Investigator Initiated Clinical Trial Protocol

Efficacy and safety of infliximab for immune checkpoint inhibitor induced colitis: a multinational, randomised, open label, phase III trial – The iCaD Study

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EU CT Number: 2022-503026-12-00

NCT (ClinicalTrials.gov Identifier): pending

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Protocol summary

Title of the study: Efficacy and safety of infliximab for immune checkpoint inhibitor induced colitis: a multinational, randomised, open label, phase III trial.

Study rationale: Immune checkpoint inhibitors (ICIs) have improved survival of patients with a wide range of cancer diseases. This benefit comes with a risk of immune related adverse events (irAE). Colitis and diarrhoea are among frequently occurring irAEs and these conditions can progress severely and even fatal. Treatment of ir-colitis and ir-diarrhoea is empirically based using corticosteroids, and if no response after three days, patients will be evaluated for biological treatment. There is an urgent need for evidence based and optimised treatment.

Objectives: The primary objective is to prospectively assess whether the early introduction of biological treatment with a TNF-alpha inhibitor (infliximab) in addition to corticosteroids for severe ir-colitis/diarrhoea will reduce the time to grade ≤ 1 ir-colitis/diarrhoea compared to corticosteroids alone. Secondary and exploratory objectives includes several efficacy parameters, safety, quality of life (QoL), and translational research.

Statistical design: Multinational, randomised, open label, comparative phase III design. The study is powered for the primary endpoint. It is calculated (proportional-hazards regression model) that with a type I error of 0.05 and a type II error of 0.2, with an estimated relative hazard of 0.5, 65 events are required. Further, with an estimated median survival time for time to ≤ grade 1 ir-colitis of 10 days for the group receiving standard of care, a censoring rate of 0.1 (for both groups), an average time for follow up at 42 days, it is calculated that 195 patients are needed (97 and 98 for Arm A and B, respectively).

Patients and key inclusion criteria: ≥ 18 years. ICI treatment regimen for solid tumours. Untreated mCTCAE grade 2-4 diarrhoea or colitis. Consenting to the study. No history of inflammatory or other bowel disease. Daily intake ≤ 10 mg prednisolone for non-irAE conditions. No signs of active colonic infection, viral hepatitis, or tuberculosis.

Study procedures: Study patients are evaluated with blood samples, faecal samples and by sigmoidoscopy. Procedures are performed before randomisation and as part of follow up. All procedures are currently standard for patients treated for ir-colitis/diarrhoea.

Treatments**:** Randomisation 1:1. All patients will receive same dose of methylprednisolone i.v. daily. Patients allocated to Arm B receive in addition infliximab i.v. day 1 or 2.

Low intervention: The investigational medicinal products are authorized and used in accordance with the terms of the marketing authorisation, i.e. for the condition inflammatory bowel disease. There are no additional diagnostic procedures as these are all performed as current standard for the patients treated for ir-colitis/diarrhea. The additional monitoring procedures are only QoL and registration of safety and does not

pose any additional risk to the safety of the subjects and only minimal burden to the subjects compared to normal clinical practice.

Adverse events, risks and disadvantages: Infliximab is commonly used as biological treatment for ir-colitis/diarrhoea and is approved. Blood, faecal and sigmoidoscopy is routinely performed in this patient group. Study patients will provide additional biological material and are expected to spend more time during study procedures.

Statistical analyses: Main analyses of the efficacy endpoints will be performed on the ITT population. The Kaplan-Meier technique will be used for the survival data, log-rank test will be used for the comparison between the groups, and Cox PH model will be used to estimate the hazard ratio.

Quality of life: QoL will be assed with EORTC-QLQ-C30 questionnaire and selected PRO-CTCAE items.

Translational research: For research biobank research blood and stool samples will be collected.

Economic aspects: the trial is fully financed through external grants from non-pharma organisations. There are no economic ties between the financial supporters and the project managers.

Publication: the study will be published in international, peer-reviewed journal. Positive, negative and even inconclusive data will be published.

Ethical aspects: Inclusion is voluntary and written informed consent is mandatory. The study will be approved by the Research Ethics Medical Committees and data will be collected, handled, and processed in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR) , including registration on the internal list of health research projects via the Executive Secretariat at Odense University Hospital.

Lægmandsresumé (Danish)

Immuncheckpoint-hæmmere (kaldes i det følgende immunterapi) er nu standardbehandling for flere store kræftsygdomme herunder lungekræft, modermærkekræft samt kræft i urinvejene. For netop disse sygdomsgrupper diagnosticeres mere end 5000 danskere årligt. Immunterapi karakteriseres ved at påvirke kroppens eget immunforsvar, således at det kan genkende og angribe kræftceller. Overordnet anses immunterapi som værende mere skånsomt end kemoterapi med færre bivirkninger til følge. Visse bivirkninger kan imidlertid være alvorlige og kræver supplerende undersøgelser samt behandling. En af disse er tarmbetændelse (tilstand med immunterapi-fremkaldt inflammation/irritation af tarmslimhinden). Tarmbetændelse kan medføre varierende grader af diarré, mavesmerter og i visse tilfælde blod eller slim i afføringen. For visse behandlingsregimer ses tarmbetændelse i op mod 16% af patienterne. Det anslås at ca. halvdelen af patienter med tarmbetændelse har behov for indlæggelse til udredning og behandling. Årsagen til tarmbetændelse og eventuelt disponerende faktorer er mangelfuldt beskrevet i verdenslitteraturen. Tilstanden kan være potentielt livstruende hvis den efterlades ubehandlet eller behandlingen iværksættes

for sent. Udredning består af blodprøver, afføringsprøver og i visse tilfælde en kikkertundersøgelse. Behandlingen består primært af binyrebarkhormon, hvis rolle er at ophæve betændelsestilstanden. Behandlingen med binyrebarkhormon strækker sig typisk over mange uger og kan medføre risiko for potentielle bivirkninger som sukkersyge, knogleskørhed og øget risiko for infektioner. Endvidere er det beskrevet, at langvarig hæmning af immunforsvaret med binyrebarkhormon, potentielt kan medføre en negativ effekt på immunterapi, og dermed en øget risiko for fornyet aktivitet i kræftsygdommen. I en gruppe patienter med tarmbetændelse kan tilstanden ikke bringes i ro med binyrebarkhormon. Disse patienter behandles med infliximab; et biologisk lægemiddel, som bringer tilstanden i ro hos 80%. Behandlingen gives under indlæggelse og er veldokumenteret med få bivirkninger. Infliximab anses internationalt som værende førstevalg når binyrebarkhormon ikke er tilstrækkeligt. Et studie viser at tidlig behandling med infliximab reducerer indlæggelsestiden og forkorter tiden med symptomer, hvilket indikerer at timingen af behandlingsstart er vigtig. Det formodes, at livskvaliteten hos patienter med immunterapiudløst tarmbetændelse er ændret, men det er aktuelt ikke undersøgt.

I dette studie vil vi undersøge den optimale behandling af alvorlig immunterapiudløst tarmbetændelse. Dette vil vi gøre ved et lodtrækningsforsøg mellem standardbehandling med binyrebarkhormon overfor primær behandling med infliximab. Vi planlægger at inkludere 225 patienter, som kan inkluderes på kræftafdelingerne i Odense og Aalborg samt the Royal Marsden Hospital, London, England. Vi håber på, at infliximab vil nedsætte andelen af patienter, som kræver langtidsindlæggelse og forkorter tiden med binyrebarkhormonbehandling. Endvidere håber vi at kunne forbedre den understøttende behandling af disse patienter og øge forståelsen omkring, hvorfor denne bivirkning opstår.

1 Background and introduction

1.1 Immune checkpoint inhibitors in cancer treatment

Immune checkpoint inhibitors (ICI) have improved survival of patients suffering from the abundance of solid cancer types [1]. For some cancers, the treatment with ICIs leads to long-term survival [2-4]. ICIs are now standard treatment in many cancer types and indications are expanding. More than 3000 patients start ICI treatment annually in Denmark and this number will increase by hundreds in the years to come. The immunological role of immune checkpoints in the adaptive immune system is to regulate inflammation and maintain self-control. Interfering with these pathways, ICIs can lead to immune-mediated tissue damage [5], collectively referred to as immune related adverse events (irAEs) which can occur in any organ of the human body[6]. Currently, inhibition of three different immune checkpoints are in clinical use in cancer treatment; cytotoxic T-lymfocyte-associated protein 4 antibodies (anti-CTLA-4), programmed cell death protein 1 antibodies (anti-PD-1), and programmed death ligand-1 antibodies (anti-PD-L1)[7]. In clinical

research, primary focus has been on efficacy of the ICIs, and enormous conquests have been achieved. Now It is time to address the management and treatment of the multiple and sometimes severe and life-threatening irAEs.

1.2 Immune checkpoint inhibitor induced adverse events

The irAEs can occur in any tissue. Grading of toxicity is based upon the common terminology criteria for adverse events (CTCAE) grading scale [8]. Some irAEs are potentially fatal. The frequency and severity of irAEs depends on ICIs dosing, cancer type and treatment regimen (single ICI, ICI combination therapy, or ICI in combination with chemotherapy or targeted drugs)[9]. Treatment of irAEs consists initially of corticosteroids. The use of corticosteroids is empirically derived from the use for many genuine autoimmune diseases.

1.3 Immune checkpoint inhibitor induced diarrhoea and colitis

1.3.1 Incidence of ICI induced diarrhoea and colitis

The incidence of ICI induced colitis (ir-colitis) and diarrhoea (ir-diarrhoea) varies between ICI drugs, combinations, and tumour type. All grade ir-colitis associated with anti-CTLA-4 treatment occurs in 8-9% of patients and grade ≥ 3 ir-colitis occurs in 5-7% of the patients. For anti-PD-1 and anti-PD-L1 the frequency is lower; 0.7-1.6% and 0.6-0.9%, for all grades and grade ≥ 3 ir-colitis, respectively. By using a combination of anti-CTLA-4 and anti-PD-1 treatment, the incidences are 13-16% (all grades) and 9-11% (grade ≥ 3). Incidence of all-grade ir-diarrhoea is described as 9-14% for patients treated with anti-PD-1/anti-PD-L1, 31-41% for anti-CTLA-4 and 39-49% for combination therapy. For grade ≥ 3 ir-diarrhoea the incidence is 0.5-1% anti-PD-1/anti-PD-L1, 6-11% for anti-CTLA-4 and 7-12% for anti-PD-1 and anti-CTLA-4 combination[10-12]. From clinical trial reports we estimate that the incidence of ir-colitis/diarrhoea grade < 3 is at least double as high as compared to grade ≥ 3[13].

1.3.2 Pathogenesis

The pathogenesis of ir-colitis and ir-diarrhoea is not fully understood. The CTLA gene is described to be important in the development of regulatory T cells (Tregs) in the intestine. Murine studies have shown that CTLA-4 knockout mice develop severe autoimmune diseases including intestinal infiltration of T cells leading to fatal enterocolitis [14]. Ir-colitis is histologically and cytologically distinct from autoimmune inflammatory bowel disease (IBD). The dominant T cell in CTLA-4 induced colitis is CD4+ T cells, whereas CD8+ T cells are dominant in PD-1/PD-L1 induced colitis. The inflammatory intestinal lesions can be seen patchy, segmental or diffuse [15]

Ir-colitis can be ulcerative and non-ulcerative, and the immune infiltrating patterns can be described as chronic inflammation, lymphocytic colitis, and acute inflammation [16]. A retrospective study on ICI

treatment in patients with pre-existing IBD describes symptomatic worsening in only one third of the patients indicating a difference in the pathogenesis despite a similar clinical picture [17].

The role of the gut microbiome in ir-colitis is not fully understood. Gut microbiome is believed to impact on cancer development, treatment response to ICI, evolvement of irAEs and even treatment of irAEs and thus the potential of gut microbiome is increasingly explored[18, 19]. Growing evidence suggests that the gut microbiome plays an important role in response to ICI treatment and in development of irAEs [10, 20]. Specific gut microbiota has been demonstrated to be favourable to treatment outcome due to enhanced systemic immunity with intratumoral immune infiltration [18, 21]. Alterations of gut microbiome by antibiotics prior to ICI treatment have been shown to negatively impact outcome in cancer patients [22]. Studies of melanoma patients treated with ipilimumab show that distinct bacterial subgroups have been associated with protection against ir-colitis. Abundance of Firmicutes in the gut microbiome was associated with improved overall survival and higher risk of ir-colitis, whereas abundance of Bacteroides was associated with worse clinical outcome and lower risk of ir-colitis [20, 23].

1.3.3 Diagnosis and treatment

Ir-colitis/diarrhoea can lead to ileus, bowel perforation, ischemia and bleeding, and in rare cases, it can be fatal [9]. Diagnostic work-up includes blood samples, stool samples, and in most cases sigmoidoscopy and computerised tomography (CT) scan of the abdomen.

1.3.3.1 Corticosteroids - efficacy and safety profile

Corticosteroids are recommended as first line treatment for ir-colitis CTCAE grade ≥ 2. Treatment duration with corticosteroids is usually 4 to 6 weeks [24-27]. Approximately 60% of patients will achieve clinical remission on steroids alone [28]. In the Checkmate-067 trial subjects were randomised to receive nivolumab, ipilimumab or combination therapy. Up to 20% of patients were treated with immune modulatory medication (IMM) for grade 1-2 gastrointestinal irAEs emphasising the need of immune suppression despite low grade irAE [13]. However, often the cumulative dose of corticosteroids required to achieve clinical remission is high. Corticosteroids potentially may lead to side effects such as bone loss, hyperglycaemia, adrenal insufficiency and increased risk of bacterial infection, and it may also impair the efficacy of the ICI treatment [29].

1.3.3.2 Infliximab - efficacy

Patients who do not respond to corticosteroid treatment or relapse on corticosteroid tapering should be considered for biological treatment (e.g. TNF-alpha inhibitor). Infliximab is commonly regarded as second line treatment [24-27]. Infliximab is a chimeric monoclonal antibody targeting TNF-alpha. Approximately 80%

of patients treated with infliximab will achieve clinical remission [28]. Furthermore, infliximab is known to reduce the time to diarrhoea resolution, reduces the cumulative corticosteroid dose and is well tolerated [28, 30]. A retrospective study described the differences in timing of infliximab use. The use of infliximab as 1st line, early treatment lead to significant reduction of number of days with symptoms, of corticosteroid tapering failure, and days of hospitalisation [31], indicating improved efficacy through early use of infliximab. The majority of patients in the Checkmate-067 trial with gastrointestinal irAEs obtained symptom resolution on IMM. However, usage of secondary immune suppressants, such as infliximab, reduced the time to resolution [13].

1.3.4 Immunosuppressive medication and cancer control

Treatment with corticosteroids also may lead to a risk of unwanted immunosuppression and negative impact on tumour control. A small Danish in vitro study showed that the activation of T cells and their killing ability is unequivocally impaired by corticosteroids and infliximab. The study described a dose-dependent negative effect of corticosteroids reducing T cell activation and killing ability with approximately 50%, respectively. In contrast, infliximab reduced T cell activation with 20% and killing ability by 10% [29]. A recent retrospective study described a correlation between high usage of corticosteroids and progression of cancer [32].

2 Objectives and study endpoints

2.1 Objectives and hypotheses

The objectives of the study are to compare the efficacy and safety of an anti-inflammatory regimen consisting of initial infliximab concomitant to corticosteroid to corticosteroid alone for the treatment of severe ICI induced colitis/diarrhoea.

We hypothesise that;

1) initial treatment with infliximab will reduce the time to resolution of ir-colitis/diarrhoea compared to corticosteroid alone
2) initial treatment with infliximab will reduce the need for rescue immunosuppressive medication compared to corticosteroid alone
3) initial treatment with infliximab will reduce the overall exposure to corticosteroid compared to corticosteroid alone
4) initial treatment with infliximab will improve patients' QoL compared to corticosteroid alone
5) initial treatment with infliximab will be safe and well tolerated compared to corticosteroid alone.

2.2 Endpoints

2.2.1 Primary endpoint

- Time (days) to persistent modified CTCAE (mCTCAE; definition according to Table 3) grade ≤ 1 ir-colitis/diarrhoea. Persistent is defined as grade ≤ 1 ir-colitis/diarrhoea for five consecutive days or more with no increase in corticosteroid intake, and the event will be calculated from the first day of grade ≤ 1 ir-colitis/diarrhoea of that period (time frame: seven weeks)

2.2.2 Secondary endpoints

2.2.2.1 Efficacy

- Proportion of study subjects with grade ≤ 1 ir-colitis/diarrhoea at 72 hours (time frame: 72 hours)
- Proportion of study subjects with persistent grade ≤ 1 ir-colitis/diarrhoea at three weeks. Persistent is defined as grade ≤ 1 ir-colitis/diarrhoea for five consecutive days or more, and the event will be calculated from the first day of grade ≤ 1 ir-colitis/diarrhoea of that period (time frame: three weeks)
- Proportion of study subjects with a corticosteroid-free clinical remission (grade ≤ 1 ir-colitis/diarrhoea) after seven weeks (time frame: seven weeks)
- Proportion of study subjects requiring rescue immunosuppressive medication; Arm A (initial corticosteroid only): infliximab if no improvement to grade ≤ 2 ir-colitis/diarrhoea after 3 days (time frame: seven weeks); Arm B (initial infliximab): second dose infliximab according to physicians decision if no improvement to grade ≤ 2 ir-colitis/diarrhoea after seven days
- Cumulative corticosteroid exposure (time frame: seven weeks)
- QoL by means of EORTC-QLQ-C30 questionnaire and selected PRO-CTCAE items at baseline, 3, 12, 24, and 52 weeks after randomisation (time frame: 52 weeks)

2.2.2.2 Safety

- Proportion of study subjects with treatment related adverse events as assessed by CTCAE v5.0 (time frame: 12 weeks)
- Proportion of study subjects with colectomy or colitis-specific mortality (time frame: seven weeks)

2.2.3 Exploratory

- Proportion of study subjects with recurrence of ir-colitis/diarrhoea on subsequent reintroduction of ICI.
- Subgroup analyses stratified for ipilimumab containing ICI for time (days) to persistent grade ≤ 1 ir-colitis/diarrhoea. Persistent is defined as grade ≤ 1 ir-colitis/diarrhoea for five consecutive days or

more, and the event will be calculated from the first day of grade ≤ 1 ir-colitis/diarrhoea of that period (time frame: seven weeks)

- Progression Free Survival stratified by cancer type (time frame: duration of time from start of randomisation to time of progression or death, whichever occurs first or up to 24 months)
- Overall Survival stratified by cancer type (time frame: the duration of time from start of randomisation to time of death or up to 24 months)
- Translational research projects to explore the diversity and evolution of the immunologic cells and faecal microbiome from initiation of immune checkpoint inhibition, to the event of ir-colitis/diarrhoea, and to resolution after immunosuppressive therapy.

3 Patient selection criteria

3.1 Inclusion criteria

- Untreated mCTCAE grade 2-4 diarrhoea or colitis, *or* persistent mCTCAE grade 2 diarrhoea after administration of loperamide or equivalent for mCTCAE grade ≤ 2 diarrhoea
- No signs of colonic perforation or infection
- Age ≥ 18
- Understands the nature and purpose of the study and the study procedures and has signed informed consent
- Is able to read, understand, and complete questionnaires and daily components of the Patient Diary for the study period
- Histologically confirmed malignant solid tumours
- Treatment with immune checkpoint inhibitors (anti-CTLA-4, anti-PD-1 or anti-PD-L1) within the past 12 weeks. Immune checkpoint inhibitors can be administered as single agents or as combination therapy with anti-CTLA-4 and anti-PD-1
- No probability of a concomitant treatment (e.g. laxatives) other than the immune checkpoint inhibitor being the causal drug for the colitis or diarrhoea
- Prior treatment with immune checkpoint inhibitors is allowed
- Usage of prednisolone ≤ 10 mg daily for non irAE is allowed
- Diagnostic work up including screening for viral hepatic infection and QuantiFERON-TB for mycobacterium tuberculosis must be requisitioned but will not need to be reported prior to study enrolment
- Women of child bearing potential must have a negative serum (preferred) or urine pregnancy test within 72 hours prior to registration.

- Note: women of childbearing potential are defined as premenopausal females capable of becoming pregnant (i.e. females who have had evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons.

- Patients of childbearing / reproductive potential should use adequate birth control measures, as defined by the investigator, during the study treatment period and after the study treatment:
  - for at least 6 months after the last study treatment, or depending on the duration antineoplastic treatment
  - Note: A highly effective method of birth control is defined as a method which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. Such methods include:
    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
    - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomized partner
    - Sexual abstinence

3.2 Exclusion criteria

- Prior history of inflammatory bowel disease, colitis, or diarrhoea requiring treatment with any corticosteroid, or any other immunosuppressant medication
- Prior history of recurrent bowel disease including symptomatic diverticulosis
- Current positive testing for Clostridium difficile or other colonic infection
- Current bacterial infection requiring antibiotic treatment, or systemic fungal infection
- Ongoing antibiotic treatment for any reason
- Treatment with systemic corticosteroids within the last four weeks prior to study enrolment (daily usage of prednisolone ≤ 10 mg for non irAE conditions is accepted)
- Concurrent immune-related adverse events requiring immunosuppressant medication of any kind

- Known hypersensitivity or contraindications to systemic corticosteroids or infliximab
- Prior history of viral hepatitis with a positive viral load, known untreated mycobacterium tuberculosis, or known active herpes zoster infection

4 Trial Design

The trial is designed as a multinational, randomised, open label, phase III trial. A total of 225 patients with previously unknown inflammatory bowel disease and no signs of other immune related toxicities requiring immunosuppressants, presenting with mCTCAE grade 2-4 ir-colitis/diarrhoea will be randomised 1:1 into arm (A) standard of care (SOC) or arm (B) investigational arm. A total of 225 patients will be included to ensure 195 eligible patients for the primary endpoint. The inclusion is planned to start in Q2 2023, recruitment period is estimated to be 36 months, initial End of study for assessment of the primary endpoint will be 12 weeks after inclusion of the last patient, and the extended follow-up period will end 24 months after all patients have stopped protocol treatment.

4.1 Current standard of care

The primary treatment of CTCAE grade ≥ 2 ir-colitis/diarrhoea is systemic immunosuppression. The current level of evidence is based upon expert opinion and empirical experience for genuine IBD treatment. CTCAE grade 2 is initially treated with per oral tablet prednisolone. Dosing from 25 mg to 50 mg daily. The patient is advised to closely monitor effect on stool frequency, abdominal pain and common well being. In case of clinical improvement tapering can be planned for 4 to 6 weeks. Patients with CTCAE ≥ 3 ir-colitis/diarrhoea, or patients with CTCAE grade 2 who do not respond to oral prednisolone are referred to hospitalisation (some centres treat patients on an ambulatory basis). Intravenous methylprednisolone 80 mg daily or 40 mg twice daily is administered. Closely monitoring of stool frequency, abdominal pain and vital signs are performed. Patients, who respond to CTCAE grade ≤ 2 on intravenous treatment can start tapering from equivalent dosing of prednisolone as described above. Patients, who do not respond on methylprednisolone evaluated on day 3, are referred to a specialist in gastroenterology and evaluated for infliximab treatment. Infliximab infusions can be repeated with intervals of 5-7 days based on expert decision. To our knowledge, no studies have evaluated dose response association for infliximab treating ir-colitis/diarrhoea. Patients who do not respond to infliximab are evaluated for second line biological treatment. Patients who develop peritoneal reaction or patients who do not respond on biological treatment are evaluated for surgical intervention. Patients, who experience worsening of symptoms during prednisolone tapering, and where infectious causality has been ruled out, will be referred to a specialist in gastroenterology including evaluation for biological treatment.

4.2 Subjects allocated to Arm A

4.2.1 Dose and schedule

Study subjects randomised to standard of care. Subjects are hospitalised Day 1 and for at least 4 days. It is accepted that participating centres handle the subjects on an outpatient basis as long as all study requirements are met. Methylprednisolone 80 mg intravenously (body weight 40-80 kg; methylprednisolone 1 mg/kg if body weight < 40 or > 80 kg) will be administered from Day 1 until mCTCAE ir-colitis/diarrhoea grade ≤ 2 and hereafter converted to oral prednisolone. Schedule for study treatment is provided in Table 1. Prednisolone tapering schedule provided in Table 2. During tapering, if ir-colitis/diarrhoea increases from grade 2 to ≥ grade 3, or from grade < 2 to ≥ grade 2, re-assessment including diagnostic workup (see section 6.1 Baseline assessments) will be performed, and the patient will be evaluated for rescue infliximab. Subjects, who do not respond to methylprednisolone, i.e. ir-colitis/diarrhoea grade ≥ 2 on Day 3 (after 72 hours), will be evaluated for infliximab to be administered Day 4 or 5. Initial dosage of rescue infliximab is 5 mg/kg. Dosage of infliximab for patients referred to a second dose of infliximab will be left to the discretion of the treating physician. In the event of failure of infliximab, second line biological immunosuppressant treatment will also be left to the discretion of the treating physician. Methylprednisolone will be continued until mCTCAE ir-colitis/diarrhoea grade ≤ 2 and hereafter converted to oral prednisolone and tapering as described.

4.3 Subjects allocated to Arm B

4.3.1 Dose and schedule

Study subjects randomised to initial treatment with infliximab. Subjects are hospitalised Day 1 and for at least 4 days. It is accepted that participating centres handle the subjects on an outpatient basis as long as all study requirements are met. Infliximab will be administered Day 1 or latest Day 2 (within 48 hours). Infliximab infusion is handled as standard by skilled staff. A second dose of infliximab will be administered if ir-colitis/diarrhoea has not resolved to grade ≤ 2 on Day 7. Methylprednisolone 80 mg (body weight 40-80 kg; methylprednisolone 1 mg/kg if body weight < 40 or > 80 kg) intravenously is co-administered from Day 1 until mCTCAE ir-colitis/diarrhoea grade ≤ 2 and hereafter converted to oral prednisolone. Schedule for study treatment is provided in Table 1. Prednisolone tapering schedule is provided in Table 2. Initial dosage of infliximab is 5 mg/kg. Dosage of infliximab for subjects referred to a second dose of infliximab will be left to the discretion of the treating physician. In the event of failure of infliximab, second line biological immunosuppressant treatment will also be left to the discretion of the treating physician.

5 Therapeutic regimens

5.1 Drugs information

The study drugs used in this protocol can be used as generics and product manufacturer may vary according to the participating centre.

5.1.1 Infliximab

5.1.1.1 General information

Infliximab is a chimeric monoclonal antibody. By blocking tumour necrosis factor alpha (TNF-α), protein binding to TNF-α receptor is prevented leading to immunosuppression. Infliximab was approved by the European Medines Agency (EMA) in 1999. Infliximab is approved for treatment of inflammatory bowel disease (IBD), psoriasis arthritis, cutaneous psoriasis, rheumatoid arthritis and ankylosing spondolylitis. Internationally [24-27], infliximab is recommended as first line biological treatment for corticosteroid non-responsive ir-colitis/diarrhoea. No current approval for ir-colitis is obtained. Tuberculosis and viral hepatitis screening is performed before infliximab treatment. In case of active infection expert opinion will decide if a patient can receive treatment. ATC code: L04AB02.

5.1.1.2 Drug supply

Infliximab is available in vials of 100 mg with pharmaceutical form of concentrate for solution for infusion. Participating sites will ensure availability of infliximab as part of the hospital's standard supply for use in the study.

5.1.1.3 Packaging, dispensing and storage

The investigator should ensure that infliximab is stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information and per local regulations. Additional information on storage, handling, dispensing, and infusion information for infliximab are described in the SmPC (Appendix B.1). Information on date, time, and dose will be collected for all drug administrations for each study participant according to Regulation EU No 536/2014.

Administration is performed by skilled staff. Observation for possible infusion reaction is mandatory after infusion is completed. Time of observation will follow local guidelines at participating centres.

5.1.1.4 Side effects to infliximab

The SmPC for infliximab is enclosed as Appendix B.1, where the complete list of side effects can be accessed in section 4.8.

5.1.2 Methylprednisolone

5.1.2.1 General information

Methylprednisolone is a synthetic corticosteroid. Methylprednisolone is primarily used for anti-inflammatory disorders as immunosuppressant. Methylprednisolone is administered intravenous with pharmaceutical form suspension for infusion. Severe ir-colitis and ir-diarrhoea are treated with intravenous methylprednisolone because the bowel inflammation is thought to reduce bowel absorption from per oral corticosteroids. Methylprednisolone were approved in 1989 by EMA. ATC code: H02AB04.

5.1.2.2 Drug supply

Methylprednisolone is available in vials of 40 mg. Methylprednisolone is a drug used for standard treatment first line for ir-colitis or diarrhoea CTCAE grade ≥ 3. Participating sites will ensure availability of methylprednisolone for use in the study as part of the hospitals standard supply.

5.1.2.3 Packaging, dispensing and storage

The investigator should ensure that methylprednisolone is stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information and per local regulations. Additional information on storage, handling, dispensing, and infusion information for methylprednisolone are described in the SmPC (Appendix B.2). Information on date, time, and dose will be collected for all drug administrations for each study participant according to Regulation EU No 536/2014.

5.1.2.4 Side effects to methylprednisolone

The SmPC for methylprednisolone is enclosed as Appendix B.2 in section 4.8, where the complete list of side effects can be accessed.

5.1.3 Prednisolone

5.1.3.1 General information

Prednisolone are synthetic corticosteroids for per oral use. Prednisolone is used as an anti-inflammatory drug with the primary effect on the glucocorticoid receptor. Prednisolone is used for treatment of moderate ir-colitis and ir-diarrhoea.

ATC code: H02AB06.

5.1.3.2 Drug supply

Prednisolone is available in tablets of 25 or 5 mg. Oral corticosteroids are internationally recommended as initial treatment for ir-colitis and ir-diarrhoea CTCAE grade 2 [24-27]. Participating sites will ensure availability of prednisolone for use in the study as part of the hospitals' standard supply.

5.1.3.3 Packaging, dispensing and storage

The investigator should ensure that prednisolone is stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information and per local regulations. Additional information on storage, handling, and dispensing information for prednisolone are described in the SmPC (Appendix B.3). Prednisolone in original packages will be provided to each study participant. Information on date, time, and dose will be collected for all drug administrations of prednisolone for each study participant according to Regulation EU No 536/2014.

5.2 Withdrawal criteria

Patients may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice.

The following conditions require permanent patient discontinuation from study treatment:

- Completion of scheduled study treatment as per protocol guidelines
- Excessive toxicity precluding further therapy, according to the responsible physician or patient
- Development of any concurrent irAE requiring additional systemic immunosuppressive therapy
- Development of any medical conditions for which the patient must permanently discontinue
- Sexually active patients who refuse to use medically accepted adequate birth control methods as described in the patient selection criteria during the course of the study
- Non compliance of patient with study treatment or requirements
- Pregnancy or intent to become pregnant

Patients who discontinue will receive standard of care treatment and will be controlled according to standard surveillance program of the respective hospitals/sites.

5.3 Concomitant treatments

5.3.1 Supportive care

All treatments considered necessary may be administered at the discretion of the investigator in alignment with the standards of care and must be adequately recorded including all prescription, herbal supplements, and intravenous medications and fluids. If changes occur during the study period, documentation of drug

dosage, frequency, route, and date must also be recorded. Use of antibiotics and corticosteroids received within 30 days before the first dose of study treatment and 30 days after the last infusion of study treatment should be recorded.

6 Study assessments and procedures

6.1 Baseline assessments - prior to randomisation

After signing informed content patients are screened for eligibility.

Screening procedure includes:

- Physical examination including ECOG performance status, body weight, abdominal examination, vital signs, stool frequency reporting and screening for further irAEs
- Concomitant medication including usage of antibiotics and corticosteroids within the last 30 days before randomisation
- Comprehensive blood test panel (standard), including:
    - Hematology panel: Haemoglobin (Hgb), leucocytes with differential count, platelets
    - Renal panel: Creatinin, sodium, potassium, ionised calcium
    - Liver panel: alanine transaminase (ALAT), alkaline phosphatase, bilirubin, lactate dehydrogenase, albumin
    - Miscellaneous: c-reactive protein
    - Human chorionic gonadotropin (hCG) for women of child bearing potential (note: urine hCG allowed)
    - Screening for chronic infection: viral hepatitis, and tuberculosis
    - Biobank blood sample (optional) for immunological cell analyses
- Faecal test panel (standard), including:
    - Stool sample with polymerase chain reaction (PCR) for bacterial or viral infection
    - Stool sample for faecal calprotectin
- Faecal test panel (optional, and only at Sponsor's site), including:
    - Biobank stool sample for microbiome analyses
- Sigmoidoscopy with random biopsies (standard)
    - Sigmoidoscopy will be performed by skilled gastroenterologists
    - Minimum three (or more if judged reasonable by the gastroenterologist) biopsies from different segments of the recto-sigmoid will be sampled and routinely investigated by the pathologist
- Patient reported outcome:

    - EORTC-QLQ-C30 questionnaire and selected PRO-CTCAE items regarding health related QoL
- Patient in- and exclusion criteria must be reviewed for eligibility before randomisation

6.2 Randomisation and initial treatment

Randomisation can be performed after completion of the baseline assessments. Treatment schedule for patients randomly assigned 1:1 to treatment Arm A or B is provided in Table 2.

6.3 During treatment

6.3.1 PROMS

6.3.1.1. Patient Diary

All study subjects in either treatment group will complete the Patient Diary on a daily basis from baseline/Day 1 to Day 49 (7 weeks). The following will be registered daily:

- Stool frequency
- Bristol stool scale type
- Abdominal pain (numerical rating scale)
- Blood in stool (yes/no)
- Remembered to take the study medication – check box

6.3.1.2 QoL questionnaires

All study subjects in both treatment groups will complete the EORTC-QLQ-C30 questionnaire and selected PRO-CTCAE items as follows:

- EORTC-QLQ-C30 questionnaire and selected PRO-CTCAE items at baseline, 3, 12, 24, and 52 weeks after randomisation

6.3.2 Day 1 until remission to mCTCAE grade ≤ 2/start prednisolone

All study subjects in both treatment groups will be assessed daily during the required minimum 4 days of hospital admission (not qualifying as SAE), or in the ambulatory setting for centres providing outpatient management, or until mCTCAE grade ≤ 2 and subsequently conversion from i.v. methylprednisolone to oral prednisolone. The below procedures are standard in relation to evaluation of patients with ir-colitis/diarrhoea:

- mCTCAE grade of ir-colitis/diarrhoea
- Signs of treatment related AEs
- Signs of concurrent irAEs
- Physical examination including

- Vital signs
- ECOG performance status
- Abdominal examination
- Body weight

- Lab values
  - Hematology panel: Haemoglobin (Hgb), leucocytes with differential count, platelets
  - Renal panel: Creatinin, sodium, potassium, ionised calcium
  - Liver panel: alanine transaminase (ALAT), alkaline phosphatase, bilirubin, lactate dehydrogenase, albumin
  - Miscellaneous: c-reactive protein

The assigned study project staff will follow up on the baseline assessments, e.g. pending lab tests.

6.3.3 Rescue treatment

Rescue treatment is needed if subjects fail to respond on initial treatment or if ir-colitis/diarrhoea increases from grade 2 to ≥ grade 3, or from grade < 2 to ≥ grade 2 during prednisolone tapering. Additional assessments are recommended before rescue treatment:

- Physical examination including
  - Vital signs
  - Abdominal examination
  - Body weight
- Lab values
  - Comprehensive blood test panel (standard), including:
    - Hematology panel: Haemoglobin (Hgb), leucocytes with differential count, platelets
    - Renal panel: Creatinin, sodium, potassium, ionised calcium
    - Liver panel: alanine transaminase (ALAT), alkaline phosphatase, bilirubin, lactate dehydrogenase, albumin
    - Miscellaneous: c-reactive protein
    - Screening for chronic infection: viral hepatitis, and tuberculosis
    - Human chorionic gonadotropin (hCG) for women of child bearing potential (note: urine hCG allowed)
  - Faecal:
    - Stool sample with polymerase chain reaction (PCR) for bacterial or viral infection
    - Stool sample for faecal calprotectin
  - Endoscopy:

- Optional and left to the discretion of the treating physician

6.3.3.1 Rescue treatment of subjects allocated to arm A

Subjects, who do not respond to methylprednisolone, i.e. ir-colitis/diarrhoea grade ≥ 2 on Day 3 (after 72 hours), will be evaluated for infliximab to be administered Day 4 or 5. Initial dosage of rescue infliximab is 5 mg/kg. Dosage of infliximab for patients referred to a second dose of infliximab will be left to the discretion of the treating physician. In the event of failure of infliximab, second line biological immunosuppressant treatment will also be left to the discretion of the treating physician. A minority of subjects are in need of surgical resection. The indication of surgery is based upon shared consultation by the subject, the oncologist, the gastroenterologist and the abdominal surgeon.

Methylprednisolone will be continued until mCTCAE ir-colitis/diarrhoea grade ≤ 2 and hereafter converted to oral prednisolone and tapering as described.

6.3.3.2 Rescue treatment of subjects allocated to arm B

Subjects who fail to respond to initial infliximab is referred to a second dose of infliximab. Dosing will be left to the discretion of the treating physician. In the event of failure of infliximab, second line biological immunosuppressant treatment will also be left to the discretion of the treating physician. A minority of subjects are in need of surgical resection. The indication of surgery is based upon shared consultation by the subject, the oncologist, the gastroenterologist and the abdominal surgeon.

6.3.4 Follow up post hospital discharge until week 12

All study subjects in both treatment groups will:

- Continue the Patient Diary registration until day 49
- Complete the QoL questionnaire as described week 3 and 12
- Follow the prednisolone tapering schedule
- Have weekly telephone calls with assigned staff for symptoms and adverse events assessment until day 49 (SAE/SAR/SUSARs will be registered and reported in this time frame)
- Biobank stool sample for microbiome analyses (optional, and only at Sponsor's site) week 3 and 12

In the event that the ir-colitis/diarrhoea worsen to mCTCAE grade > 2, the study subject will be hospitalised or managed in an ambulatory manner, subjected to diagnostic re-assessment for ir-colitis/diarrhoea (not including endoscopy), and will be assessed for rescue infliximab. Methylprednisolone will be reinitiated until mCTCAE grade ≤ 2. Such hospitalisations qualifies as an SAE.

6.4 Follow-up after week 12

Patients who achieved clinical remission (mCTCAE grade ≤ 1 ir-colitis/diarrhoea) and successfully weaned off the prednisolone enter the follow up phase. At follow up visits, patients are evaluated clinically, with blood samples, and imaging according to cancer type. Surveillance programmes are dependent on cancer type and local guidelines. Follow up visits are usually scheduled every third months the first two years, every sixth months the following three years for a total of five years. Follow up can be altered due to clinical indication. For every follow up visit, patients are screened for irAEs and cancer treatment response evaluation. Potential use of corticosteroids will be registered with information on dosing and indication.

The following data will be collected in the follow-up phase:

- QoL data completed by patients at week 24 and 52
- Tumour response evaluation/treatment response until two years after randomisation or death whatever comes first
- Death if occurring before or at two years after randomisation

7 Criteria of evaluation for response and adverse events

7.1 Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Common Terminology Criteria for Adverse Events (CTCAE) is a descriptive terminology which can be utilised for AE reporting. A grading (severity) scale is provided for each AE term. At the time this protocol was issued, the full CTCAE document was available on the NCI web site, at the following address:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Treatment response to ir-colitis/diarrhoea is evaluated according to mCTCAE to assess the severity of the irAE. Descriptions are provided in Table 3.

8 Statistical considerations

8.1 Statistical design

This trial is designed as a multinational, randomised, open-label, phase III trial.

8.1.1 Sample size

The primary endpoint of this trial is to prospectively assess the time (days) to persistent grade ≤ 1 ir-colitis/diarrhoea. Persistent is defined as grade ≤ 1 ir-colitis/diarrhoea for five consecutive days or more, and the event will be calculated from the first day of grade ≤ 1 ir-colitis/diarrhoea of that period.

With the primary endpoint time to ≤ grade 1 ir-colitis, to demonstrate a statistically significant difference, it is calculated (proportional-hazards regression model) that with a type I error of 0.05 and a type II error of 0.2, with an estimated relative hazard of 0.5, 65 events are required. Further, with an estimated median survival time for time to ≤ grade 1 ir-colitis of 10 days for the group receiving standard of care, a censoring rate of 0.1 (for both groups), an average time for follow up at 42 days, it is calculated that 195 patients are needed (97 and 98 for Arm A and B, respectively).

8.1.2 Randomisation and stratifications

Patients will be centrally randomised (for practical details, see section registration/randomisation procedure). Random treatment allocation will be stratified by:

- mCTCAE grade colitis/diarrhoea:
    - Grade 2
    - Grade 3-4
- ICI regimen:
    - Anti-CTLA-4 (ipilimumab) containing regimens
    - Non-anti-CTLA-4 (ipilimumab) containing regimens
- Cancer disease:
    - Melanoma
    - Renal cell cancer
    - Other
- Centre

8.2 Statistical analysis plan

8.2.1 Analysis populations

- Intention-to-treat (ITT) population: All randomised patients will be analysed in the group they were allocated by randomisation
- Safety population (SP): All patients who have started their allocated treatment (at least one dose of the study drug)

A patient will be considered to be eligible if he/she did not have any deviation from the patient entry criteria. Potential eligibility problems will be assessed by the Clinical Research Physician at time of medical review.

8.2.2 Patient disposition

Patient and disease characteristics at baseline will be displayed by treatment group in the Intent-to-treat population.

For categorical variables, frequency tables (with %) will be presented with descriptive listings of details specified in text fields, when appropriate. Continuous variables will be reported using median, range and interquartile range.

A consort diagram will be used to document the flow of patients through the various stages of the study. Number of patients in the various analysis populations will be presented in a table, and reasons for exclusions will be detailed by patient in listings.

8.2.2.1 Treatment exposure

Frequency tables and summary statistics (median, range, interquartile range) of the following parameters will be provided in both groups:

- In treatment Arm A
    - Number of injections and dose in mg/kg of methylprednisolone during the 12 weeks period
    - Cumulative dose of prednisolone during the 12 weeks period
    - Duration of exposure: study day for the last dose of oral prednisolone
    - If administration of corticosteroid was delayed and/or skipped: reason
    - Reason for stopped corticosteroid
    - Rescue infliximab
        - Number of infusions and dose in mg/kg of infliximab during the 12 weeks period
        - Duration of exposure: study day for the last infusion of infliximab
- In treatment arm B:
    - Number of infusions and dose in mg/kg of infliximab during the 12 weeks period
    - Duration of exposure: study day for the last infusion of infliximab
    - If administration of infliximab was delayed and/or skipped: reason
    - Reason for stopped infliximab
    - Number of injections and dose in mg/kg of methylprednisolone during the 12 weeks period
    - Cumulative dose of prednisolone
    - Duration of exposure: study day for the last dose of oral prednisolone
    - If administration of corticosteroid was delayed and/or skipped: reason

- Reason for stopped corticosteroid
- Rescue second line biologic treatment [drug name/2. line bioX]
    - Number of infusions and dose in mg/kg of [drug name/2. line bioX] during the 12 weeks period
    - Duration of exposure: study day for the last infusion of [drug name/2. line bioX]

8.2.2.2 Safety

For the safety parameters, the worst CTCAE v5.0 grade of each adverse event will be tabulated, irrespective of relationship to treatment. The percentage of patients on each treatment group presenting severe treatment-related AE (grade ≥ 2) will also be calculated.

Treatment-related toxicity resulting in death including colitis-specific mortality, resulting in colectomy, or that stopped treatment will be calculated and listed.

Safety endpoints will be reported for the safety population.

Serious Adverse Events and a list of Serious Adverse Reactions and Suspected Unexpected Serious Adverse Reactions, if any, will be reported annually.

8.2.3 Statistical methods

8.2.3.1 Analysis methods for efficacy endpoints

All the main analyses of the efficacy endpoints will be performed on the ITT population using the ITT principle: patients will be considered in the treatment group as indicated at randomisation, regardless the treatment duration, cause of going off-protocol treatment, possible switch to another treatment, etc.

8.2.3.1.1 Survival analyses

Data for the primary endpoint (time to grade ≤ 1 ir-colitis/diarrhoea) are of the time-to-event/survival analysis type and the Kaplan-Meier technique will be used to obtain estimates of the time-to-event distribution. The comparison of the time to grade ≤ 1 ir-colitis/diarrhoea between the two treatment groups will be done using the log-rank test at a 1-sided alpha level of 5% (2-sided alpha level of 20%).

The hazard ratio (HR) between the two treatment groups along with its two-sided 95% confidence interval (CI) will be obtained by fitting a Cox proportional hazards (PH) model with the treatment group variable as unique covariate.

The exploratory endpoint stratifying for ipilimumab containing ICI regimens will be handled in a similar manner including the stratification by ipilimumab in the model.

The exploratory endpoints PFS and OS stratified by cancer disease will in addition to the above use of the Kaplan-Meier technique and the Cox PH model include median survival time, and rates at fixed timepoints

(PFS and OS at 6-, 12-, 18- and 24 months) will be derived from the Kaplan-Meier estimate and corresponding CI will be derived based on Greenwood formula.

8.2.3.1.2 Analyses for group comparisons

Proportions of study subjects in the two groups for the relevant secondary endpoints will be calculated and summarised. Proportions will be compared using Fisher's exact test with p-values < 0.05 demonstrating statistical significance of the observed differences.

Assuming a normal distribution of the sample, difference in cumulative corticosteroid exposure between the two groups will be analysed using the unpaired two-sample t-test for the sample means providing 95% CI and p-value < 0.05 demonstrates statistical significance of the observed difference.

8.2.3.2 Analysis methods for the translational research project

Analyses methods for the translational research projects will be addressed in a specific protocol with a comprehensive statistical analysis plan.

8.2.3.4 Analysis methods for patient reported outcomes

The guidelines for reporting the EORTC QLQ-C30 questionnaires and selected PRO-CTCAE items will be followed.

8.2.4 Missing data

Missing data is a potential major source of bias in HRQoL assessment. Information on the nature of missing data (e.g. single items on the scale, complete missing of the scale) will be reported.

8.2.5 Data recoding and display

Frequency tables will be tabulated (by treatment group) for all categorical variables by the levels of the variables as they appear on the case report form (CRF) (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the study subject fulfilling the condition for the specification (study subject id, institution, treatment group, value of the item and text field contents).

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories. For adverse events, the CTCAE v5.0 grading scale will be used. Other continuous variables (e.g. age, drug dose) are presented using the median and range. If appropriate, continuous data may also be presented in categories (e.g. age may also be grouped in decades).

8.3 End of study

End of study occurs when all of the following criteria have been satisfied:

- Last patient last visit, i.e. 12 weeks after inclusion of the last patient
- The database has been fully cleaned and frozen for the study primary efficacy endpoints

The follow-up period will continue 24 months after all patients have stopped protocol treatment. Data during the follow-up period will be collected at time points for patients' normal follow-up for the cancer disease.

9 Data monitoring and quality control

9.1 Monitoring

The study will be conducted in accordance with the protocol and will comply with applicable legislation, ICH-GCP, and the Regulation EU No 536/2014.

Prior to the start of the study the Sponsor/Study-coordinator or a designee will review with the local site staff the protocol, study requirements, and their responsibilities to satisfy regulatory and ethical requirements. For monitoring the study the Sponsor is responsible for adequate monitoring (i.e. local GCP units will be used).

The monitors will monitor the study consistent with the demands of the study and site activity to verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of patients are being protected
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements

The Investigator agree to allow the monitor direct access to all relevant source documents.

A Monitoring Plan agreed between sponsor and the GCP units will be issued and required to follow.

9.2 Quality assurance

If an audit or inspection occurs, each Investigator and each study site/institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

9.3 Records retention

Following closure of the study, the Investigator must maintain all site study records in a safe and secure location specified in the Site File. The records must be maintained to allow easy and timely retrieval, when

needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The Investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The period for retaining these records will be twenty-five (25) years after closure of the study, defined as last patient last visit.

The Investigator must notify Sponsors/Study-coordinator of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the Investigator leaves the site.

9.4 Provision of study results and information to investigators

When the clinical study report is completed, Sponsors/Study-coordinator will provide the Investigator with a full summary of the study results. The investigator is encouraged to share the summary results with the subjects, as appropriate. In addition, the Investigator will be given reasonable access to review the relevant statistical tables, figures, and reports and will be able to review the results for the entire study at a site provided by Sponsors/Study-coordinator.

10 Translational research

10.1 Objectives

In order to explore the pathogenesis of ir-colitis/diarrhoea and in parallel assessing the prognostic and/or predictive value of potential biomarkers, this protocol includes a prospective biobanking of human biological material (HBM) in view of future biomarker discovery and validation studies.

Blood and stool samples will be collected.

Future translational research projects may include but are not restricted to:

- Immuno-pathology analyses
    - T- and B-cell characterisation
    - Auto-antibody analyses
    - Cytokines analyses
- Faecal microbiome analyses

10.2 Biobank for future research

Provided patients' written informed consent, specimens (blood and stool samples) will be stored in a biobank for future research (OPEN Biobank, Odense University Hospital). The ICiTox Data- and Biobank, which will be used for this purpose, is registred on the internal list of health research projects via the Executive Secretariat at Odense University Hospital (Acadre file id 22/51509). Application for future research projects will be submitted to the Research Ethics Medical Committees. If a patient withdraws his/her informed consent, all biological material will be destroyed at the patients' request. Biobank samples are stored for a maximum of fifteen (15) years.

10.3 General principles for human biological material collection

Study subject consenting to the HBM collection will have to sign a separate informed consent sheet.

Study subjects from Sponsor's institution have had the opportunity to participate in a concurrent biobank for future research with collection of blood and stool samples prior to the first dose of ICI, and at specified time intervals. These baseline samples will be analysed in the relation to emerging irAE, e.g. colitis/diarrhoea. We aim at pairing samples to elucidate the pathogenesis and potential future treatment strategies of ir-colitis/diarrhoea.

10.3.1 Blood samples

Blood samples will be collected

1. Before receiving the first dose of study medication
2. After 3 weeks +/- 1 week
3. After 12 weeks +/- 2 weeks

10.3.2 Stool samples

Stool samples will be collected

1. Before receiving the first dose of study medication
2. After 3 weeks +/- 1 week
3. After 12 weeks +/- 2 weeks

11 Patient registration and randomisation procedure

11.1 General procedure

Only authorised investigators can include patients for registration and randomisation. The registration procedure can proceed when verification of written informed consent and verification of eligibility is performed. Eligible patients are registered by a unique patient identification number. This number is used to identify the study subject and will be used in the eCRF. Randomisation is electronically through Research Electronic Data Capture (REDCap) Randomization Module and will be performed by trained staff appointed by the principal investigator. Each study subject ID will be allocated a randomisation code. The randomisation code correlates to either Arm A or B. Stratification will be done according to the listing in section 8.1.2.

11.2 Registration and randomisation

A patient can only be registered after signature of the Patient Informed Consent. The procedure for randomisation in REDCap will be thoroughly explained in the Randomisation standard operating procedure document (Appendix C)

12 Forms and procedures for collecting data

12.1 Case report forms and schedule for completion

An eCRF will be created as a REDCap database for the collection of data. All required data will be listed and the source of the data specified in a source data document for each participating site. Direct registration of source data in the eCRF will be performed by study subjects when using the electronic option for completion of the QoL data. Subjects are not obliged to use the same registration method for all assessment points.

12.2 Patient reported outcomes measurements

A paper Patient Diary will provided to the study subject at study entry. This is a key document for the study, containing the data for the primary endpoint. To ensure study subjects are trained to properly complete the diary, experienced staff will perform bedside educational reviews as part of initial hospitalisation. A thorough review of the patient diary is mandatory in the daily medical ward round. When discharged weekly telephone interviews are planned to assure correct completion.

The QoL questionnaires will be handed to the patient at the specified time points. QoL questionnaires can be completed on paper or electronically.

12.3 Data flow

The forms must be completed electronically. The PROM paper forms (Patient Diary, QoL questionnaires) will be collected by the staff and data entered electronically.

The list of staff members authorised to enter data/to sign case report forms (with a sample of their signature) must be identified on the signature log at each participating site.

In all cases, it remains the responsibility of the principal investigator to check that data are entered in the database/case report forms, are sent to the Sponsor/Study-coordinator as soon as possible, and that the (electronic) forms are filled out completely and correctly.

The data manager appointed by Sponsor/Study-coordinator will perform consistency checks on the received data. Queries will be issued in order to resolve other inconsistent data.

A copy of the PROMs should be sent electronically to Sponsor/Study-coordinator as soon as possible, while the original source document should be kept on site. If there are queries to the PROM forms, they will be raised electronically. The data manager will subsequently apply the corrections into the database.

If an investigator (or an authorised staff member) needs to modify an eCRF after the form has been locked by the local investigator, he/she should create a request for data correction in the data management system.

13 Immediate safety reporting

ICH GCP and the Regulation EU No 536/2014 require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

13.1 Definitions

AE: An Adverse Event is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. An adverse event can therefore be any unfavourable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An Adverse Reaction of an investigational medicinal product is defined as “any noxious and unintended response to a medicinal product related to any dose administered”.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An Unexpected Adverse Reaction is “any adverse reaction, the nature, or severity of which is not consistent with the applicable product information" (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTCAE grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A Serious Adverse Event is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- requires inpatient hospitalisation or prolongation of existing patient hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a medically important event or reaction
- Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

SAR: A Serious Adverse Reaction is defined as any SAE which is considered related to the protocol treatment

SUSAR: Suspected Unexpected Serious Adverse Reaction. SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate regulatory authorities

Inpatient hospitalisation: a hospital stay equal to, or greater than, 24 hours

13.2 Exceptions

The following situations do not need to be reported as SAEs:

- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalisation which was planned before the patient consented for study participation and where admission did not take longer than anticipated.
- A hospitalisation planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital.
- Medical or surgical procedure deemed not related to the cancer or the cancer treatment; the condition that leads to the procedure is an (S)AE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

13.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v5.0.

13.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following the definitions in this table:

Relationship to the protocol treatment	**Description**
Reasonable possibility	There is a reasonable possibility that the protocol treatment caused the event
No reasonable possibility	There is no reasonable possibility that the protocol treatment caused the event

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the SAE form and if necessary, the reason for the decision will also be recorded.

13.5 Reporting procedure for investigators

This procedure applies to all Serious Adverse Events (SAEs) occurring following the seven (7) weeks after randomisation of a study subject. After this, only SAEs which are considered to have a reasonable possibility to be related to the protocol treatment or study participation must be reported. For subjects randomised and never treated with study drug, SAEs are not required to be reported.

- All reporting must be done by the Investigator or authorised staff member (i.e. on the delegation log) to confirm the accuracy of the report.
- All SAE data must be collected on the study-specific SAE form provided electronically in the REDCap study database.
- All SAEs must be reported immediately and no later than 24 hours from the time the Investigator or staff became aware of the event.
- All SAE related information needs to be provided in English.
- All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.
- Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report.
- Queries to the report sent out by the Sponsor's data manager need to be answered within 7 calendar days.

13.6 Reporting responsibilities for Sponsor

It is the responsibility of the Sponsor to report the following safety items:

- SUSARs will be reported to EudraVigilance.
    - The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days. All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor. The sponsor shall also inform all investigators.
- Unexpected events, i.e. events that affect the benefit-risk balance of the study that were unforeseen, (e.g. an unexpected increase in the incidence of expected serious adverse reactions that may be

clinically important), will be reported to the Clinical Trials Information System (CTIS). Unexpected events do not include SUSARs.

- Urgent safety measures, i.e. measures taken to protect clinical trial subjects due to an unexpected event that is likely to seriously affect the benefit-risk balance of the study, will be reported to the CTIS.
- Serious breaches, i.e. transgressions against the study protocol or the Clinical Trials Regulation that are likely to significantly affect the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial, will be reported to the CTIS.
- Annual safety report, i.e. yearly update on the safety of all the investigational medicinal products used in the study will be reported collectively to the CTIS.

13.7 Pregnancy reporting

For females of childbearing potential, urine or blood hCG results must be negative at screening. A pregnancy test need only be repeated if the investigator feels there is any possibility that pregnancy has occurred while the subject was being treated on protocol therapy. If pregnancy should occur, the subject will be immediately withdrawn from the study. The subject will receive counseling from the Investigator or his/her designee, regarding the nature of the study medications and the potential risk to fetal development.

14 Ethical considerations

14.1 Patient insurance

All patients in the study are covered by a state insurance scheme: http://patienterstatningen.dk. For Danish patients the Patient Compensation Association decides compensation claims for injured in connection to treatment by the Danish Health Service.

The sponsor cannot be held responsible for any damage or harm to the study subjects.

14.2 Subject identification

The name of the patient will be recorded on the inclusion log at the specific study site to link the patient with the allocated study identification (ID) number. Only the study ID will be reported to the Data Centre. The study ID will identify the patient and will be included on all case report forms. In order to avoid identification errors, the patient's study ID will consist of the allocated number followed by year of birth (as allowed per applicable legislation) will also be reported on the case report forms.

14.3 Informed consent

14.3.1 Recruitment

Recruitment will take place in the participating departments. All patients will receive written and verbal information regarding the study held in an uninterrupted location. This information will emphasise that participation in the study is voluntary and that the patient may withdraw from the study at any time and for any reason. All patients will be given the opportunity to ask questions about the study and will be given sufficient time to decide whether to participate in the study. Due to the acute nature of the toxicity investigated (colitis/diarrhoea) and the need for acute treatment, we will apply for an exception from the 24 hours rule, and it is thus accepted that most patients who accept will do so immediately or within few hours after the information. Information will further be supplied from the ministry of Science and the Ethical Committee: ”Your rights as a study person in a biomedical investigation” (Appendix D).

The patients will be informed by one of the investigators or co-investigators who are experienced in ir-toxicity, have GCP-experience, and who are trained in the study protocol.

Before performing any study-related procedures, the informed consent form will be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

A copy of the patient information including the signed consent form will be provided to the patient.

The interview will take place in accordance with the guidelines of the Danish National Committee on Health Research Ethic.

In order to find eligible patients for the study, it is necessary that the treating physician, before written consent, obtain information in the patient's medical record about diagnosis, histology, previous diagnoses, and treatments, medication, and scans. This is part of standard practice, as information helps to determine whether the patient should be offered standard treatment or meets the criteria for protocol screening/inclusion.

If the patient meets the inclusion criteria and gives consent, this information is collected and disclosed to the Principal Investigator/Study co-coordinator. If the patient does not meet the inclusion criteria or does not wish to consent, no data is recorded.

14.3.2 Information of the patient

All patients will be informed about:

- The aims of the study
- The possible adverse events
- The procedures and possible hazards to which the patient will be exposed
- Strict confidentiality of any patient data

- Medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

Participation in the study is voluntary. If the patient declines participation, this will not have any consequences for any other treatment of the patient.

14.3.3 Rights and responsibilities

At any time, the patient has the right to withdraw from the investigation without influencing on further treatment. The patient must be aware that personal information will be examined closely under audit of relevant authorised personal, but that this personal information will be handled strictly confidential and will not be available for anyone outside the study team. No personal information will be published, and the patient is guaranteed to remain anonymous.

Signed informed consent gives the permission to direct access to the patient's medical records, including the electronic record, by the sponsor, sponsor's representatives as well as any control authority. This will be done to retrieve information about the subject's health condition that is needed as part of the inclusion in the study, as well as control purposes, including self-monitoring, quality control, monitoring, and audits.

The study may start when the protocol is approved by the Health Research Medical Ethics Committees, the Danish Medicines Agency, and is included in the internal list of health research projects via the Executive Secretariat at Odense University Hospital. For EU or EEA countries participating in the study, an umbrella approval will be obtained through The Clinical Trials Information System (CTIS).

15 Administrative responsibilities

The Primary Investigator/Sponsor's Delegate/Study-coordinator and the Study co-coordinator are in charge of the all requirements for the approval of the study for European Union sites. The study will be approved by the Clinical Trials Information System (CTIS, European Medicines Agency) before any study specific assessments can be performed.

In the United Kingdom, the study will be approved by the Medicines & Healthcare products Regulatory Agency (MHRA) including ethics approval, before any study specific assessments can be performed. This will be the responsibility of the UK Principal Investigator.

16 Trial sponsorship and financing

The legal Sponsor of the study is:

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Financing of the study is provided by research grants obtained and listed below.

- OUH PhD Fund
- Region Syddanmark PhD Fund
- ICiTox Frontline Center
- Ingeniør K.A. Rohde og hustrus legat
- NEYE Foundation
- Novo Nordisk Foundation

17 Publication policy

17.1 Manuscript and publication

The study will be published once it has reached the primary endpoint and the final analysis has been performed and by preference been presented at an international scientific congress (e.g. ESMO or ASCO). The Vancouver declaration will be followed for all publications based on this study. We aim at publication in a high impact factor peer-reviewed international journal. Negative, positive and inconclusive results will be published. Any publication based on the data from this study proceeds from the investigator group, with specification of the participating sites and responsible contacts. The names on the author list will be given according to the active participation in the design of the protocol, in the recruitment of eligible and evaluable patients, in the compilation of results and in the production of the manuscript. The manuscript will be drafted by the Study co-coordinator Søren Kjær, and the assigned protocol committee will further contribute to the manuscript by review and comments. The final manuscript will be completed and submitted by the Study coordinator and Study co-coordinator. The first author of the manuscript will be Study co-coordinator Søren Kjær, and the last/senior author will be Principal Investigator/Study coordinator Christina H. Ruhlmann. Authorships will be assigned to Principal Investigators or Study co-investigators responsible for own site activation, only after successful activation and enrolment of at least five (5) eligible study subjects. Number of authorships for each site will be part of the specific site contracts.

17.2 Databases for public sharing of data

Prior to study initiation, the study will be registered at www.clinicaltrials.gov. No later than six months after Follow-up completion, a study report will be completed and data displayed on www.clinicaltrials.gov. Study results will also be available through the Clinical Trials Information System (CTIS). In addition, the anonymised data will be made public available through the Zenodo open data repository (CERN), or an equivalent public database.

18 Appendices

A References

List of references

1. Vaddepally, R.K., et al., *Review of Indications of FDA-Approved Immune Checkpoint Inhibitors per NCCN Guidelines with the Level of Evidence.* Cancers, 2020. **12**(3): p. 738.
2. Larkin, J., et al., *Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma.* N Engl J Med, 2019. **381**(16): p. 1535-1546.
3. Reck, M., et al., *Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50.* J Clin Oncol, 2021: p. Jco2100174.
4. Motzer, R.J., et al., *Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma.* N Engl J Med, 2018. **378**(14): p. 1277-1290.
5. Pardoll, D.M., *The blockade of immune checkpoints in cancer immunotherapy.* Nat Rev Cancer, 2012. **12**(4): p. 252-64.
6. Champiat, S., et al., *Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper.* Ann Oncol, 2016. **27**(4): p. 559-74.
7. Vaddepally, R.K., et al., *Review of Indications of FDA-Approved Immune Checkpoint Inhibitors per NCCN Guidelines with the Level of Evidence.* Cancers (Basel), 2020. **12**(3).
8. Oken, M.M., et al., *Toxicity and response criteria of the Eastern Cooperative Oncology Group.* Am J Clin Oncol, 1982. **5**(6): p. 649-55.
9. Wang, D.Y., et al., *Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis.* JAMA Oncol, 2018. **4**(12): p. 1721-1728.
10. Bellaguarda, E. and S. Hanauer, *Checkpoint Inhibitor-Induced Colitis.* Am J Gastroenterol, 2020. **115**(2): p. 202-210.
11. Wang, D.Y., et al., *Incidence of immune checkpoint inhibitor-related colitis in solid tumor patients: A systematic review and meta-analysis.* Oncoimmunology, 2017. **6**(10): p. e1344805.
12. Arnaud-Coffin, P., et al., *A systematic review of adverse events in randomized trials assessing immune checkpoint inhibitors.* Int J Cancer, 2019. **145**(3): p. 639-648.
13. Tivol, E.A., et al., *Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4.* Immunity, 1995. **3**(5): p. 541-7.
14. Coutzac, C., et al., *Colon Immune-Related Adverse Events: Anti-CTLA-4 and Anti-PD-1 Blockade Induce Distinct Immunopathological Entities.* J Crohns Colitis, 2017. **11**(10): p. 1238-1246.
15. Wang, Y., et al., *Endoscopic and Histologic Features of Immune Checkpoint Inhibitor-Related Colitis.* Inflamm Bowel Dis, 2018. **24**(8): p. 1695-1705.
16. Abu-Sbeih, H., et al., *Immune Checkpoint Inhibitor Therapy in Patients With Preexisting Inflammatory Bowel Disease.* J Clin Oncol, 2020. **38**(6): p. 576-583.
17. Helmink, B.A., et al., *The microbiome, cancer, and cancer therapy.* Nat Med, 2019. **25**(3): p. 377-388.
18. Liu, L. and K. Shah, *The Potential of the Gut Microbiome to Reshape the Cancer Therapy Paradigm: A Review.* JAMA Oncol, 2022. **8**(7): p. 1059-1067.
19. Chaput, N., et al., *Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab.* Ann Oncol, 2019. **30**(12): p. 2012.
20. Hakozaki, T., et al., *The Gut Microbiome Associates with Immune Checkpoint Inhibition Outcomes in Patients with Advanced Non-Small Cell Lung Cancer.* Cancer Immunol Res, 2020. **8**(10): p. 1243-1250.

21. Wilson, B.E., et al., *The effect of antibiotics on clinical outcomes in immune-checkpoint blockade: a systematic review and meta-analysis of observational studies.* Cancer Immunol Immunother, 2020. **69**(3): p. 343-354.
22. Dubin, K., et al., *Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis.* Nat Commun, 2016. **7**: p. 10391.
23. Haanen, J., et al., *Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol, 2017. **28**(suppl_4): p. iv119-iv142.
24. Brahmer, J.R., et al., *Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline.* J Clin Oncol, 2018. **36**(17): p. 1714-1768.
25. Dougan, M., et al., *Multinational Association of Supportive Care in Cancer (MASCC) 2020 clinical practice recommendations for the management of severe gastrointestinal and hepatic toxicities from checkpoint inhibitors.* Support Care Cancer, 2020. **28**(12): p. 6129-6143.
26. Brahmer, J.R., et al., *Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events.* J Immunother Cancer, 2021. **9**(6).
27. Ibraheim, H., et al., *Systematic review with meta-analysis: effectiveness of anti-inflammatory therapy in immune checkpoint inhibitor-induced enterocolitis.* Aliment Pharmacol Ther, 2020. **52**(9): p. 1432-1452.
28. Larkin, J., et al., *Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma.* N Engl J Med, 2015. **373**(1): p. 23-34.
29. Draghi, A., et al., *Differential effects of corticosteroids and anti-TNF on tumor-specific immune responses: implications for the management of irAEs.* Int J Cancer, 2019. **145**(5): p. 1408-1413.
30. Johnson, D.H., et al., *Infliximab associated with faster symptom resolution compared with corticosteroids alone for the management of immune-related enterocolitis.* J Immunother Cancer, 2018. **6**(1): p. 103.
31. Abu-Sbeih, H., et al., *Early introduction of selective immunosuppressive therapy associated with favorable clinical outcomes in patients with immune checkpoint inhibitor-induced colitis.* J Immunother Cancer, 2019. **7**(1): p. 93.
32. Romanski, N.A., et al., *Characterization of risk factors and efficacy of medical management of immune-related hepatotoxicity in real-world patients with metastatic melanoma treated with immune checkpoint inhibitors.* Eur J Cancer, 2020. **130**: p. 211-218.

B Summary of Product Characteristics

B.1 Infliximab

B.2 Methylprednisolone

B.3 Prednisolone

C Randomisation

Randomisation standard operating procedure

D Ethics

Your rights as a study person in a biomedical investigation

E List of abbreviations

ALAT: Alanine transaminase

Anti-CTLA-4: Cytotoxic T-lymfocyte-associated protein 4

Anti-PD-1: Programmed cell death protein 1 antibody

Anti-PD-L1: Programmed cell death ligand-1 antibody

CTCAE: Common terminology criteria for adverse events

ECOG: Eastern cooperative oncology group

eCRF: Electronic case report form

EMA: European medicine agency

GCP: Good clinical practice

hCG: human chorionic gonadotropin

Hgb: Haemoglobin

HBM: Human biological material

IBD: Inflammatory bowel disease

ICH: International conference of harmonisation

ICI: Immune checkpoint inhibitor

irAE: Immune-related adverse event

mCTCAE: modified CTCAE

OS: Overall survival

PCR: Polymerase chain reaction

PFS: Progession free survival

OPEN: Open Patient data Explorative Network

QoL: Quality of life

REDCap: Research Electronic Data Capture

SOC: Standard of care

F Tables and figures

Figure 1: Randomisation flow chart

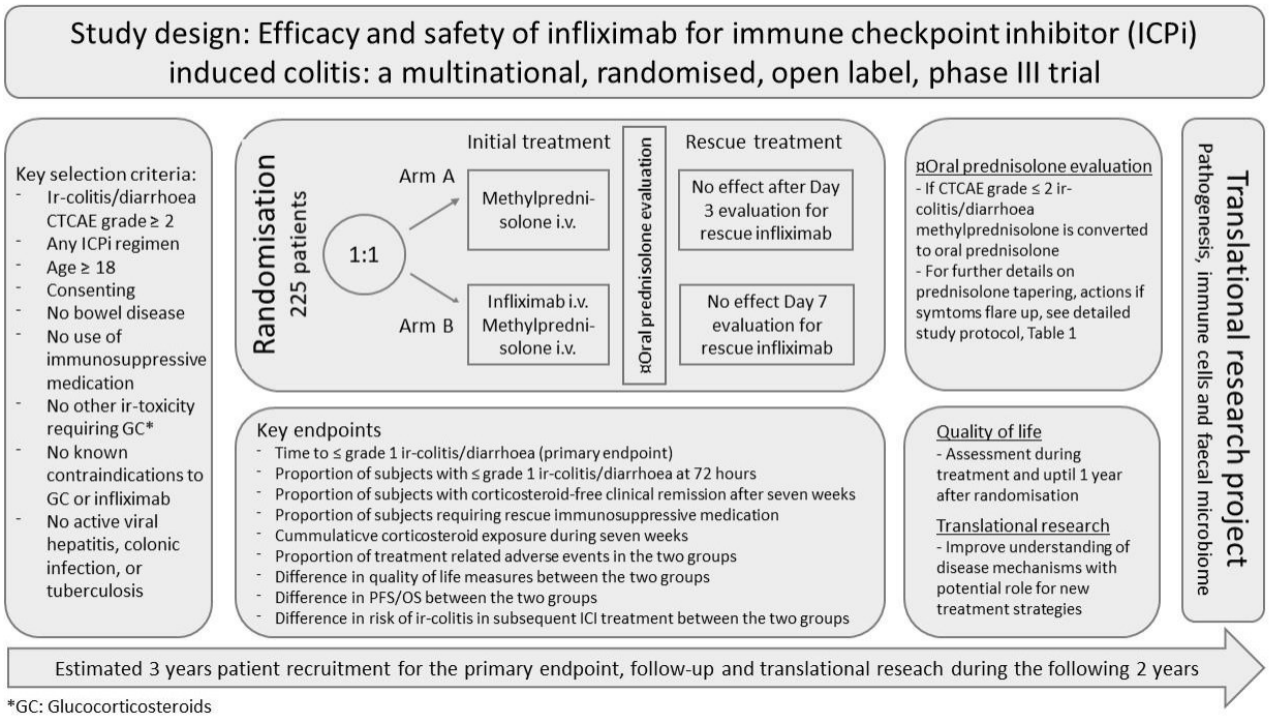

Table 1: Treatment schedule for study groups A and B

Table 1: Overview of study treatment schedules for study subjects randomised to Arm A and Arm B	
Arm A: standard of care	Arm B: infliximab* + standard of care
Day 1: - Methylprednisolone 80 mg i.v. ¤	Day 1: - Methylprednisolone 80 mg i.v.¤ - Infliximab 5 mg/kg
Day 2 (≥ 24 hours since first dose of methylprednisolone): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v.	Day 2 (≥ 24 hours since first dose of methylprednisolone, 0-24 hours after the first dose of infliximab): - If infliximab was not administered Day 1 o infliximab 5 mg/kg - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v.
Day 3 (≥ 48 hours since first dose of methylprednisolone): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v.	Day 3 (≥ 48 hours since first dose of methylprednisolone, 24-48 hours after the first dose of infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v.
Day 4 (≥ 72 hours since first dose of methylprednisolone): - If ir-colitis/diarrhoea ≤ 2 convert to oral prednisolone tapering schedule (Table 2) - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea: o continue daily methylprednisolone 80 mg i.v. o preparation for rescue infliximab to be administered Day 4 or 5 o rescue infliximab	Day 4 (≥ 72 hours since first dose of methylprednisolone, 48-72 hours after the first dose of infliximab): - If ir-colitis/diarrhoea ≤ 2 convert to oral prednisolone tapering schedule (Table 2) - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea continue daily methylprednisolone 80 mg i.v.
Day 5 (≥ 96 hours since first dose of methylprednisolone, 0-24 hours since first dose of rescue infliximab): - If ir-colitis/diarrhoea ≤ 2 convert to oral prednisolone tapering schedule (Table 2)	Day 5 (≥ 96 hours since first dose of methylprednisolone, 72-96 hours after the first dose of infliximab): - If ir-colitis/diarrhoea ≤ 2 convert to oral prednisolone tapering schedule (Table 2)

- If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea: o continue daily methylprednisolone 80 mg i.v. o rescue infliximab if not administered Day 4	- If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea continue daily methylprednisolone 80 mg i.v.
Day 6 (≥ 120 hours since first dose of methylprednisolone, 24-48 hours since first dose of rescue infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v.	Day 6 (≥ 120 hours since first dose of methylprednisolone, 96-120 hours after the first dose of infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v.
Day 7 (≥ 144 hours since first dose of methylprednisolone, 48-72 hours since first dose of rescue infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v.	Day 7 (≥ 144 hours since first dose of methylprednisolone, 120-144 hours after the first dose of infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v. o preparation for rescue infliximab to be administered Day 8 or 9
Day 8 (≥ 168 hours since first dose of methylprednisolone, 72-96 hours since first dose of rescue infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v.	Day 8 (≥ 168 hours since first dose of methylprednisolone, 144-168 hours after the first dose of infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v. o rescue infliximab
Day 9 (≥ 192 hours since first dose of methylprednisolone, 96-120 hours since first dose of rescue infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea	Day 9 (≥ 192 hours since first dose of methylprednisolone, 168-192 hours after the first dose of infliximab, 0-24 hours after first dose of rescue infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule

o continue daily methylprednisolone 80 mg i.v.	- If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v. o rescue infliximab if not administered Day 8
Day 10 (≥ 216 hours since first dose of methylprednisolone, 120-144 hours since first dose of rescue infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v. o preparation for second dose rescue infliximab to be administered Day 11 or 12	Day 10 (≥ 216 hours since first dose of methylprednisolone, 192-216 hours after the first dose of infliximab, 24-48 hours after first dose of rescue infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v.
Day 11 (≥ 240 hours since first dose of methylprednisolone, 144-168 hours since first dose of rescue infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v. o second dose rescue infliximab	Day 11 (≥ 240 hours since first dose of methylprednisolone, 216-240 hours after the first dose of infliximab, 48-72 hours after first dose of rescue infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v.
Day 12 (≥ 264 hours since first dose of methylprednisolone, 168-192 hours since first dose of rescue infliximab, 0-24 hours after second dose of rescue infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v. o second dose rescue infliximab if not administered Day 11	Day 12 (≥ 264 hours since first dose of methylprednisolone, 240-264 hours after the first dose of infliximab, 72-96 hours after first dose of rescue infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v. o evaluation for second line biologic rescue treatment per investigators choice[#] o second line biologic rescue treatment per investigators choice

Day 13 (≥ 288 hours since first dose of methylprednisolone, 192-216 hours since first dose of rescue infliximab, 24-48 hours after second dose of rescue infliximab):
- If ir-colitis/diarrhoea ≤ 2
  o convert to oral prednisolone tapering schedule
- If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea
  o continue daily methylprednisolone 80 mg i.v.
	Day 13 (≥ 288 hours since first dose of methylprednisolone, 264-288 hours after the first dose of infliximab, 96-120 hours after first dose of rescue infliximab):
	- If ir-colitis/diarrhoea ≤ 2
	  o convert to oral prednisolone tapering schedule
	- If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea
	  o continue daily methylprednisolone 80 mg i.v.
	  o second line biologic rescue treatment per investigators choice if not administered Day 12

Day 14 (≥ 312 hours since first dose of methylprednisolone, 216-240 hours since first dose of rescue infliximab, 48-72 hours after second dose of rescue infliximab):
- If ir-colitis/diarrhoea ≤ 2
  o convert to oral prednisolone tapering schedule
- If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea
  o continue daily methylprednisolone 80 mg i.v.
	Day 14 (≥ 312 hours since first dose of methylprednisolone, 288-312 hours after the first dose of infliximab, 120-144 hours after first dose of rescue infliximab):
	- If ir-colitis/diarrhoea ≤ 2
	  o convert to oral prednisolone tapering schedule
	- If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea
	  o continue daily methylprednisolone 80 mg i.v.
	  o treatment per investigators choice

Day 15 (≥ 336 hours since first dose of methylprednisolone, 240-264 hours since first dose of rescue infliximab, 72-96 hours after second dose of rescue infliximab):
- If ir-colitis/diarrhoea ≤ 2
  o convert to oral prednisolone tapering schedule
- If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea
  o continue daily methylprednisolone 80 mg i.v.
  o evaluation for second line biologic rescue treatment per investigators choice[#]
  o second line biologic rescue treatment per investigators choice
	Day 15 and forward:
	- assess and treat as Day 14

Day 16 (≥ 360 hours since first dose of methylprednisolone, 264-288 hours since first dose of rescue infliximab, 96-120 hours after second dose of rescue infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule	

- If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v. o second line biologic rescue treatment per investigators choice if not administered Day 15	
Day 17 (≥ 384 hours since first dose of methylprednisolone, 288-312 hours since first dose of rescue infliximab, 120-144 hours after second dose of rescue infliximab): - If ir-colitis/diarrhoea ≤ 2 o convert to oral prednisolone tapering schedule - If ir-colitis/diarrhoea > 2 or no improvement for patients included on the basis of loperamide persistent grade 2 ir-colitis/diarrhoea o continue daily methylprednisolone 80 mg i.v. o treatment per investigators choice	
Day 18 and forward: - assess and treat as Day 17	

*Infliximab dose: Initially, patients will receive infliximab 5 mg/kg. Patients referred to rescue infliximab will receive dosage of infliximab a

¤ Methylprednisolone 80 mg intravenously (body weight 40-80 kg; methylprednisolone 1 mg/kg if body weight < 40 or > 80 kg)

#Rescue treatment per investigators choice: information on any rescue treatments for each study subject will be noted in the eCRF.

Table 2: Oral prednisolone tapering schedule

Table 2: Oral prednisolone tapering schedule		
Step	Prednisolone dose	Number of days
1	50 mg	3
2	37,5 mg	5
3	25 mg	5
4	12,5 mg	5
5	5 mg	5

Table 3: Modified CTCAE grading of ir-colitis and ir-diarrhoea

Table 3: mCTCAE grading of ir-colitis and ir-diarrhoea		
mCTCAE grading	Severity	Ir-diarrhoea/colitis
Grade 1	Mild	Increased stool frequency < 4 daily
Grade 2	Moderate	Increased daily stool frequency 4-6 daily
Grade 3	Severe	Increased daily stool frequency > 7 daily
Grade 4	Potential fatal	Life-threatening symptoms, or any grade of diarrhoea and one of the following: haematochezia, abdominal pain, mucus in stool, dehydration, fever