tumor assessment day (-5 days).

- ACTH, ANA, ANCA, RF will be measured at Week 13, Week 25, and if clinically indicated for all subjects.

- FT4 and TSH will be measured at baseline and at least every 8 weeks during treatment

7.3 End of Treatment

Discontinuation visit

Any subject who experiences an AE that mandates discontinuation of trial treatment should have a Discontinuation visit as soon as possible after the decision to discontinue trial treatment (at least within 7 days).

For all these subjects, the Discontinuation visit will include the following:

- Subject-reported outcomes will be completed
- Documentation of AEs and concomitant medication
- Physical examination, including vital signs and body weight
- 12-lead ECGs
- Laboratory hematology, hemostaseology, full serum chemistry, and basic urinalysis
- ECOG PS

Once the Discontinuation visit has been performed, subjects must return for the End-of-Treatment visit within 28 days (± 5 days) after discontinuation.

End-of-Treatment visit

The End-of-Treatment visit is scheduled 4 weeks (28 days ± 5 days) after the last administration of trial treatment, but before any new therapy is started, if possible, whichever occurs earlier. The End-of-Treatment visit will comprise a full assessment for safety, immunogenicity, and tumor response as appropriate, andwill include the following:

- Subject-reported outcomes
- AEs, concomitant medications, and ECOG PS
- Physical examinationincluding vital signs andbody weight
- 12-lead ECGs
- Laboratory hematology, hemostaseology, full serum chemistry, and full urinalysis (dipstick plus microscopic evaluation)
- Urine or serum β-HCG pregnancy test (in females of childbearing potential)
- Tumor evaluation (only to be performed if no disease progression was documented previously)
- ACTH, ANA, ANCA, RF, T4, and TSH levels

- Blood sample for determination of soluble factors
- Blood samples for gene expression profiling

7.4 Safety Follow-up

Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days after the last dose of avelumab administration.All subjects will have a subsequent visit scheduled 30 days after the last administration of trial treatment. The visit will include the following full assessment of safety parameters:

- After the End-of-Treatment visit only treatment related AEs have to be documented until the Safety Follow-up visit
- Concomitant medications will be documented, including further anticancer therapy
- Vital signs and body weight will be measured
- Physical examination will be performed
- ECOG PS will be assessed

Laboratory testing consisting of the following will be assessed:

- Hematology, hemostaseology, coreserum chemistry, and basic urinalysis
- ACTH, ANA, ANCA, RF, T4, and TSH levels
- A urine or serum β-HCG pregnancy test (in females of childbearing potential) will be conducted

The extended safety follow-up beyond 30 days after last avelumab administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

7.5 Long-term Follow-up

All SAEs ongoing at the Safety follow-up visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up." Any SAE assessed as related to the IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of the IMP.
Subjects without PD according to RECIST 1.1 at the End-of-Treatment visit will be followed up for disease progression (CT/MRI scans every 8 weeks[± 5 days] using the same procedures and review as while on treatment) until disease progression, lost to follow-up, or withdrawal of informed consent.
After the End-of-Treatment visit, subjects will be followed quarterly (that is, every 3 months ±1week) for survival (including assessment of any further tumor therapy). The survival follow-up will continue until 2 years after the last subject receives the last dose of study drugs.

7.6 Demographic and Other Baseline Characteristics

The assessments and procedures described in this section must be performed during the Screening period.

7.6.1 Demographic Data

The following demographic data will be recorded:

- Subject identifier

- Date of birth
- Sex
- Race
- Ethnicit

7.6.2 Diagnosis of mCRC

The tumor disease information that will be documented and verified at the Screening visit for each subject includes:

- detailed history of the tumor, including histological/citological diagnosis, grading, and staging in accordance with the International Union Against Cancer Tumor Node Metastasis Classification of Malignant Tumors at diagnosis;
- all therapy used for prior treatment of the tumor (including surgery, radiotherapy and chemotherapy, immunotherapy);
- any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy;
- current cancer signs and symptoms and side effects from current and previous anticancer treatments; and
- currentcancerdisease status.

7.6.3 Medical History

In order to determine the subject's eligibility to the trial, a complete medical history of each subject will be collected and documented during Screening, which will include, but may not be limited to, the following:

- Past and concomitant nonmalignant diseases and treatments
- All medications (including herbal medications) taken and procedures carried out within 28days prior to Screening

For the trial entry, all of the subjects must fulfill all inclusion criteria described in Section 5.5, and none of the subjects should have any exclusion criteria from the list described in 5.5.

7.6.4 Vital Signs and Physical Examination

Vital signs including body temperature, respiratory rate, heart rate (after 5-minute rest), and arterial blood pressure (after 5-minute rest) will be recorded at trial entry. A physical examination (including, in general, appearance, dermatological, head/neck, pulmonary, cardiovascular, gastrointestinal, genitourinary, lymphatic, musculoskeletal system, extremities, eyes [inspection and vision control], nose, throat, and neurologic status) will be performed and the results documented. The ECOG PSwillbe documented during the Screening phase and at each scheduled visit. Body weight and height (Screening only) will be recorded.

7.6.5 CT or MRI Scans for Tumor Assessment at Baseline

Baseline imaging will be performed within 28 days prior the start of treatment in order to establish Baseline disease status of target and nontarget lesions according to RECIST 1.1. Acceptable modalities include CT scans (chest, abdomen, and pelvis), CT chest with contrast (or chest MRI in Germany) together with MRI of the abdomen and pelvis or positron emission tomography / CT scans. The use of IV contrast is preferred unless there is a history of allergy or other risk in the opinion of the Investigator (chest X-ray is not acceptable and other imaging modalities may be

performed at the discretion of the Investigator and as clinically indicated). Bone scans should be performed if clinically indicated. Baseline tumor burden should be determined as outlined in Section 7.7. A brain CT/MRI scan is required at Screening if one has not been performed within 8 weeks prior to starting treatment. In general, lesions detected at Screening/Baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

7.6.6 Cardiac Assessments

A 12-lead ECG will be recorded at Screening and at the Early Discontinuation/End-of Treatment visit after the subject has been in a supine position breathing quietly for 5 minutes. The ECG results will be used to evaluate the heart rate, atrial-ventricular conduction, QR and QT intervals, and possible arrhythmias. Left-ventricular function evaluation (echocardiogram or multigated acquisition scan) will be also performed

7.6.7 Ophthalmologic Assessment

An ophthalmologic assessment will be also performed prior to study treatment start and clinically indicated, including at least visual acuity and slit-lamp tests

7.6.8 Clinical Laboratory Tests

Blood samples will be collected at Screening for clinical laboratory parameter evaluations. These clinical laboratory test results will serve not only as the Baseline values for subsequent safety clinical laboratory evaluations during the trial, but will also help to make sure that each enrolled subject fulfills all the trial entry criteria and does not meet any of the trial exclusion criteria for laboratory parameters.

7.7 Assessment of Efficacy

Radiographic images and physical findings (physical assessments) will be used for the local determination of tumor response or progression according to RECIST 1.1.
For each subject, tumor response assessment will be performed by CT scan or MRI (if MRI is used, CT of chest is mandatory) imaging of the chest/abdomen/pelvis (plus other regions as specifically required) and other established assessments of tumor burden if CT/MRI imaging is insufficient for the individual subject.
All the scans performed at Baseline and other imaging performed as clinically required (other supportive imaging) need to be repeated at subsequent visits (except for brain scans, unless clinically indicated). In general, lesions detected at Baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits. A brain CT/MRI scan is required at Screening if not performed within 8 weeks prior the start of treatmnet. Brain CT/MRI scans should be performed after Screening, if clinically indicated by development of new specific symptoms. A bone scan should be done as clinically indicated at Screening and beyond. For each subject, the Investigator will designate 1 or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and/or metastatic tumor masses, physical examination findings, and the results of other assessments. All available images collected during the trial period will be considered. The most appropriate measures to evaluate the tumor status of a subject should be used. The measure(s) to be chosen for sequential evaluation during the trial must correspond to the measures used to

document the progressive tumor status that qualifies the subject for enrollment. The tumor response assessment will be assessed and listed according to the Schedule of Assessments.
Treatment decisions will be made by the Investigator based on the Investigator's assessment of tumor status. For efficacy determination, tumor responses to treatment will be assigned based on the evaluation of the response of target, nontarget, and new lesions according to RECIST 1.1 (all measurements should be recorded in metric notation, as described in RECIST 1.1).

To assess objective response, the tumor burden at Baseline will be estimated and used for comparison with subsequent measurements. At Baseline, tumor lesions will be categorized in target and nontarget lesions as described in RECIST 1.1. Results for these evaluations will be recorded with as much specificity as possible so that pre-and post-treatment results will provide the best opportunity for evaluating tumor response. Any CR or PR should be confirmed, preferably at the scheduled 8-week interval, but no sooner than 5 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR. The Investigator may perform scans in addition to a scheduled trial scan for medical reasons or if the Investigator suspects PD.
Subjects who withdraw from the trial for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort should be made to confirm a clinical diagnosis of PD by imaging.

7.8 Assessment of Safety

The safety profile of the trial treatments will be assessed through the recording, reporting, and analyzing of Baseline medical conditions, AEs, physical examination findings, including vital signs, and laboratory tests.
Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the trial, from the time of the subject's signature of informed consent.
Trial site personnel will report any AE, whether observed by the Investigator or reported by the subject. Given the intended mechanism of action of avelumab, particular attention will be given to AEs that may follow the enhanced T-cell activation, such as dermatitis, colitis, hepatitis, uveitis, or other immune-related reactions. Ophthalmologic examinations should be considered, when clinically indicated, for signs or symptoms of uveitis.. The safety assessments will be performed according to the Schedule of Assessments (refer to Appendix I)

7.9 Adverse Events

7.9.1 Adverse Event Definitions

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of 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 product, whether or not considered related to the medicinal product.
In cases of surgical or diagnostic procedures, the condition / illness leading to such a procedure is considered as the AE rather than the procedure itself.
The Investigator is required to grade the severity/intensity of each AE.
Investigators will reference the NCI-CTCAE v 4.0. This is a descriptive terminology that can be used for AE reporting. A general grading (severity / intensity; hereafter referred to as severity) scale is provided at the beginning of the referenced document, and specific event grades are also

provided. If a particular AE severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The 5 general grades are:

Grade 1: Mild
Grade 2: Moderate
Grade 3: Severe
Grade 4: Life-threatening
Grade 5: Death

According to the Sponsor's convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE; however, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.
If death occurs, the primary cause of death (or event leading to death) should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this respective event; death will not be recorded as a separate event. Only if no cause of death can be reported (for example,sudden death, unexplained death), the death per se might be reported as an SAE.
Investigators must also systematically assess the causal relationship of AEs to the trial treatment using the following definitions. Decisive factors for the assessment of causal relationship of an AE to trial treatment include, but may not be limited to, temporal relationship between the AE and treatment administration, known side effects of trial treatment, medical history, concomitant medication, course of the underlying disease, trial procedures.

Not related: Not reasonably related to the trial treatment. The AE could not medically (pharmacologically/clinically) be attributed to the trial treatment in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the trial treatment. The AE could medically (pharmacologically/clinically) be attributed to the trial treatment.

Abnormal laboratory findings and other abnormal investigational findings (for example, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

Adverse Drug Reaction (ADR)
Adverse drug reactions are defined in this trial as any AEs suspected to be related to trial treatment by the Investigator and / or Sponsor.

Serious Adverse Events (SAE)
A SAE is any untoward medical occurrence that at any dose

- results in death,

- is life-threatening (NOTE: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event; not an event that hypothetically might have caused death if it was more severe),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- is otherwise considered as medically important.

Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a trial drug is also considered a SAE, as described in Section 7.9.

Events that do not meet the definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (for example, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered as SAEs; however, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events not to be considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are NOT to be considered AEs.

AEs/SAEs observed in association with disease progression

Disease progression recorded in the course of efficacy assessments only, but without any adverse signs and symptoms should not be reported as AEs. However, if adverse signs or symptoms occur in association with disease progression then these should be recorded, and reported as SAEs if meeting any seriousness criteria.

Predefined AEs of special interest for safety monitoring

Any AE that is suspicious to be a potential irAE will be considered AEs of special interest (AESI).

7.9.2 Methods of Recording and Assessing Adverse Events

At each trial visit the subject will be queried on changes in his or her condition. During the reporting period of the trial any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

Complete, accurate, and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF.

All SAEs must be additionally documented and reported using the appropriate report formas described in Section 7.9.

It is important that each AE report include a description of the event, its duration (onset and resolution dates and times to be completed when it is important to assess the time of AE onset relative to the recorded treatment administration time), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of the trial drug), and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

7.9.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of informed consent) and continues through the trial's End-of-Treatment visit, defined as 28 days (± 5 days) after last trial drug administration. After the End-of-Treatment visit only treatment related AEs have to be documented until the Safety Follow-up visit, defined as 12 weeks (± 2 weeks) after the last trial treatment administration.
Any SAE suspected to be related to the trial treatment must be reported whenever it occurs, irrespective of the time elapsed since the last administration.
Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days after the last dose of avelumab administration.
The extended safety follow-up beyond 30 days after last avelumab administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

7.9.4 Procedure for Reporting Serious Adverse Events

The Sponsor-Investigator primary responsibilities for safety reporting are to identify and follow-up on Serious Adverse Events (SAEs) experienced by participants in the study and to forward the information to the local regulatory authorities and Merck, as required by local regulations (for regulatory reporting) and as required by the ISS agreement (for reporting to Merck).

The following reportable events must be submitted to the Sponsorwithin 24 hours (or immediately for death or life-threatening events)* using the applicable safety report form provided. The Sponsor will assume responsibility for submitting the reportable event(s) to Merck within 2 business days or 3 calendar days (whichever comes first), as well as ensuring that any local reporting requirements are completed in parallel.

- Serious Adverse Events
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.

Contact information for submission of reportable events toFortunato Ciardiello*:

Fax: [## ### ### ###]*
OR
E-mail: [xxxxxxxxxxxxxxx]*
Specifying:

- PROTOCOL Number and/or Title
- Merck assigned Study Number
- SUBJECT Number
- SITE Number/PI Name
- SAE/ONSET DATE

*Sponsor/Chief Investigator (CI): the lead Institution/Investigator responsible for the ISS who has entered into a contractual agreement with Merck – please update red text as applicable depending on reporting arrangements for your study.

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (that is, within a maximum of 24 hours after becoming aware of the event) inform the Sponsor or designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions. In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone. In these cases, a written report must be sent immediately thereafter by fax or e-mail.
Reporting procedures and timelines are the same for any new information on a previously reported SAE (= follow-up).

Names, addresses, telephone, and fax numbers for SAE reporting will be included in the trial specific SAE report form.
Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, autopsy report).

In all cases, the information provided on the SAE report form must be consistent with the data about the event recorded in the eCRF. The Investigator must respond to any request for follow-up information (for example, additional information, outcome final evaluation, other records where needed) or to any question the Sponsor or designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure a prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made by the responsible Clinical Trial Monitor, although in exceptional circumstances, the Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event

7.9.5 Safety Reporting to Health Authorities, Independent Ethics Committees/Institutional Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations. The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his or her subjects to the IEC / IRB that approved the trial.

In accordance with ICH GCP guidelines, the Sponsor or designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the IEC/ IRB approval / favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor will inform the Investigator of AEs that are both serious and

unexpected and are considered to be related to the administered product (SUSARs). The Investigator should place copies of Safety reports in the Investigator Site File. National regulations with regard to Safety report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor or the designee will provide appropriate Safety reports directly to the concerned lead IEC / IRB and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC / IRB of any Safety reports provided by the Sponsor or designee and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs / SUSARs / Safety Issues will be carried out in accordance with that directive and with the related detailed guidance.

7.9.6 Monitoring of Subjects with Adverse Events

Adverse events are recorded and assessed continuously throughout the trial (see Section 7.9) and are assessed for final outcome at the End-of-Treatment visit. After the End-of-Treatment visit, only treatment related AEs have to be documented until the Safety Follow-up visit, defined as 30 days after the last trial treatment administration.

All SAEs ongoing at the Safety Follow-up visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up." Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.10 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator as related to trial treatment (for example, resulting from a drug interaction with a contraceptive medication) are considered to be AEs; however, all pregnancies with an estimated conception date during the period must be recorded by convention in the AE page / section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor or designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.9.4.

Investigators must actively follow up, document, and report on the outcome of all these pregnancies, even if the subjectiswithdrawn from the trial. The Investigator must notify the Sponsor or designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event, and the Parent-Child / Fetus Adverse Event Report Form, if the child / fetus sustains an event. Any abnormal outcome must be reported in an expedited manner as described in Section 7.9.4, while normal outcomes must be reported within 45 days from delivery. In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from the trial drug immediately.

The Sponsor or designee must be notified without delay and the subject must be followed as mentioned above.

7.11 Clinical Laboratory Assessments

It is essential that the Sponsor or designee be provided with a list of laboratory normal ranges before shipment of trial drug. Any change in laboratory normal ranges during the trial will additionally be forwarded to the CRO and the Sponsor.

Blood samples will be taken from nonfasted subjects. All routine laboratory analyses will be performed at a laboratory facility local to the trial site and relevant results must be available and checked before administration of trial treatment. The report of the results must be retained as a part of the subject's medical record or source documents. Blood samples for the full safety tests listed in Table 6 will be taken from nonfasted subjects during the Screening phase (28 days prior starting treatment), during the treatment phase as specified in Table 6 and in Appendix I, at the End-of-Treatmentvisit, and at the Safety Follow-up visit.

The ACTH, ANA, ANCA, RF, T4, TSH, and urinalysis will only be assessed at the time points defined in Table 6 and Appendix I. If confirmation of a subject's postmenopausal status is necessary, a FSH level will also be performed at Screening, see Section 7.1.

Table 6. Required Full Laboratory Safety Tests

Full Chemistry	**Core Chemistry**[a]	**Hematology**
Albumin	Alkaline phosphatase	Absolute lymphocyte count
Alkaline phosphatase	ALT	ANC
ALT	AST	Hematocrit
Amylase	BUN/total urea	Hemoglobin
AST	Calcium	Platelet count
GGT	Chloride	RBC count
BUN/total urea	Creatinine	WBC count and differential count
Calcium	Glucose	Reticulocytes
Chloride	Phosphorus/Phosphates	MCH
Cholesterol	Magnesium	Mean corpuscular volume
Creatine kinase	Potassium	MCHC
Creatinine	Sodium	
CRP	Total bilirubin	
Glucose		**Hemostaseology**
LDH		aPTT
Lipase		Prothrombin time/INR
Phosphorus/Phosphates		
Magnesium		**Basic Urinalysis** (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Full urinalysis(dipstick plus microscopic evaluation)to be performed only at the Screening and End-of-Treatment visits and a basic urinalysis prior to each administration of the trial drug.
Potassium		
Sodium		
Total bilirubin		
Total protein		
Uric acid		**TSH and T4** To be assessed at the Screeningvisit,

		and every 8 weeks
Triglycerides		
		ACTH, ANA, ANCA, RF To be assessed at the Screeningvisit, Week 13, Week 25, and at the End-of Treatment visit
Hormone		
FSH (yes / no if applicable)		

ACTH=adrenocorticotropic hormone, ALT=alanine aminotransferase, ANA=antinuclear antibody, ANC=absolute neutrophil count, ANCA=antineutrophil cytoplasmic antibody, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, FSH=follicle-stimulating hormone, GGT=gamma-glutamyltransferase, INR=international normalized ratio, LDH=lactate dehydrogenase, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, RBC=red blood cell, RF=rheumatoid factor; TSH=thyroid-stimulating hormone, T4=free thyroxine, WBC=white blood cell.

If a subject has a clinically significant abnormal laboratory test value that is not present at Baseline, the test will be repeated weekly and the subject will be followed until the test value has returned to the normal range or the Investigator has determined that the abnormality is chronic or stable.

7.12 Vital Signs, Physical Examination and Other Assessments

The ECOG PSwill be assessed at Screeningand at subsequent visits as indicated in the Schedule of Assessments (Appendix I) and documented in the eCRF. Body weight will be measured at Screening and at subsequent visits as indicated in the Schedule of Assessments (Appendix I) and documented in the eCRF. Body height will be measured at Screening only.

A physical examination will be conducted at Screening and at subsequent visits as indicated in the Schedule of Assessments (Appendix I) and documented in the eCRF (detailed description in Section 7.1). Results of the physical examination, including any abnormalities, will be documented in the eCRF. Abnormal findings are to be reassessed at subsequent visits. Also a 12-lead ECG will be recorded as indicated in the Schedule of Assessments (Appendix I). All newly diagnosed or worsening conditions, signs, and symptoms observed from Screening, whether related to trial treatment or not, are to be reported as AEs.

For female subjects of childbearing potential, a serum β-HCG pregnancy test will be carried out during the Screening phase. A urine or serum β-HCG test will be performed before each administration of trial drugduring the treatment phase and at the End-of-Treatmentvisit. Results of the most recent pregnancy test should be available prior to the next dosing of trial drug. Subjects who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and FSH>40mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

8Description of Statistical Analyses

8.1 Primary Endpoint

The primary endpoint of the trial is the OS, defined as the time (in months) starting treatment to the date of death, regardless of the actual cause of the subject's death.

The survival follow-up will continue until 2 years after the last subject receives the last dose of avelumab and cetuximab. For subjects who are still alive at the time of data analysis or who are

lost to follow- up, OS time will be censored at the last recorded date that the subject is known to be alive (date of last contact, last visit date, date of last trial treatment administration, or date of last scan, whichever is the latest) as of the data cut-off date for the analysis. If the date of last known status of alive or death date is after the data cut-off date, subjects will be censored at the data cut-off date.

8.2 Secondary Endpoints

8.2.1 Progression-Free Survival

The PFS will be determined according to RECIST 1.1. It is defined as the time from date of starting treatment until date of the first documentation of PD or death by any cause (whichever occurs first).

8.2.2Overall response rate (ORR)

The ORR will be determined according to RECIST 1.1. The ORR is defined as the proportion of all randomized subjects with a confirmed Best Overall Response (BOR) of PR or CR according to RECIST 1.1. The BOR is defined as the best response obtained among all tumor assessment visits after the date of starting treatment until documented disease progression.

8.2.3 Safety Endpoints

Safety endpoints include AEs, clinical laboratory assessments, vital signs, physical examination, ECG parameters, and ECOG PS

8.3 Description of Statistical Analyses

8.3.1 General Considerations

Baseline characteristics summary and the efficacy analysis will be performed on the total population enrolled in the study.

In order to provide overall estimates of treatment effects, data will be pooled across trial centers.

In general, descriptive summaries will be presented for the efficacy and safety variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages.

8.3.2 Analysis of Primary Endpoint

The primary endpoint of this trial is OS. The primary analysis population will be the ITT population. We consider the results from phase 3 studies with standard third line treatment as comparator (CORRECT, RECOURSE). The current study aims to demonstrate a median OS of 11.0 months (alternative hypothesis) by experimental combination for comparison with historical median OS 8.0 (null hypothesis) with standard third line treatment, which correspond to an improvement of OS at 6 months from 35% to 46%. It was estimated that we would need to enroll 66 patients to achieve with a 1-sided 5% level test in this single stage, single arm trial. The accrual period will be of 18 months and the total duration of the stud will be of 36 months. Considering a potential drop-out of approximately 15% of patients a total of 75 patients will be recruited.

8.3.3 Analysis of Secondary Endpoints

Secondary efficacy analyses will be performed on the ITT analysis set.

For the secondary endpoint analysis of PFS time according to RECIST 1.1 the statistical analysis will be the same as described for the primary analysis of OS time.

For the secondary endpoint analysis of ORR according to RECIST 1.1, the ORR in terms of having a confirmed BOR of CR or PR will be calculated along with corresponding two-sided exact Clopper-Pearson 95% CIs.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at his/her site. He/she will ensure that the trial is performed in accordance with the clinical trial protocol and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on GCP (ICH Topic E6, 1996) and applicable regulatory requirements. In particular, the Investigator must ensure that only subjects who have given their informed consent are included in the trial.

In 1998, the USA FDA introduced a regulation (21 Code of Federal Regulations, Part 54) entitled "Financial Disclosure by Clinical Investigators." For trials conducted in any country that could result in a product submission to the FDA for marketing approval and could contribute significantly to the demonstration of efficacy and safety of the trial drug (named "covered trials" by the FDA), the Investigator and all sub-Investigators are obliged to disclose any financial interest that they, their spouses, or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the trial and for 12 months following completion of the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the trial is his/her written informed consent. The subject's written informed consent to participate in the trial must be given before any trial-related activities are carried out. A separate specific PGx ICF will be provided to subjects who are willing to participate in this optional procedure, which refers to the extraction and analysis of DNA from blood and/or tumor biopsy in order to better understand how gene(s) may affect the efficacy of avelumab.

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). A subject information sheet in the local language and prepared in accordance with the Note for Guidance on GCP (ICH Topic E6, 1996) will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or his / her designate will inform the subject verbally of all pertinent aspects of the trial. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

Depending on national regulations, a person other than the Investigator may inform the subject and sign the ICF, as above.

Where the information is provided by the Investigator, the ICF must be signed and personally dated by the subject and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived by the Investigator so that the forms can be retrieved at any time for monitoring, auditing, and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor or designee and be submitted again to the IEC / IRB for review and favorable opinion. The agreed, revised information will be provided to each subject in the trial for signing and dating. The Investigator will explain the changes to the previous version.

9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database.

The subject's data collected in the trial will be stored under this number. Only the Investigator will be able to link the subject's trial data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the Clinical Trial Monitor, audits, and Health Authority inspections will be kept strictly confidential.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with national regulations.

9.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be furnished by the Sponsor or designee. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial.

Clinical trial Investigators, who are already aware of the clinical trial protocol and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, she or he will answer any questions. Any subsequent action will follow the standard processes established for the Investigators.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage shall be provided for each center participating in the trial. Insurance conditions shall meet good local standards, as applicable.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, the clinical trial protocol will be submitted together with its associated documents (such as the ICF) to the responsible IEC/IRB for its favorable opinion / approval. The written favorable opinion/approval of the IEC/IRB will be filed in the Investigator Site File, and a copy will be filed with the CRO.

The trial must not start at a site before the Sponsor or designee has obtained written confirmation of favorable opinion / approval from the concerned IEC/IRB. The IEC/IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion / approval that clearly identifies the trial, the clinical trial protocol version, and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the clinical trial will also be submitted to the concerned IEC/IRB before implementation in case of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC/IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (for example, Investigational Medicinal Product Dossier, Subject Information, and ICF) will be submitted or notified to the Health Authorities in accordance with the regulations of the countries involved in the trial.

10 Trial Management

10.1 Case Report Form Handling

The Investigator or designee will be responsible for entering trial data in the eCRF provided by the CRO and follow the data entry guidelines. It is the Investigator’s responsibility to ensure the accuracy of the data entered in the eCRFs and to sign the case report forms.

The data will be entered into a validated database. The CRO will follow the standards of the Sponsor in the database design and data structure. The CRO will be responsible for data review and processing, in accordance with the CRO’s data management procedures. Database lock will occur once quality control procedures and quality assurance procedures (if applicable) have been completed. Copies of the eCRFs will be provided to the Investigators at the completion of the trial.

10.2 Source Data and Subject Files

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the trial. This file will contain the available demographic and medical information for the subject, and should be as complete as possible.

In particular, the following data should be available in this file:

- Subject's full name
- Date of birth
- Sex
- Race
- Height
- Weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Tumor disease information
- Trial identification
- Date of subject's inclusion into the trial (that is, date of giving informed consent)
- Subject number in the trial
- Dates of the subject's visits to the site
- Any medical examinations and clinical findings predefined in the clinical trial protocol
- All AEs observed in the subject
- Date of subject's end of trial
- Date of and reason for early withdrawal of the subject from the trial or from trial drug, if applicable

It must be possible to identify each subject by using this subject file.

Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, photographic negatives, X-rays, CT or MRI scan images, ECG recordings, laboratory value listings, etc. Such documents must include at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the Investigator.

10.3 Investigator Site File and Archiving

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the Monitor, and must be ready for Sponsor audit as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and / or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance, and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH Note for Guidance on GCP (ICH Topic E6, 1996). The Clinical Trial Monitor will perform visits to the trial site at regular intervals.

Representatives of the Sponsor's Quality Assurance unit or a designated organization, as well as Health Authorities, must be permitted to inspect all trial-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs, the trial drug, and the subjects' original medical records/files.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent quality assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations.

Any amendment that could have an impact on the subject's agreement to participate in the trial requires the subject's informed consent prior to implementation (see Section 9.2).

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report according to ICH Topic E3 will be written by the Sponsor in consultation with the Coordinating Investigator.

10.6.2 Publication

The first publication will be a publication of the results of the analysis of the primary endpoint(s) that will include data from all trial sites.

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc), either in whole or in part, by Investigators or their representatives will require presubmission review by the Sponsor. The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

12. References

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11. Appendices

Appendix I Schedules of Assessments

Table 7. Screening/Baseline, Treatment Phase and Follow-up procedures

Measure	Screening/ Baseline Assements	Treatment Phase[a]								Discontinuation(x)/ End-of-Treatment Visit (X)	Safety Follow-up Visit	Long-term Follow-up[b]
	Day -28 to starting treatment	V1 W1 D1	V2 W2 D8	V3 W3 D15	V4 W4 D21	V5 W5 D28	V6 W6 D35	V7 W7 D43	Until Progression	Up to 7/28 Days (±5 days) after Last Treatment[c,d]	12 Weeks (±2weeks) after Last Treatment	Every 3 moths (±1 week)[b]
Written Informed Consent	X											
Collection of tumor tissue (when available)	X											
Inclusion/exclusion criteria	X											
Medical history[e]	X											
Demographic data	X											
HBV and HCV testing	X											
Physical examination, including Height at Screening	X	X	X	X	X	X	X	X	1 week	x/X	X	
Vital Signs	X	X	X	X	X	X	X	X	1 week	x/X	X	
Weight	X	X	X	X	X	X	X	X	1week	x/X	X	
ECOG PS	X[f]	X	X	X	X	X	X	X		x/X	X	
Enrollment (if eligible)[g]	X											
Cardiac assessment[h]	X									x/X		
Ophtalmologicassessment[i]	X											
Hematology and hemostaseology	X	X		X		X		X	2 weeks	x/X	X	
Full serum chemistry[j]	X	X		X		X		X	2 weeks	x/X	X	
	Screening/ Baseline Assements	**Treatment Phase**								**Discontinuation(x)/ End-of-Treatment Visit (X)**	**Safety Follow-up Visit**	**Long-term Follow-up[b]**
	Day -28 to starting treatment	**V1 W1 D1**	**V2 W2 D8**	**V3 W3 D15**	**V4 W4 D21**	**V5 W5 D28**	**V6 W6 D35**	**V7 W7 D43**	**Until Progression**	**Up to 7/28 Days (±5 days) after Last Treatment[c,d]**	**12 Weeks (±2weeks) after Last**	**Every 3 moths (±1 week)[b]**

Measure											**Treatment**	
Urinalysis[k]	**X**	**X**		**X**		**X**		**X**	**2 weeks**	**x/X**	**X**	
β-HCG pregnancy test[l]	**X**					**X**			**28 days**	**-/X**	**X**	
Tumor evaluation by CT scan or MRI (a bone scan should be done at Screening as clinically indicated)[m,n]	**X**							**X**	**8 weeks for 40weeks and every 12 weeks thereafter**	**-/X**		**X**
Documentation of AEs and concomitant medications[o]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**1 week**	**x/X**	**X**	**X**
ACTH, ANA, ANCA, RF	**X**								**Week 13, week 25, as indicated**	**-/X**	**X**	
T4, and TSH	**X**								**8 weeks**	**-/X**	**X**	
Pretreatment and trial drug administration[p]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**1 week**			

ACTH=adrenocorticotropic hormone, ADR=adverse drug reaction; AE=adverse events,ALT=alanine aminotransferase, ANA=antinuclear antibody, ANCA=antineutrophil cytoplasmic antibody, AST=aspartate aminotransferase,β-HCG=β-human chorionic gonadotropin, BUN=blood urea nitrogen, CR= complete response, CT=computedtomography, D=Day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology GroupPerformance Status, HAHA=human antihuman antibody, HBV=hepatitis B virus, HCV=hepatitis C virus, ICF=Informed Consent Form, IV=intravenous, MRI=magnetic resonance imaging, PR=partial response, RECIST=ResponseEvaluation Criteria in Solid Tumors version 1.1, RF=rheumatoid factor, T4=free thyroxine, TSH=thyroidstimulating hormone, V=visit, W=Week.

a A time window of up to 1 day before or 1 day after the scheduled visit day (-1 / +1 days) will be permitted for all trial procedures. The calculation of the dose of avelumab will be based on the weight of the subject determined on the day prior to or the day of each drug administration. Complete blood count and core chemistry samples must also be drawn and results reviewed within 48 hours prior to dose administration.

b Subjects with an SAE ongoing at the Safety follow-up must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up." Any SAE assessed as related to IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP. Subjects without progressive disease at End-of-Treatment visit will be followed up for disease progression (CT / MRI scans every 6 weeks [±5days]) for up to 1 year. In addition, survival information (including assessment of any further anticancer therapy) will be collected quarterly (that is, every 3 months ±1week). The survival follow-up will continue until 2 years after the last subject receives the last dose of avelumab (see Section 7.5. for details).

c Tumor evaluation at the End-of-Treatmentvisit should only be performed if no disease progression has beendocumented previously

d If another antineoplastic therapy is administered before the end of this 28-day period, the End-of-Treatmentvisit should be conducted,if possible,prior to the start of this new therapy.

e Medical history should includehistory of mCRC, previous and ongoing medications, , and Baselinemedical condition.

f If the ScreeningECOGPSwas performed within 3 days prior to Day 1,it does not have to be repeated at Visit 1.

g Enrollment will be done after the confirmation of fulfilling all screening inclusion criteria without matching any exclusion criterion (Section5.6.1).

hCardiac assessment includes: 12-lead ECG that should be assessed during screening and at the Discontinuation / End-of-Treatment visit andLeft-ventricular function evaluation (echocardiogram or multigated acquisition scan).

l Ophtalmologic assessment : visual acuity and slit-lamp test

jFull chemistry includes core serum chemistry and other laboratory studies are detailed in Table 6. Follicle-stimulating hormone at Screening, if applicable (Section 7.1).

k Full urinalysis (dipstick plus microscopic evaluation) at the Screening and End-of-Treatment visits and a basic urinalysis (dipstick only) at each visit indicated prior to administration oftrial drug. If the basic urinalysis is abnormal, then a full urinalysis should be performed.

l β-HCG should be determined from serum at Screening and from a urine or serum sample thereafter. Results of the most recent pregnancy test should be available prior to next dosing of trial drug.

m In general, the tumor visit time window is 5 days prior to the scheduled tumor assessment. In case a tumor response according to RECIST 1.1 is documented during the course of the trial, confirmation of the response should be performed according to RECIST 1.1, preferably at the regularly scheduled 6-week assessment interval, but no sooner than 5weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR. A CT scan or MRI should always be used (if MRI is used, CT of chest is mandatoryin all countries except Germany, in which case a MRI of the chest is allowed).

n A brain CT / MRI scan is required at Screening if not performed within 6 weeks prior to starting treatment, and beyond as clinically indicated. A bone scan should be done as clinically indicated at Screeningand beyond. Bone metastases detected at Screeningneed to be followed at the tumor evaluation visits.

o Adverse events and concomitant medications will be documented at each trial visit. The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of informed consent) and continues through the trial's End of Treatment visit, defined as 28 days (± 5 days) after last trial drug administration. After the End of Treatment visit only treatment related AEs have to be documented until the Safety Follow up visit, defined as 12 weeks (± 2 weeks) after the last trial treatment administration.

pPremedication: in order to mitigate infusion related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to the infusions of avelumabplus cetuximab is mandatory (for example, 25 50 mg diphenhydramine and 500 650 mg paracetamol IV or oral). This may be modified based on local treatment standards and guidelines, as appropriate.

Table 8. Soluble factors, Gene Expression profiling and Immunogenicity sampling times

Measure	Screening/ Baseline Assements	Treatment Phase[a]				
	Day -28 to starting treatment	V1	V3	V5	V7	Until Progression
		W1	W3	W5	W7	
		D1	D15	D28	D43	
		Prior to infusion	Prior to infusion	Prior to infusion	Prior to infusion	
Blood and plasma sample[a]	X					X
Tumor Tissue[b]	X					

a Blood samples will be collected from all subjects prior to infusion on Day1 (Week 1; Baseline samples for soluble factors may also be collected at Screening, instead of on Day 1 prior to dosing) and at progression.

B Tumor Tissue when availble

Appendix II Eastern Cooperative Oncology Group Performance Status

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ECOG PS[a]	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2	Ambulatory and capable of all self-care,but unable to carry out any work activities; up andabout> 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

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2298 aOken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J ClinOncol
2299 1982;5: 649-55 (40).